

20th SSBP International Research Symposium Genetic Disorders and Neurobehavioural Phenotypes Programme Book 14th – 16th September 2017 • Leiden, the Netherlands



Save the date!

21st SSBP International Research Symposium will be held in Melbourne, Australia, in August 2018

Registration and abstract submission open: 12th March 2018 Deadline for online abstract submission: 22nd April 2018 Deadline for discounted early bird registration: 16th July 2018 Research Symposium: 28th – 29th August 2018 Educational Day: 30th August 2018

Join us in Melbourne, Australia for our 21st Research symposium, the theme will be *Translating knowledge of phenotype towards improved outcomes in neurodevelopmental disability*

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



The Society for the Study of Behavioural Phenotypes

14th – 16th September 2017

The 20th SSBP International Research Symposium

Genetic Disorders and Neurobehavioural Phenotypes

Leiden, the Netherlands

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Welcome to Leiden

We are honored to welcome you to Leiden, host city of the 20th "International Research Symposium and Educational Day" of the Society for the Study of Behavioural Phenotypes.

Leiden is a relatively small, but bustling and lively university city, near the coast of the Netherlands. It is also very close to the larger cities of Amsterdam and The Hague. The city could be described as sort of a mini-Amsterdam, as, like the capitol of the Netherlands, it has many canals and historic buildings dating from the Golden Age, but with a more relaxed atmosphere. However, this probably does not do justice to Leiden's own identity and achievements throughout the centuries.

Leiden is home of the oldest (est. 1575) and one of the most prestigious universities in the Netherlands: despite its size, it has the highest number of Nobel and Spinoza-laureates in the country. It is best known for the studies of Law & Politics and Physics & Chemistry, with strong positions in more recently established fields, such as Social and Biomedical Sciences, as well. The fact that world-famous artists such as Rembrandt van Rijn and Jan Steen also came from Leiden, that the Dutch political "elite" is largely educated in this city, and that it bred an unusually high number of Olympic athletes underline Leiden's diversity.

We are grateful to be able to present to you a very ambitious program, spanning both the Educational Day and Research Symposium, with speakers from all around the world. It may be stated that the program truly fits its host and vice versa. In order to accommodate the 20th SSBP-conference, we have picked some excellent venues: the Educational Day will take place at the *Oranjerie of the Hortus Botanicus*, and the two-day Research Symposium will take place at *Scheltema*, an old blanket factory located at the quay of one of the most beautiful canals in central Leiden. Other venues, such as the *Rijksmuseum voor Oudheden* for the conference's gala dinner, and *City Hall* for the conference's welcome reception, were also chosen to fit the occasion.

We hope you will enjoy the 20th anniversary SSBP-conference, allowing time for knowledge sharing and expansion, for connecting with many like-minded individuals, and for exploring some of the less academic (but equally fun) sides of Leiden as well!

Stephan Huijbregts and Anna Jansen

Conference Coordinators

Leiden Conference Organisers

Dr Stephan Huijbregts

Dr. Stephan Huijbregts received his PhD in 2002 from the Vrije Universiteit Amsterdam at the Department of Clinical Neuropsychology (Title of thesis: Attention and Information Processing in Early and Continuously Treated Phenylketonuria). Between 2002 and 2004 he worked as a postdoctoral researcher at the University of Montreal/Ste Justine's hospital in Canada, and between 2004 and 2006 as a lecturer at the University of Southampton, School of Psychology in the United Kingdom. He has been an Assistant Professor at Leiden University, Department of Clinical Child and Adolescent Studies in the Netherlands, since 2006, and is also Senior



Researcher at the Leiden Institute for Brain and Cognition (at Leiden University Medical Center). Dr. Huijbregts is a pediatric neuropsychologist, whose main research interest is the cognitive, behavioural, and social functioning of children with genetic disorders (e.g. Phenylketonuria (PKU), Tyrosinemia Type1, and Neurofibromatosis Type 1 (NF1), and children pre- and postnatally exposed to environmental adversity (e.g. prenatal exposure to substances, poor rearing practices, familial psychopathology). In his research, Stephan Huijbregts looks for links between socio-cognitive profiles and neural and neurobiological substrates using techniques such as MRI, PET and fNIRS. Huijbregts has published 60+ scientific articles and book chapters, and is a member of several advisory boards aimed at optimizing treatment of PKU and NF1.

Prof Dr Anna Jansen

Prof Dr Anna Jansen is Head of Clinics at the Pediatric Neurology Unit UZ Brussel and holds a part-time research appointment as FWO Senior Clinical Investigator at the Vrije Universiteit Brussel. She is affiliated to the Department of Public Health and teaches in Youth Health. She obtained her PhD in 2008 addressing the role of genetic factors in epilepsy. Her current research focuses on the genetic basis of developmental brain malformations. She coordinates a multidisciplinary clinic for tuberous sclerosis complex (TSC), is Vice-Chair of the TOSCA registry and of NeuroMIG, participates in EPISTOP (FP7),



and serves as PI on clinical trials in epilepsy and TSC. Her research has resulted in the publication of over 60 peerreviewed articles, and has been presented internationally.

Local Organizing Committee

Dr. Agnies van Eeghen

ENCORE Expertise Center, Erasmus Medical Center, Rotterdam, the Netherlands De Hartekamp Groep, Haarlem, the Netherlands

Prof. Dr. Hanna Swaab

Department of Clinical Child and Adolescent Studies and Leiden Institute for Brain and Cognition, Leiden University, Leiden, the Netherlands.

Prof. Dr. Francjan van Spronsen

Beatrix Children's Hospital, University Medical Center, University of Groningen, Groningen, the Netherlands

Scientific Committee

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Assistant Professor Leiden Institute for Brain and Cognition/Department of Clinical Child and Adolescent Studies, Leiden University, the Netherlands

Prof. Dr. Anna Jansen (Co-chair)

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

Prof. Dr. Petrus de Vries

Sue Struengmann Professor of Child & Adolescent Psychiatry Division of Child & Adolescent Psychiatry, Department of Psychiatry and Mental Health, University of Cape Town, South Africa

Prof. Dr. Patricia Howlin

Emeritus Professor of Clinical Child Psychology Department of Psychology, King's College, London, UK *Professor of Developmental Disorders* Brain & Mind Research Institute, University of Sydney, Australia

Dr. Andre Strydom

Reader in Intellectual Disabilities Division of Psychiatry, Faculty of Brain Sciences, University College London, UK

Dr. Jane Waite

Postdoctoral Research Fellow Cerebra Centre for Neurodevelopmental Disorders, School of Psychology, University of Birmingham, UK

Dr. Kate Woodcock

Lecturer School of Psychology, Queen's University Belfast, Ireland

Dr. Honey Heussler

Associate Professor Mater Research Institute, University of Queensland, Brisbane, Australia Medical Director Child Development at the Lady Cilento Children's Hospital, Brisbane, Australia

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 :

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President	Professor Patricia Howlin (UK) (patricia.howlin@kcl.ac.uk)
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	Global –Pat Howlin (London) (patricia.howlin@kcl.ac.uk)
Administrator	<i>Elizabeth Walmsley</i> (ssbpliz@gmail.com)
Conference Administrator	Rebecca Windram (conference@ssbp.org.uk)



Meetings of the SSBP

1991	Kings Fund, London, UK	Workshop
1992	Welshpool, UK	2 nd International
1993	Royal Society of Medicine, London, UK	4 th Annual
1994	Maastricht, the Netherlands	3 rd International
1995	Edinburgh, UK	6 th Annual
1996	Dublin, Ireland	4 th International
1997	Cambridge, UK	7 th Annual
1998	Baltimore, USA	5 th International
1999	Birmingham, UK	8t ^h Annual
2000	Venice, Italy	6 th International
2001	Oxford, UK	9 th Annual
2002	Whistler, Canada	7 th Scientific
2003	Newcastle, UK	10 th Annual
2004	Barcelona, Spain	8 th International
2005	Cairns, Australia	9 th International
2006	Dublin, Ireland	11 th Annual
2007	MIND Institute, Sacramento & Lake Tahoe, USA	10 th International
2008	Cologne, Germany	11 th International
2009	Cambridge, UK	12 th International
2010	Pavia, Italy	13 th International
2011	Brisbane, Australia	14 th International
2012	Leuven, Belgium	15 th International
2013	Stellenbosch, South Africa	16 th International
2014	New York, USA	17 th International
2015	London, UK	18 th International
2016	Siena, Italy	19 th International
2017	Leiden, the Netherlands	20 th International

Forthcoming Meetings of the SSBP

2018 Melbourne	e, Australia 21 st International	

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

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

2017 Tom Oppé Distinguished Lecturer: Professor James Harris

Dr. James C. Harris is the founding Director of Developmental Neuropsychiatry at the Johns Hopkins University School of Medicine and the Kennedy Krieger Institute. He is past Director of the Division of Child Psychiatry at Johns Hopkins and past president of American Association of Directors of Child and Adolescent Psychiatry (AADCAP). The focus of his research is in understanding the neurodevelopmental basis of social communication, emotion regulation, self-injurious behaviors and cognition. He has actively pursued these



interests though research in Lesch-Nyhan Syndrome (LNS), Rett Syndrome, Prader Willi Syndrome and Autism. His NICHD funded research has focused on understanding the mechanisms underlying the self-injurious behavioral phenotype in LNS and establishing treatments. This research has examined pathways from genes to cognition and complex behavior in classic and variant Lesch Nyhan cases. It has involved gene sequencing, HPRT enzyme measurement in whole cells, MRI anatomical studies, MRS investigation of brain metabolites, PET imaging of the dopamine transporter, DTI studies of White Matter Tracks, neuropsychological testing, and specific behavioral ratings to allow correlation among these features. Dr. Harris's current research focuses on LNS and on the role of oxytocin and vasopressin in the neurobiology of social engagement. He has published over 300 articles, book, chapters, commentaries and abstracts.

Patricia Howlin and the Patricia Howlin Prize Lecture



Patricia Howlin

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

Pat Howlin Prize Lecture: Area of Research:

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

Eligibility of applicants:

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

2017 Pat Howlin Lecturer:

The Patricia Howlin Lecture Prize has not been awarded in 2017, as no eligible abstracts were submitted. The SSBP would like to encourage any students or early stage researchers working on intervention-based research to consider submitting an abstract for consideration at the SSBP 2018 conference.

Award Procedure:

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

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

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

Patricia Howlin Lecturers

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

Sponsors

The SSBP is extremely grateful to the following organisations for their sponsorship of SSBP 2017 in Leiden.

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Keynote Speaker Profiles

(in order of presentation)

Dr Honey Heussler

Helen (Honey) Heussler MB BS FRACP DM is an Associate Professor at the University of Queensland and the Mater Medical Research Institute. She is the Medical Director of Child Development for Children's Health Queensland and is a Senior Medical Officer at The Lady Cilento Children's Hospital in Brisbane, Queensland working in dual specialities of Developmental Paediatrics and Sleep Medicine. Her research interests are in her areas of clinical practice. Her clinical work involves children with a variety of Developmental and Behavioural problems as well as a number of clinics that specialise in Sleep disorders for this population. She also runs specialised clinics for some genetic disorders including VCFS.

Dr Luci Wiggs

Reader in Psychology, Oxford Brookes University, Oxford, UK.

Dr Luci Wiggs BSc (Hons) DPhil CPsychol is a chartered psychologist who conducts clinical research into sleep, its disorders and treatments and the effects of sleep disruption on daytime functioning. She has a special interest in children with developmental disorders (DD) and their families. She has published her work in a variety of scientific journals and co-edited an internationally authored book about sleep disruption and its treatment in children with DD. She is currently an Associate Editor for the Journal of Sleep Research.

She has previously served as a board member of the British Sleep Society's Executive and Scientific Committees and the European Paediatric Sleep Group as well as Chairing the European Sleep Research Society's Education Committee and the British Sleep Society Paediatric Group.

Dr Mark Andermann

Mark Andermann, Ph.D., is a researcher in the Division of Endocrinology, Diabetes, and Metabolism at Beth Israel Deaconess Medical Center (BIDMC). He is also a faculty member of the Harvard PhD Program in Neuroscience and PhD Program in Biophysics and an assistant professor of medicine at Harvard Medical School (HMS).

Dr. Andermann graduated from McGill University in 1999 with a joint honors degree in mathematics and physics, and received his Ph.D. in biophysics and neuroscience in 2005 from Harvard University, where he began to investigate the brain mechanisms

underlying sensory perception in rats. He completed a one-year postdoctoral fellowship at the Helsinki University of Technology, where he designed a novel non-invasive sensory brain-computer interface for use in humans. Dr. Andermann then went on to complete his postdoctoral training at HMS in the laboratory of Clay Reid, Ph.D., where he developed a mouse model for studying visual perception in which neural activity in the same individual brain cells can be recorded for many months in behaving mice. He opened his laboratory at BIDMC in 2012.

Dr. Andermann's lab develops and uses leading-edge brain imaging techniques to study the brain networks guiding hunger-dependent attention to food cues — a key first step toward developing cognitive therapies for obesity, binge eating, and other eating disorders.







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Dr Marianne Nordstrøm

Marianne Nordstrøm graduated as clinical dietitian from University of Oslo in 2002. She is currently working at Frambu Resource Centre for Rare Disorders from where she has more than ten years of experience. Frambu is a part of the Norwegian National Advisory Unit on Rare Disorders. She defended her PhD at the Faculty of Medicine, University of Oslo in 2015. Her research activity has focused on diet and nutritional issues and lifestyle related health risk in Prader-Willis syndrome, Williams syndrome and Downs syndrome.

Dr Agnies van Eeghen

Agnies van Eeghen works as an Intellectual Disability Physician, which is a relatively new medical specialty in the Netherlands. She is specialized in the neurobehavioral phenotypes of genetic syndromes such as Tuberous Sclerosis Complex (TSC) and Fragile X Syndrome (FXS).

After obtaining her medical degree, she followed the Intellectual Disability specialization at the Erasmus Medical Center in Rotterdam. Subsequently, she worked as a research fellow at Massachusetts General Hospital in Boston, resulting in a PhD on the

neuropsychiatric phenotype of Tuberous Sclerosis Complex at the Erasmus Medical Center. After moving back to the Netherlands, she rejoined the Erasmus Medical Center as coördinator of the adult expertise centers of TSC and FXS. Additionally, she works at an outpatient clinic at the Hartekamp Group in Haarlem, and recently joined Academic Medical Center in Amsterdam to perform tertiary care for patients with intellectual disability.

In addition to clinical work, Agnies is active in research on manifestations and treatment of neuropsychiatric phenotypes in teenagers and adults with genetic neurodevelopmental disorders. She is also chairman of the guideline committee of the Dutch association for physicians with intellectual disability.

Dr Andrea Pilotto

Dr Pilotto graduated at the University of Padova School of Medicine, Italy in 2009. From 2010 to 2015 he worked on the Adult Neurology Residency Program at the Neurology Department of Brescia, Italy under the supervision of Prof. Padovani, a leading expert in neurodegenerative disease. In 2013 – 2016 he joined the Research group of Prof. Berg, in Tuebingen, Germany for a research fellowship focused on early Parkinson's disease neurodegenerative biomarkers. In 2017 he works as research assistant Professor in Neurology at the University of Brescia and at the Parkinson's Disease Rehabilitation Centre

of Trescore Balneario, Italy. His special research interests are clinical, neuroimaging and genetics aspects of neurodegenerative disorders, especially presenile dementia and parkinsonism. Since 2014 he is the coordinator of the EN-ETPKU study in Tuebingen in collaboration with Prof. Berg and Prof. Trefz (University of Heidelberg). This study evaluates middle aged ETPKU patients with a special focus on neurodegenerative markers.







Professor Raoul Hennekam

Raoul Hennekam received his specialty trainings in Paediatrics and in Clinical Genetics at Utrecht University. He was appointed as professor of Paediatrics and of Clinical Genetics in 2002 at the Academic Medical Centre of University of Amsterdam. During 2005 – 2010 he worked in London at the Institute of Child Health and Great Ormond Street Hospital as professor of Clinical Genetics and Dysmorphology. He is presently working as professor of Paediatrics and of Translational Genetics in Amsterdam.

Main scientific interests include intellectual disabilities, autism and other behavioural disturbances, aging, connective tissue disorders, natural history studies and (molecular) dysmorphology. He is member of the Dutch Health Council, EUCERD, European Research Council, Editor of American Journal of Medical Genetics, European Journal of Medical Genetics and European Journal of Paediatrics, author of 500 papers in peer-reviewed journals (H-index 69) and 24 chapters in international texts, co-chair of the international Morphology Nomenclature Committee, and senior editor of 'Gorlin's Syndromes of the Head and Neck'.

Dr Anthony Isles

Anthony Isles is Professor of Molecular and Behavioural Neuroscience at Cardiff University, where his research investigates the genetic and epigenetic mechanisms that influence brain function and mental disease. Anthony received his PhD from the University of Cambridge, and did post-doctoral research at the Babraham Institute and Department of Psychiatry in Cambridge.

Since moving to Cardiff University in 2006, he has continued to address his main interest, specifically what imprinted genes are doing in the brain and how they influence

neurodevelopmental disorders. His group are also interested in whether imprinted genes expressed in the brain are affected by the maternal environment (e.g. diet). Similarly, more recent research is investigating whether changes in the placental expression of imprinted genes can influence both maternal behaviour and later offspring outcomes.

Professor Kathrin Thedieck

Kathrin Thedieck studied at the Ecole Supérieure de Biotechnologie Strasbourg (ESBS) in France, Germany, and Switzerland. She developed proteomic methods for biomarker discovery at the startup company BioVisioN in Hannover, and did her PhD at the Helmholtz Center for Infection Research in Braunschweig (Germany). For her postdoc Kathrin Thedieck joined the lab of Michael N. Hall (Basel, Switzerland), who discovered the kinase mammalian target of rapamycin (mTOR), recognized as a key driver of TSC and many

other tumor diseases. Since then Kathrin Thedieck has dedicated her research to the better understanding of tumor and patient specific features and regulators of the mTOR network. Since being a group leader at Freiburg University (Germany), Kathrin Thedieck has developed systems approaches to unravel the complex structure of the mTOR network and predict drug responses. In the frame of the European Medical School Groningen-Oldenburg, Kathrin Thedieck works since 2013 at the University Medical Center Groningen (Dept. Pediatrics) and the University of Oldenburg (Dept. Neuroscience). Further information: www.metabolic-signaling.eu.



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Professor Francjan van Spronsen

Francjan van Spronsen is a pediatrician Metabolic Diseases at the Beatrix Children's Hospital, University Medical Centre of Groningen (UMCG), with a long-standing research interest in the effects of abnormal amino acid metabolism, especially in phenylketonuria (PKU) and Tyrosinemia type I. He was appointed as full professor in pediatrics with special interest in defects in amino acid metabolism at the University of Groningen, and became in charge of the Division of Metabolic Diseases in the children's hospital of the UMCG. He currently treats patients with metabolic diseases from birth into adulthood.

His research focus is on the causes and consequences of defects in amino acid metabolism and the relationships between metabolic control, metabolic pathways and neurocognitive outcomes, and the improvement of these abnormalities, resulting in some 100 articles on PKU and Tyrosinemia type I only.

At a national level, he chairs the Advisory Committee on Neonatal Screening with respect to inherited metabolic diseases, and is a member of the Dutch Committee on Neonatal Screening. At an international level, he chairs the Scientific Advisory Board of the European Society of PKU and Allied Disorders, and is a member of various European and international advisory boards and working groups for various defects in amino acid metabolism. He is in the lead of a group of some 19 colleagues who just published their first paper on the European guidelines for PKU.

Dr Manuel Schiff

Dr Manuel Schiff is an Associate Professor of Pediatrics and Head of the Reference Centre for Inborn Errors of Metabolism at the Robert-Debré University Hospital in Paris, France. After an undergraduate degree in Biochemistry and a residency in Paediatrics, he completed a PhD in mitochondrial biology, under the supervision of Dr Pierre Rustin at the University of Paris Descartes. He then was a post-doctoral fellow at Dr Jerry Vockley's laboratory at the University of Pittsburgh, USA. His clinical research interests include mitochondrial energy metabolism, CDG and homocystinurias/ B12 and folate metabolism

disorders for which he is a partner in the European collaborative network (EHOD). His basic research interest is mitochondrial energy metabolism. He has been appointed Honorary Secretary of the SSIEM (Society for the Study of Inborn Errors of Metabolism) in September 2016.

Dr Robin Lachmann

Dr Robin Lachmann is one of two consultants at the Charles Dent Metabolic Unit, London, UK, where over 1,500 adult patients with a wide range of inherited metabolic diseases are cared for. After qualifying in 1990, Dr Lachmann continued his training in Internal Medicine and Metabolic Medicine, as well as performing PhD research on herpes simplex virus-mediated gene delivery to the brain and postdoctoral work on glycosphingolipid lysosomal storage disorders. He has no qualifications in clinical psychology, but he does enjoy talking to his patients.







Dr Belinda Barton

Department Head & Psychologist, Children's Hospital Education Research Institute (CHERI) and NF1 Neurocognitive Research Team Leader, Institute for Neuroscience and Muscle Research (IMNR), The Children's Hospital at Westmead, Sydney Australia.

Dr Barton is an experienced paediatric psychologist with a major research interest in understanding the cognitive, behavioral and social aspects of genetic and neurodevelopmental disorders, as well as therapeutic interventions that aim to improve the clinical outcomes of children diagnosed with these disorders. She has a particular and

long standing clinical and research interest in neurofibromatosis type 1 (NF1). She established the NF1 Educational Clinic, is the team leader of cognitive research on NF1 at The Children's Hospital at Westmead and regularly supervises doctoral students within this field. She was also an investigator and study co-chair of an international clinical trial investigating the efficacy of lovastatin as a treatment for learning and attention deficits in children with NF1.

Dr Ines Violante

Ines Violante is a Sir Henry Wellcome Fellow at Imperial College London, investigating the use of brain stimulation to target the function of large-scale networks that sustain cognitive functions. She obtained her PhD in Biomedical Sciences from the University of Coimbra, Portugal, where she focused on the neurobiological basis of the cognitive deficits in Neurofibromatosis type 1 (NF1). Her research is interdisciplinary and translational, applying neuroimaging and neurophysiological techniques to translate the inhibitory hypothesis in NF1 from the animal model to the human disorder. She has applied

spectroscopy, molecular imaging and magnetic resonance imaging to provide a comprehensive understanding of the pathophysiological alterations present in NF1. These methods are now being applied to Autism Spectrum Disorders.

Professor Therese van Amelsvoort

Professor van Amelsvoort is professor of Transitional Psychiatry and consultant Psychiatrist at Maastricht UMC. She has had a longstanding interest in neurobiological mechanisms underlying psychosis and neurodevelopmental disorders, with a special interest in 22q11.2 deletion syndrome (22q11DS) which she has been studying since 1997. She obtained her PhD on brain structure and function in velo-cardio-facial syndrome (22q11DS) with and without psychosis in 2004 at the University of Amsterdam. Since 2012 she is working at Maastricht University where she is currently heading The Department of Psychiatry and

Psychology in the European Graduate School of Neuroscience at Maastricht University. The group has specific expertise in momentary assessment technology and gene-environment interactions including epigenetics. Professor van Amelsvoort has been head of the Dutch Adult 22q11DS clinic for several years. The current clinic at Maastricht University Medical Centre is registered with Orphanet, and has a multidisciplinary approach. International collaborations within the field of 22q11DS have been very successful for over 15 years.







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Professor Patricia Howlin

Patricia Howlin is Emeritus Professor of Clinical Child Psychology at the Institute of Psychiatry, King's College London and Professor of Developmental Disability at the University of Sydney. Her principal research interests focus on the long-term prognosis for individuals with autism spectrum and other developmental disorders and on developing intervention programmes that may help to improve outcome. Professor Howlin is a Fellow of the British Psychological Society, and has served as Chair of the UK Association of Child Psychology and Psychiatry and the Society for the Study of Behavioural Phenotypes.



She is a founding editor of the journal Autism. Recent awards include the INSAR Life-time Achievement Award and the Kanner -Asperger medal from the German, Austrian, Swiss Society for Research in Autism Spectrum Conditions.

Conference Programme

Venue: Hortus Botanicus Leiden – Oranjerie

Educational Day

Day One: Thursday 14 th September 2017		
08:00 - 09:00	Registration and coffee	
09:00 – 09:15	Welcome from the SSBP and the Conference Organisers Stephan Huijbregts and Anna Jansen	
Thursday Sess	sion 1: (Chair: Prof. Patricia Howlin)	
09:15 – 10:00	Keynote 1: <i>Dr. Honey Heussler</i> – Sleep Disorders in Individuals with Neurodevelopmental Disorders (Part 1)	
10:00 - 10:45	Keynote 2: <i>Dr. Luci Wiggs</i> – Sleep Disorders in Individuals with Neurodevelopmental Disorders (Part 2)	
10:45 - 11:00	Questions and Discussion	
11:00 - 11:30	Morning refreshments	
Thursday Sess	sion 2: 4 Free Communications (15 min + 5 min Q&A) (Chair: Prof. Stewart Enfield)	
	Talk 1: <i>K. Woodcock</i> – Intervening with behavioural phenotypes piece by piece: a focus on temper outbursts triggered by change	
	Talk 2: J. Waite – The phenomenology of temper outbursts in intellectual disabilities	
11:30 – 12:50	Talk 3: <i>J. Wolstencroft</i> – Turner syndrome: mental health and social skills from childhood to adolescence	
	Talk 4: A. Rietman – Worries and needs of patients with NF1 or TSC and their parents, from transition to adulthood	
12:50 - 14:00	Lunch	
Thursday Sess	sion 3: (Chair: <i>Dr. Jane Waite</i>)	
14:00 - 14:40	Keynote 3: <i>Dr. Mark Andermann –</i> Tracking Hunger-Dependent Food-Cue Biases from Hypothalamus to Cortex	
14:40 - 15:20	Keynote 4: <i>Dr. Marianne Nordstrøm</i> – Diet, Obesity and Atherosclerotic Cardiovascular Risk in Williams Syndrome, Down Syndrome and Prader-Willi Syndrome	
15:20 – 15:30	Questions and Discussion	
15:30 - 16:00	Afternoon refreshments	
Thursday Session 4: (Chair: André Rietman, MSc.)		
16:00 - 16:35	Keynote 5: <i>Dr. Agnies van Eeghen</i> – Growing Up with Genetic Neurodevelopmental Disorders; Management of Problems in the Transitional Age	
16:35 – 17:10	Keynote 6: <i>Dr. Andrea Pilotto</i> – Ageing brain, movement disorders and dementia: what is the link with monogenic diseases?	
17:10 - 17:20	Questions and Discussion	
17:30 - 19:00	Conference Reception – Leiden City Hall	

Research Symposium

(Venue – Theaterzaal at Scheltema, Leiden)

Day Two: Friday 15 th September 2017		
00.00 00.00	Registration and coffee	
08:00 - 09:00	Poster set-up	
09:00 - 09:05	Welcome	
Session I: (Chai	ir: Prof. Petrus de Vries)	
09:05 – 09:45	Keynote 7: Professor Raoul Hennekam – 30 years of research into behavioural phenotypes	
09:45 – 10:30	Keynote 8: <i>Dr. Anthony Isles</i> – Investigating the Contribution of Imprinted Genes to Neurodevelopmental Disorders	
10:30 - 11:25	3 Free Communications (12min + 3min Q&A)	
	Talk 5: M. Erwood – Intellectual disability and copy number variants: mental health in the IMAGINE ID cohort	
	Talk 6: <i>F. Erhardt</i> – Integration of omics data and database knowledge reveals downstream pathways of MECP2 in Rett syndrome	
	Talk 7: J. Fitzgerald – Clinical characterisation of neurexin1 deletions and their role in neurodevelopmental disorders	
11:25 – 11:55	Morning refreshments and Poster Viewing	
Session 2: (Cha	ir: Anna Jansen)	
11:55 – 12:25	Keynote 9: Professor Kathrin Thedieck – Possible novel strategies in the treatment of TSC.	
12:25 – 13:10	3 Free Communications (12min + 3min Q&A)	
	Talk 8: <i>P. de Vries</i> – Tuberous Sclerosis complex-associated neuropsychiatric disorders (TAND): further results from the TOSCA natural history study	
	Talk 9: <i>A. Jansen</i> – Quality of life and burden of disease in Tuberous Sclerosis Complex (TSC): findings from TOSCA research project	
	Talk 10: <i>L. Leclezio</i> – Multivariate data analysis identifies natural clusters of Tuberous Sclerosis Complex associated neuropsychiatric disorders (TAND)	
13:10 - 14:15	Lunch and Poster Session	
Session 3: (Chair: Dr. Stephan Huijbregts)		
14:15 – 14:55	Keynote 10: Professor Francjan van Spronsen – Optimizing Treatment and Monitoring of Phenylketonuria (PKU) Based on 30 Years of Research into Behavioural Phenotypes	
14:55 – 15:25	2 Free Communications (12min + 3min Q&A)	
	Talk 11: <i>R. Jahja</i> – Long-term follow-up of cognition and mental health in adult phenylketonuria: a PKU-cobeso study	
	Talk 12: <i>K. Van Vliet</i> – Mental health and quality of life and their relation to metabolic control in NTBC treated Tyrosinemia type 1 patients	

Day Two: Friday 15 th September 2017		
15:30 - 16:00	Afternoon Refreshments and Poster Viewing	
Session 4: (Chair: Prof. Francjan van Spronsen)		
16:00 – 16:40	Keynote 11: <i>Dr. Manuel Schiff</i> – An Expanding Genetic Spectrum Causing Hyperphenylalaninemia and Central Monoamine Neurotransmitter Deficiency	
16:40 – 17:20	Keynote 12: <i>Dr. Robin Lachmann</i> – Behavioural Phenotypes in Adults with Inherited Metabolic Disease	
17:20 – 18:00	Tom Oppé Distinguished Lecture: <i>Professor James Harris</i> – Transgenic non-human primate research: prospects and ethical issues	
19:30 – 23:00	Gala Dinner Venue: Temple Hall at the Rijksmuseum voor Oudheden, Leiden	

Research Symposium

(Venue - Scheltema, Leiden)

Day Three: Saturday 16 th September 2017	
08:30 - 09:00	Registration and coffee
Session 5: (Cha	air: Dr. Stephan Huijbregts)
09:00 – 09:40	Keynote 13: Dr. Belinda Barton – Interventions for Cognitive Impairment in Children with Neurofibromatosis Type 1 (NF1): What Works and Future Directions
09:40 – 10:20	Keynote 14: <i>Dr. Ines Violante</i> – The GABA Hypothesis in NF1: From Animal Models to the Human Disease
10:20 – 10:35	Free Communication (12min + 3min Q&A)
	Talk 13: <i>E. Plasschaert</i> – Disease burden and symptom structure of autism in Neurofibromatosis Type 1 - a study of the international NF1-ASD consortium team (INFACT)
Session 6: (Cha	air: Dr. Flora Tassone)
10:20 – 10:35	4 Free Communications (12min + 3min Q&A)
	Talk 14: <i>K. Vermeulen</i> – Adaptive and maladaptive functioning in Kleefstra syndrome compared to other rare genetic disorders with intellectual disabilities
	Talk 15: <i>F. Tassone</i> – Identification of molecular biomarkers predictive of response to targeted treatment in Fragile X Syndrome and Autism Spectrum Disorder
	Talk 16: <i>H. Crawford</i> – Differential effects of anxiety and autism on social scene scanning in males with Fragile X syndrome
	Talk 17: R. Hagerman – Metformin is a new targeted treatment for individuals with FXS
11.40 - 11.45	Questions and Discussion
11:45 – 12:10	Morning Refreshments
Session 7: (Chair: Prof. Hanna Swaab)	
10:20 – 10:35	3 Free Communications (12min + 3min Q&A)
	Talk 18: <i>N. Tartaglia</i> – Using pharmacogenomics in clinical treatment of children with Fragile X syndrome and Sex Chromosome Aneuploidy
	Talk19: <i>S. Van Rijn</i> – Socio-emotional functioning of children and adults with 47,XXY: A focus on underlying mechanisms
	Talk 20: C. Samango-Sprouse – Early childhood development of rare X and Y chromosomal disorders (XYD) 49,XXXXY and 49,XXXYY
12:55 – 13:00	Questions and Discussion
13:00 - 14:15	Lunch and Poster Session

Day Three: Saturday 16th September 2017 14:15 - 14:45 SSBP AGM and Award Ceremony Session 8: (Chair: Dr. Erik Boot) 14:45 - 15:25 Keynote 15: Professor Therese van Amelsvoort – Stress Reactivity, Cortisol Levels and Experience Sampling in Adults with 22q11DS 15:25 - 16:10 3 Free Communications (10mins + 2min Q&A) Talk 21: D. McDonald-McGinn – Maternal origin of familial 22q11.2 deletions negatively impacts FSIQ scores Talk 22: A. Swillen – High prevalence of fatigue in individuals with 22q11.2 deletion syndrome: an update Talk 23: E. Van den Heuvel – Developmental trajectories of socio-communicative abilities in children with 22q11.2 deletion syndrome **Questions and Discussion** 16:10 - 16:15 16:15 - 17:00 Keynote 16: Professor Patricia Howlin – SSBP into the future **Farewell and Coffee** 17:00

Abstracts for Educational day:

(in order of presentation)

KEYNOTE 1 & 2: Sleep Disorders in Individuals with Neurodevelopmental Disorders.

Helen Heussler^{1,2} and Luci Wiggs³

¹Department of Respiratory and Sleep medicine, Children's Health Queensland. ²Mater Research Institute, University of Queensland. ³Department of Psychology, Oxford Brookes University, Oxford, UK

High rates of sleep disturbance have been consistently reported in individuals with neurodevelopmental disorders. Increased vulnerability is likely due to a range of physiological, genetic and psychosocial risk factors, the relative importance of which might differ due to multiple factors including the individual's clinical condition. The presence of sleep disturbance has been associated with daytime cognitive-behavioural dysfunction and the stressful effect of sleep disturbance on other members of the family should not be underestimated. Resolution of sleep disturbance is often followed by an amelioration of these individual and family difficulties, emphasising the importance of addressing sleep disturbance as part of overall care.

This session will a) provide an orienting overview of normal sleep, common ways in which it can be disturbed and the impact of impaired sleep on the child and family and b) emphasise approaches to the assessment and management of sleep difficulties, including physiological and psychological assessment and contemporary pharmacological and non-pharmacological management. Attention will be drawn to where an understanding of individual behavioural phenotypes could play a role in the recognition, assessment and management of sleep difficulties.

Although not without limitations, existing research suggests that there is a range of therapeutic options for the management of sleep difficulties, choice of which should be driven by careful assessment of sleep with a view to diagnosing the underlying sleep disorder. Whilst the general approach to sleep disorders may be similar for children with and without neurodevelopmental disorders special considerations need to be emphasised for the latter group, including the individual's behavioural phenotype. Examples of how sleep medicine can be tailored will be provided, along with discussion of how best to further refine such an approach to optimise outcomes for children and their families.

Keywords: sleep, children, assessment, management, phenotype, syndrome

TALK 1: Intervening with Behavioural Phenotypes Piece by Piece: A Focus on Temper Outbursts Triggered by Change

Woodcock K.A.¹, Bull L.E.², Dounavi K.³, Fitzpatrick A.¹, Mcgeady C.¹, Preston G.¹ and Robb N.^{1,4}

¹School of Psychology, Queen's University Belfast. ²The Meadow Centre, Solihull, Birmingham. ³School of Social Sciences, Education and Social Work, Queens University Belfast. ⁴SMARTIab, University College Dublin.

Background: Resistance to change is comprised in the behavioural phenotypes of Prader-Willi (PWS) fragile X (FXS) and autism spectrum disorder (ASD), and often precipitates temper outbursts. Pilot work shows that signalling changes using a distinctive cue card to individuals with PWS can reduce the disruptive behavioural response following specific changes. Here, change signalling or visual scheduling to avoid change were implemented by caregivers following web-based training, and compared in a randomised controlled trial. Methods: The caregivers of 122 children (8 – 16 years) with a range of neurodevelopmental disorders, recruited via support groups and research databases, expressed an interest in participating. Of these, 60 were willing and eligible to participate based on their child evidencing temper outbursts following changes. Blended face-to-face and remote focus groups of parents and professionals, allowed the collaborative design of a web-based temper outburst diary; and caregiver training on the two intervention strategies. Semi-structured interview and/or questionnaire measures assessed temper outbursts and cost to services before baseline; following a 6M baseline; and 6M following training being made available. The diary was available throughout; and included intervention process information. Following baseline, 36 families were allocated to change signalling or planning ahead using randomised minimisation (balancing frequency of temper outbursts, diary usage, adaptive behaviour and diagnosis). At the end of the study, semi-structured interviews were conducted with all available caregivers on intervention process.

Results: Engagement with training resources, perceived success in applying the allocated strategy and changes in reported temper outbursts, varied extensively across caregivers. And individual variability was greater than group difference.

Conclusion: There is potential to intervene with specific aspects of behavioural phenotypes via careful measurement and targeting of individuals for whom that aspect is a particular problem. However, there is a need for an individualised approach to providing caregivers with the strategies most likely to be effective for their child.

Keywords: Behavioural flexibility; Temper outbursts; Intervention; Digital health; Prader-Willi syndrome; Autism spectrum disorder.

TALK 2: The Phenomenology of Temper Outbursts in Intellectual Disabilities

Cressey H.¹, Oliver C.¹, Tunnicliffe P.¹, Bull L.¹, Penhallow J.¹, Woodcock K.² and Waite J.¹

¹ University of Birmingham.

² Queen's University Belfast.

Background: Temper outbursts are recognised as a common form of challenging behaviour, with deleterious effects on people with intellectual disabilities and their carers. However, very few studies have examined this phenomenon in detail. Previous studies indicate high levels of challenging behaviour in Lowe syndrome, with temper outbursts identified as a difficulty. This study provides a detailed description of the behavioural sequence, antecedents and consequences of temper outbursts in Lowe syndrome in comparison to Prader-Willi syndrome, with a view to furthering the understanding of the phenomenology and aetiology of temper outbursts across syndromes.

Methods: Semi-structured interviews were conducted with primary caregivers of nine adults (18 years or over) and eight children (<18 years) diagnosed with Lowe syndrome. The study replicated earlier work on temper outbursts in Prader-Willi syndrome, and comparisons are made with the results of that study.

Results: Frequent temper outbursts in Lowe syndrome were associated with higher levels of physical aggression than reported in Prader-Willi syndrome (Fisher's exact, p = .010). Similarities were found in the pattern of behaviours in across syndromes, such as the proportion of outbursts occasioned by a change in routine. Interruption to a preferred activity and being asked to do something the person did not want to do were significantly more likely to be antecedents of temper outbursts in the Lowe syndrome group in comparison to the Prader-Willi syndrome group (X2 = 7.04; p = .008; X2 = 7.24, p = .007).

Conclusion: This study provides an important foundation for further research into the aetiology of temper outbursts across syndrome groups. Recent studies in Prader-Willi syndrome have found links between outbursts and cognitive task switching difficulties. It is possible that executive function difficulties could be implicated in Lowe syndrome.

Keywords: Lowe syndrome, temper outbursts, function, aggression, property destruction.

TALK 3: Turner Syndrome: Mental Health and Social Skills from Childhood to Adolescence

Wolstencroft J., Srinivasan R., Mandy W., Imagine I.D. and Skuse D.

Great Ormond Street Institute of Child Health, University College London, UK.

Background: Turner Syndrome (XO; TS) is one of the most common sex chromosome aneuploidies, however research into the psychological wellbeing and social skills of girls with TS is scarce. This study aims to examine the mental health problems and social skills difficulties in girls with TS from childhood to adolescence.

Methods: The Development and Wellbeing Assessment (DAWBA; n=58), the Strengths and Difficulties Questionnaire (SDQ; n=58) and the Social Responsiveness Scale (SRS; n=31) were administered online to the caregivers of girls aged 4 – 20. All assessments are widely used and validated. Participants were recruited through the IMAGINE ID and SOAR research studies.

Results: SRS and SDQ scores showed that girls with TS experienced social difficulties. Mean total SRS scores were in the mildly impaired range (M=67.9, SD=8.8). The SDQ showed that peer problems were greatest in adolescence, despite improvements in prosocial behaviours. DAWBA analysis showed elevated rates of mental health disorder. Most notably 34% met criteria for at least one mental health diagnosis. 21% met criteria for autism spectrum disorders (ASD), 14% for oppositional defiant disorder, 13% for anxiety disorders and 10% for attention deficit hyperactivity disorders (ADHD). Except for ADHD and ASD, most mental health disorders were diagnosed in adolescence.

Conclusion: Girls with TS have higher rates of mental health and social skills difficulties than the general population. Their difficulties become more apparent in adolescence. Given the high rates of mental health disorder and social skills difficulties, more research is warranted. Understanding the patterns of improvement in prosocial behaviours and the increase in peer problems may provide insights for intervention. If increased attempts to engage in social interaction are associated with peer problems, social skills interventions may require careful planning in order to avoid peer rejection.

Keywords: XO, Turner Syndrome, sex chromosome aneuploidies, autism, social skills, mental health.

TALK 4: Worries and Needs of Patients with NF1 or TSC and Their Parents, from Transition to Adulthood

Rietman A.B.¹, Van Helden H.¹, Both P.H.¹, Ten Holt L.S.¹, Mous S.E.¹, Van Staa A.L.², Moll H.A.¹, De Wit M.C.Y.1, Taal W.¹ and Van Eeghen A.M.1³

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³ De Hartekamp Groep, Care and Service Center for People with Intellectual Disabilities, Haarlem, the Netherlands.

Background: Neurofibromatosis type 1 (NF1) and Tuberous Sclerosis Complex (TSC1 and TSC2) are genetic disorders associated with lifelong tumour growth propensity and neurocognitive impairments. Although follow-up of adults often focuses on somatic problems such as tumour growth and epilepsy management, follow-up of cognitive or social problems and other NF1-related comorbidity is often not a part of standardized care. **Methods**: In order to provide optimal care services for this patient group, we explored the care needs of adults with NF1 or TSC and their parents. A qualitative study was performed using semi-structured group interviews, exploring worries and care needs during and after the transition period in medical, psychological and socio-economic domains. Individual interviews and five focus groups were conducted, including young adult patients (17 – 30), patients over age 30, and parents of young adult patients. This patient-driven data were transcribed verbatim and analysed by computerized thematic analysis. Themes were organized using the WHO International Classification of Functioning, disability, and health (ICF).

Results: In total, 29 patients with NF1, 16 patients with TSC, and 25 parents participated. Results indicated many and diverse worries and care needs. Worries could be categorized into thirteen themes, organized into ICF domains: impairment of body functions and structures, activity limitations and participation restriction, and environmental factors. Parents reported high stress levels and difficulties with their parental role. Participants expressed the need for more information, access to NF1 or TSC experts, daily living support, care for mental health and socio-economic participation, and closer communication between healthcare providers.

Conclusion: In conclusion, worries and needs of patients and parents underline the importance of multidisciplinary follow-up and continuity of care during and after the transitional period. Recommendations were formulated to address somatic, neuropsychiatric, and socio-economic limitations. Additionally, parental stress requires more attention from care providers.

Keywords: Neurocognitive disorders; Neurofibromatosis 1 (NF1); Tuberous sclerosis complex (TSC); Qualitative research; Transition; ICF classification.

KEYNOTE 3: Tracking Hunger-Dependent Food-Cue Biases from Hypothalamus to Cortex

Mark L. Andermann

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Hunger selectively enhances attention to food-associated visual cues, which can lead to excessive eating and refractory obesity. Functional neuroimaging studies in humans have consistently demonstrated that temporal lobe cortical areas that are more strongly activated by food-associated cues than by other sensory stimuli during hunger, but not during satiety. By contrast, such effects are not evident in 'dorsal visual stream' cortical areas believed to be more involved in action guidance than object recognition. Imaging studies in obese individuals and in those with anorexia nervosa demonstrate dysfunction in these same neural circuits.

To understand the cellular mechanisms underlying these hunger-dependent biases, we recorded neural responses to food-associated and other visual cues in early and higher-order visual cortical neurons, and in amygdala feedback axons to cortex, using methods we've helped improve for two-photon calcium imaging in behaving mice. We found that, as in humans, mice exhibit hunger-dependent biases to food cues in temporal association cortex but not in primary visual cortex. Amygdalo-cortical feedback axons, which innervate temporal cortex but not primary visual cortex, showed an even stronger food-cue bias, highlighting a potential direct pathway by which the lateral amygdala may bias state-dependent cortical processing of motivationally-relevant sensory cues.

A key advantage of studying hunger in mice is that rapid optogenetic or pharmacogenetic activation of a few hundred hypothalamic agouti-related peptide (AgRP) neurons at the base of the brain has been shown to drive a fully sated mouse to forage for and consume large amounts of food. We are using this entry node in order to dissect out the neural pathways that link specific needs of the body (e.g. the need for food) to increased processing of specific, goal-relevant stimuli (e.g. of food cues during states of hunger) in insular cortex.

Keywords: Two-photon imaging, awake mouse, hunger, hypothalamus, cortex, dieting

KEYNOTE 4: Diet, Obesity and Atherosclerotic Cardiovascular Risk in Williams Syndrome, Down Syndrome and Prader-Willi Syndrome

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Background: Adult persons with intellectual disability experience reduced health and life expectancies compared to the general population. Increased risk of obesity and poor diets have been suggested to be contributing factors. We aimed to investigate dietary aspects with focus on intakes of fruit and vegetables, fish and omega-3 fatty acids (FA), degree of obesity and risk of atherosclerotic cardiovascular disease (CVD) in persons with Williams syndrome (WS) (n=21), Down syndrome (DS) (n=40) and Prader-Willi syndrome (PWS) (n=20). Methods: Diets were assessed by self-reported intake frequencies and measurement of plasma carotenoids and erythrocyte content of omega-3 FA. Established metabolic risk factors of CVD were also investigated. Results: Daily intakes of fruit was found in 15 % with WS, 33 % with DS and 70 % with PWS, whereas 20 %, 29 % and 85 % with WS, DS and PWS respectively, had daily intakes of vegetables. In DS, body mass index was negatively associated with plasma carotenoids. A larger proportion of participant with WS were low-frequency consumers of fish (p=0.005), were less likely to use omega-3 FA supplements (p=0.023), and had reduced erythrocyte concentrations of long-chain omega-3 FAs (p<0.001), compared to participants with PWS and DS. High prevalence of hypertension and type 2 diabetes was found among participants with PWS and WS, whereas low prevalence rates were found in the DS-group. WS was furthermore associated with a better blood cholesterol and lipoprotein profile. Abdominal obesity was prevalent in all three groups and was associated with an increased risk of CVD.

Conclusions: Differences in dietary intakes and CVD risk profile were found among the included genetic syndromes. WS had a less favorable dietary pattern. PWS and WS were found have increased risk of CVD, whereas DS was associated with reduced risk.

Keywords: Diet, obesity, cardiovascular disease, Williams syndrome, Down syndrome, Prader-Willi syndromeKeynote 5 - Growing Up with Genetic Neurodevelopmental Disorders; Management of Problems in the Transitional Age

KEYNOTE 5: Growing Up with Genetic Neurodevelopmental Disorders; Management of Problems in the Transitional Age

Agnies M. van Eeghen, MD, PhD.

Intellectual Disability physician, Erasmus Medical Center Rotterdam, the Netherlands; a.vaneeghen@erasmusmc.nl; 'De Hartekamp Groep', Haarlem, the Netherlands.

Young adulthood is a difficult phase for already vulnerable patients with genetic neurodevelopmental disorders. Young adults with learning disabilities often have poor access to health care, have limited disease knowledge, and are often lost to follow-up; this occurs more often in patients with mild intellectual disability (ID) and from a lower socio-economic background. Often appropriate care is not available for adults for comorbidity, and when expert care is in place, often the neuropsychiatric phenotype is not addressed.

Young adult patients with ID often experience severe psychosocial problems and lower quality of life. Limited social participation and inappropriate working and living environments often lead to low self-esteem and psychological or behavioral problems.

For some syndromes, somatic comorbidity exacerbates in young adulthood. Also other issues often arise in the transition age; family planning and regulation of menstruation; management of behavioral disorders in teens and young adults; financial problems; problems around substance abuse and sexual abuse; and questions around mental competence, autonomy and decision-making.

More data are needed on care needs of young adults and their parents, and these will also be addressed in more detail later in the conference. Management of medical and psychosocial issues in adolescence and young adulthood are discussed, and suggestions for appropriate transition of care will be formulated.

Keywords: transition, adult, adolescence, genetic syndrome, intellectual disability

KEYNOTE 6: Ageing Brain, Movement Disorders and Dementia: What is the Link With Monogenic Diseases?

Pilotto A.^{1,2}, Trefz F.³, Blau N.³, Zipser C.⁴, Charyasz E.⁵, Freisinger P.⁶, Gramer G.³, Kölker S.³, Haas D.³, Piel D.⁷, Burgard P.⁸, Nawroth P.⁸, Schaeffer E.¹, Liepelt-Scarfone I.¹, Schulte C.¹, Deuschl T.¹, Maetzler W. ^{1,9}, Scheffler K.⁵, Hoffmann G.F.³, Padovani A.² and Berg D.^{1,9}

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Ageing is an important risk factor for neurodegenerative diseases. The accumulation of specific proteins in different brain regions according to the specific disease explains the heterogeneity of symptoms, ranging from movement disorder, mild cognitive deficits up to severe dementia. Monogenic neurodegenerative disorders are quite common in different forms of parkinsonism and dementia and can benefit from new target therapies. Moreover, genetics plays an important role in phenotype and prognosis modulation.

Recently, several inherited childhood disorders - such as Gaucher, Nieman-Pick diseases and Phenylketonuria - have been linked to neurodegenerative diseases. Specifically, the presence of heterozygous mutations within the glucocerebrosidase gene is at the moment the most common monogenic form of both Parkinson's disease and dementia with Lewy bodies. Brain ageing may increase the risk for neurological decline also in classical metabolic disorder, such as phenylketonuria, given the co-presence of risk of phenylalanine aggregation, metabolic abnormalities, oxidative damage and biogenic amine depletion.
Abstracts for Research Symposium Oral Presentations (in order of presentation)

KEYNOTE 7: 30 Years of Research into Behavioural Phenotypes

Raoul C. Hennekam

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We are humans because we look physically like humans, but we are especially humans because we behave like humans. The study of our physical characteristics, in health and disease, has made an enormous progress in the last decades. Main reasons have been better classifications of traits and disorders, increased potential of molecular genetics, and more sophisticated functional studies. The study of our behaviour has offered us good insight as well but has not been as successful. There is a series of causes for this but the main reason is the complexity of behaviour, and, with this, the difficulty to apply adequate classifications: if the behaviour of a group is studied but it is uncertain whether this behaviour is indeed the same in the study participants, results are difficult to explain, and molecular and functional studies are less likely to be successful.

Gradually three ways have been developed to overcome this problem. One is being sure that one studies the same, or at least related, behaviour because study participants show other, more easily recognizable signs or symptoms. The studies of behaviour in syndromes has shown the power of this. Second is the study of extreme phenotypes: behaviour that is that exceptional that likely individuals demonstrating the behaviour have the same trait. The third option is reverse genetics: searching for variants in the same genes in a group of individuals irrespective of their behaviour, and subsequently dissect the behaviour of those that share these variants. It may be this will cause long existing classifications to be markedly changed.

Research in the last three decades have offered us more insight. One does not need to have supernatural gifts to predict that research in the coming three decades will yield a multifold of this. It will be exciting times for behavioural studies

Keywords: behaviour; classifications; extreme phenotypes; molecular genetics; reverse genetics

KEYNOTE 8: Investigating the Contribution of Imprinted Genes to Neurodevelopmental Disorders

Anthony R. Isles

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Imprinted genes are a group of mammalian genes subject to epigenetic control ("genomic imprinting") resulting in expression from one parental copy only. This unusual and robust epigenetic regulation means that any deviation in expression, up or down, can result in abnormalities. Aberrant imprinted gene expression has been identified as directly causal of a number of disorders, including the neurodevelopmental disorder Prader-Willi syndrome (PWS).

PWS is caused by loss of paternal gene expression from the 15q11-q13 interval, which contains several imprinted genes expressed solely from the paternal chromosome, and two expressed from the maternal chromosome only. A number of different mutations at 15q can lead to the core PWS phenotype, but some are particularly associated with the development of psychotic illness. Here I will give an overview of our work exploring the behaviour of a mouse model for PWS, with particular focus on endophenotypes of relevance to psychotic illness. We have also used human genetic studies to examine the contribution of paternally and maternally expressed imprinted genes at 15q11-q13 to developmental delay and psychotic illness more generally. Taken together, these findings from our group and others suggest that over-expression of maternal genes in the 15q11-q13 are the primary cause of psychotic illness.

Finally, I will introduce a new area of research, investigating the brain role of the gene *EHMT1*. *EHMT1* is associated with Kleefstra syndrome, autism and developmental delay. Whilst it is not imprinted itself, I suggest that mutations affecting *EHMT1*, which encodes a protein important for regulating at least two discrete aspects of epigenetic marking, leads to abnormalities in genomic imprinting generally. This may contribute to the disorders with which *EHMT1* is associated.

Overall, I hope to convince you that imprinted genes, although only small in number, play a critical role in brain function and, consequently, neurodevelopmental disorders.

Keywords: Prader-Willi syndrome; mouse models; 15q11-q13; CNVs; EHMT1

TALK 6: Intellectual Disability and Copy Number Variants: Mental Health in the IMAGINE ID Cohort

Erwood M.^{1,4,5}, Wicks F.², Wolstencroft J.¹, Srinivasan R.¹, Hall J.³, Van Den Bree M.³, Denaxas S.^{4,5}, Skuse D.¹, Imagine I.D.^{1,2,3} and Raymond F.L.¹

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Background: Increasingly, rare alterations in the genetic code can be found in individuals who have intellectual disability (ID). These alterations range from large copy number variants (CNV) of groups of genes to alterations in single genes. The association of genetic variants with psychiatric morbidity is still poorly understood. IMAGINE ID is a national study of behavioural problems and psychiatric risk in children with ID of known genetic origin. No previous study has systematically evaluated the behaviour of children with ID of genetic aetiology.

Methods: 902 children and young people were recruited via UK Genetic Services and patient support groups. Caregivers completed the Development and Wellbeing Assessment (DAWBA). It assesses psychiatric symptomatology and provides DSM-5 classifications based on clinical ratings.

Results: A higher rate of children met criteria for mental health diagnoses in the IMAGINE ID sample (48%) compared to national surveys of children both with and without ID (ID 39%; Non-ID 8.1%). The cohort is 57% male and the mean age is 6.3 years. The mean age of genetic diagnosis after 2010 was 2.9 compared to 9.6 for those diagnosed pre-2007. 39% of the cohort have CNVs associated with known neurosusceptibility loci. 19% of participants had more than one CNV. Where CNV inheritance is known, 49.1% were de novo, 32.5% were maternally inherited and 18.4% were paternally inherited.

Conclusion: Children with ID of genetic origin have higher rates of mental health and behavioural difficulties than both the general population and children with ID of unknown genetic cause. This suggests that CNVs may confer additional psychiatric risk. Identification and early intervention and support for children and families with ID may improve their long-term mental health outcomes. Further work on the IMAGINE ID cohort will be important in delineating the behavioural phenotypes associated with specific CNVs and single gene disorders.

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

TALK 7: Integration of Omics Data and Database Knowledge Reveals Downstream Pathways of MECP2 in Rett Syndrome

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² Department of Bioinformatics, Maastricht University, the Netherlands.

Background: RRett syndrome is a severe neurological disorder caused by mutations in MECP2. This gene is responsible for many molecular events and its downstream pathways which lead to the disorder phenotype are not yet fully understood. Transcriptomics studies allow investigation of all currently available transcripts in a cell or tissue sample. Using bioinformatics methods it is possible to gain hypothesis-free information about genes, pathways and processes which are differently active in the disorder. A single analysis delivers a single snapshot of the current processes and is always influenced by different genetic background of the donor, experimental design, time of the day etc. Integration of a number of these studies allows getting more reliable information about involved genes and affected pathways.

Methods: We used raw data from five previously published studies (GEO: E-GEOD-21037/E-MEXP-1956/E-GEOD-6955/E-GEOD-4600/E-GEOD-50584) which are online available and provided sample data from Rett syndrome patients or cell cultures and matching controls. Using standardized quality control, normalization and statistical methods we extracted gene expression profiles for each of the samples and compared the affected biological pathways.

Results: Integrating the information of five different studies we extracted a list of genes which are found to be differentially expressed and not mentioned before in the context of Rett syndrome. Most of these genes belong to molecular pathways or biological functions which are known to be affected in Rett syndrome. Investigating their known transcription factors we found a possible connection between MECP2, MEF2C and CAPG which may explain the effect of MECP2 disruption on the cytoskeleton. Effects in fibroblasts and neuronal related cells were different which suggests further study of at the non-neuronal tissue effects of MECP2.

Conclusion: Pathway analysis of transcriptomics datasets combined with transcription factor evaluation revealed regulations related to MECP₂, MEF₂G and CAPG not previously known to be involved in Rett syndrome.

Keywords: Rett syndrome, pathway analysis, network analysis, transcriptomics, integrated study.

TALK 7: Clinical Characterisation of Neurexin1 Deletions and Their Role in Neurodevelopmental Disorders

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Background: The Neurexin1 (NRXN1; 2p16.3) gene has been identified as a rare but significant genetic risk factor for neurodevelopmental disorders including autism spectrum disorder (ASD) schizophrenia, intellectual disability (ID) and bipolar disorder. NRXN1 encodes Neurexins, neuronal adhesion molecules on axon terminals, which bind postsynaptic Neuroligins (encoded by NLGN). The primary function of NRXN1 is to stabilise synapse formation and facilitate neuronal transmission. Common clinical features are associated with NRXN1 deletions but these have not been deconstructed using in-depth neuropsychological, neurocognitive and neuroimaging techniques. Methods: 21 participants with NRXN1 deletions and 21 age and gender matched controls were recruited. Semistructured neuropsychological assessments (CAPA, PAS-ADD) were performed and questionnaires to probe for existing and/or sub-threshold psychiatric disorders or symptoms were collated. The Wechsler Abbreviated Scale of Intelligence-second edition (WASI-II) and a comprehensive cognition battery (CANTAB), which included tests of reaction time, attention, executive functioning, working memory, cognitive flexibility and social cognition was administered to all participants to assess neurocognitive functioning. Independent t-tests were performed to compare cognitive performance variables between groups. High angular resolution diffusion imaging (HARDI) data were acquired (n=17 per group) to evaluate neuroanatomical differences. Preprocessing was completed using ExploreDTI software. Data quality checks were performed and subject motion and eddy current induced geometric distortions were corrected for in one interpolation step to minimise blurring effects. Fractional anisotropy (FA) values were extracted and voxelwise statistical analysis of the FA data was carried out using Tract-Based Spatial Statistics (TBSS) in FSL.

Results: The groups did not differ in age (t(40)=-0.015, p=0.988) but there was a significant difference in IQ (t(40)=-6.3, p=0.00) thus IQ was included as a covariate in all statistical analyses. Neuropsychological assessments indicated that 6 individuals have met criteria for ASD, 3 for mild ID, 2 for ADHD, 1 for a psychotic disorder and 1 for a conduct disorder. Neurocognitive assessments indicate a trend towards executive dysfunction and aberrant social cognition in individuals with NRXN1 deletions characterised by greater number of errors on spatial working memory, spatial organisation and emotion recognition tasks, p<0.1. TBSS analyses demonstrated reduced FA in the left body of the corpus callosum, left superior longitudinal fasciculus and the left inferior longitudinal fasciculus in the NRXN group relative to controls, p < 0.05, corrected for multiple comparisons.

Conclusions: Interesting clinical characteristics of NRXN1 deletions are emerging. This study indicates that NRXN1 deletions may contribute to neurocognitive deficits related to executive functioning and social cognition, two domains that are consistently described as aberrant in neurodevelopmental disorders. Furthermore, individuals with NRXN1 deletions demonstrate a pattern of disrupted structural connectivity, which has also been described in neurodevelopmental disorders such as ASD and schizophrenia. Further clinical and neurobiological phenotyping in addition to mapping of the NRXN1 genotype may elucidate the underlying neurobiological processes contributing to neurodevelopmental disorders.

Keywords: neurexin, neurodevelopmental disorders, cognition, brain, MRI, white matter.

KEYNOTE 9: Exploring new avenues for TSC treatment

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Mammalian target of rapamycin (mTOR) is a prime drug target in tuberous sclerosis complex (TSC) disease. The kinase mTOR is embedded in a highly dynamic signaling network that exhibits complex crosstalk with other metabolic and signaling pathways, such as TGFbeta and stress signaling or glucose metabolism. The complex wiring of this network, often differing in individual patients, renders the prediction of drug responses and rational therapy design challenging. Computational models, simulating and predicting the response of mTOR and its ancillary networks to drug treatments, can help to unravel this complexity. This approach has proven successful for the discovery of new signaling connectivities in the mTOR network, and we now embark to apply our computational models to predict drug responses. This talk will explore the potential of targeting mTOR's ancillary networks in TSC, and will present concepts of computational model-driven drug response prediction.

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TALK 8: Tuberous Sclerosis Complex-Associated Neuropsychiatric Disorders (TAND): Further Results from the TOSCA Natural History Study

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Background: TOSCA is an ongoing international natural history study of Tuberous Sclerosis Complex (TSC). We previously reported baseline data on TSC-Associated Neuropsychiatric Disorders (TAND). Here is explored baseline data in more detail to compare childhood and adult patterns, age bands of TAND, and genotype-TAND correlations.

Methods: Data from the fourth interim analysis of TOSCA were used. TAND data were extracted to generate frequency tables for children and adults, for a range of age bands, and for those with TSC1 versus TSC2 mutations. Results: Data were available for 2216 patients across 170 sites in 31 countries. Behavioural problems, reported in >10% of participants, included overactivity, sleep difficulties, impulsivity, anxiety, mood swings, severe aggression, depressed mood, self-injury, and obsessions. Psychiatric disorders included autism spectrum disorder (21.6%), attention deficit hyperactivity disorder (19.2%), anxiety disorder (9.9%), and depressive disorder (6.2%). An intelligence quotient (IQ) score was available for 894(40.3%) participants. Of these, 398 participants (44.5%) had normal IQ, while mild, moderate, severe, and profound intellectual disability (ID) was observed in 28%, 15.2%, 9.2%, and 3.1%, respectively. Academic/scholastic difficulties were identified in 59.1% of 1245 participants assessed. Neuropsychological deficits (performance <5th percentile) were reported in 331 (56.2%) of 589 participants evaluated for neuropsychological skills. The rates of ID were similar between children and adults. However, there was a pattern of higher rate of overactivity and impulsivity in children, and higher rates of anxiety and depressed mood in adults. The genotype-intellectual phenotype pattern showed a greater likelihood of ID in individuals with TSC2 than those with TSC1 mutations, and identified some potential additional genotype-TAND correlations. **Conclusion**: Results from this interim analysis confirmed the high rates of TAND, replicated some age-based findings and suggested some new directions for future exploration. We hope that further results from the ongoing TOSCA registry may improve assessment and treatment of TAND.

Keywords: Tuberous sclerosis complex, TuberOus SClerosis registry to increase disease Awareness (TOSCA), Tuberous sclerosis complex (TSC) -associated neuropsychiatric disorder (TAND).

TALK 9: Quality of Life and Burden of Disease in Tuberous Sclerosis Complex (TSC): Findings From TOSCA Research Project

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Background: This study aimed to assess the impact of TSC on the lives of patients/caregivers in terms of quality of life (QoL) and burden of illness (BOI).

Methods: Patients meeting eligibility criteria for TOSCA registry were enrolled after receiving informed consent. Enrolled patients/caregivers completed validated QoL questionnaires and disease-specific questions on BOI. Results: 111 patients (45 adults) from 6 European countries were enrolled. Of these, 54 (48.6%; 27 adults) had epilepsy. The median duration of TSC was 11.3 years (1.6 – 41). Career/education had been adversely impacted by TSC in 55.6% of adults, 50% of primary caregivers of children, and 26.7% of other family members of children. Interpersonal relationships within or outside the family were adversely affected in 55.6% of adults and 42.4% of children. Educational needs were adequately met in only 39.4% of children. 28.8% of children needed extra assistance at home. 42.2% of adults and 25.8% of children had no health insurance. Where social services were provided (<23%), 40% of adults and 62.1% of parents felt inadequately supported. 77.8% of adults and 54.5% of children were managed by a TSC specialist. 31% of patients had access to adult care, with smooth transition in 47%. 40.5% of patients did not have any TSC-related visits in the past year. Only 40% of adults and 47% of children's families were in contact with a TSC association. Significant pain/discomfort was self-reported in 40% of adults, in 70% of adults reported by caregivers, and in 37.9% of children; anxiety/depression was reported in 48.6%, 60% and 40.9%, respectively. Genetic testing was performed in 82.9% of patients, but counselling was lacking in 21.6%.

Conclusion: These results indicate that TSC has substantial impacts on patients and their families' health and social wellbeing. We propose that these could be markedly ameliorated through improvements in educational, social and medical support.

Keywords: Tuberous sclerosis complex, Quality of life, Burden of illness, TuberOus SClerosis registry to increase disease Awareness (TOSCA).

TALK 10: Multivariate Data Analysis Identifies Natural Clusters of Tuberous Sclerosis Complex Associated Neuropsychiatric Disorders (TAND

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Background: Tuberous Sclerosis Complex (TSC) is a multi-system, genetic disorder with birth incidence estimated to be 1 in 5800 newborn babies. TSC is associated with a wide range of neurodevelopmental, psychiatric, learning and behavioural difficulties referred to as TAND. The lifetime prevalence of TAND is in the region of 90%. Each individual appears to present with their very own unique TAND profile, posing significant challenges for psycho-education and intervention planning. The identification of natural TAND clusters will significantly improve our ability to detect and treat TAND. A recent pilot study showed that multivariate data analyses techniques may be able to identify clinically-meaningful natural TAND clusters. In this study our aim was to confirm and expand these findings in a larger dataset.

Methods: TAND Checklist data were collected at 6 international sites from 453 individuals with a confirmed clinical diagnosis of TSC. Using R, the open-source statistical platform, various cluster analyses and exploratory factory analysis (EFA) were examined.

Results: WARD's cluster analysis method rendered seven natural TAND clusters with good clinical face validity. This data-driven strategy identified a 'Scholastic' cluster of TAND manifestations, a 'Neuropsychological' cluster, a 'Mood/Anxiety' cluster, an 'ASD-like' cluster, a 'Behaviours that Challenge' cluster, a 'Hyperactive/Impulsive' cluster, and an 'Eating/Sleeping' cluster. Results showed significant convergence with an exploratory factor analysis solution.

Conclusion: This study applied an innovative data-driven approach and identified seven natural TAND clusters from within highly variable TAND Checklist data. The larger-scale study findings were consistent with findings from the pilot study, supporting the vigor of these naturally occurring clusters. These natural TAND clusters identified can be used to develop novel approaches to identification and treatment of TAND.

Keywords: Tuberous Sclerosis Complex, TAND, natural TAND clusters, Neuropsychiatric, ASD, Cluster analysis, Factor analysis.

KEYNOTE 10: Optimizing Treatment and Monitoring of Phenylketonuria (PKU) Based on 30 Years of Research into Behavioural Phenotypes

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Background: Phenylketonuria is an inborn error of metabolism. Left untreated, PKU leads to severe intellectual disability, epilepsy and behavioural issues. PKU can be discovered with newborn screening. With early and continuous dietary treatment and monitoring, intellectual disability is prevented and patients can lead relatively normal lives.

Methods: As PKU is characterized by abnormal functioning of the Phenylalanine Hydroxylase (PAH)-gene, leading to high blood and brain phenylalanine (Phe-) levels, blood Phe-levels have most frequently been used as biomarker in PKU-research. Neural correlates of behavioural phenotypes have been established using techniques such as Magnetic Resonance Spectroscopy (MRS), Positron Emission Tomography (PET), electroencephalography (EEG), and Magnetic Resonance Imaging (MRI). Outcome measures included neurocognitive functioning, sleep problems, eating disorders, psychosocial functioning and Quality of Life, with a focus on the transition between childhood and adolescence/early adulthood.

Results: Although the majority of early-treated PKU-patients fall within the normal range for intellectual/ cognitive functioning, mental health, and Quality of Life, many studies have shown Phe-related difficulties in these domains. Treatment and monitoring has therefore mainly been aimed at keeping Phe-levels within safe margins. Treatment forms include a Phe-restricted diet, supplementation of PAH-chaperone tetrahydrobiopterin (BH4), and enzyme replacement therapy using phenylalanine ammonia lyase (PAL), all of which reduce Phe-levels in (subgroups of) PKU-patients. Apart from that, Large Neutral Amino Acid (LNAA-) supplements and BH4 have been suggested to improve brain function without decreasing the blood Phe level.

Conclusion: Although treatment of PKU is considered a major success story, further optimization is required. All forms of treatment pose a significant burden for the patients. Therefore, the necessity for continued treatment after adolescence needs to be further established, groups of patients needing less strict treatment need to be identified, and different types of medication may have to be introduced.

TALK 11: Long-Term Follow-Up of Cognition and Mental Health in Adult Phenylketonuria: A PKU-CoBeSo Study

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Background: Cognitive and mental health problems in individuals with the inherited metabolic disorder phenylketonuria (PKU) have often been associated with metabolic control and its history. These issues were examined in adult PKU patients, as outcomes and long-term effects in adulthood have not been investigated extensively.

Methods: For the present study executive functioning (EF) was assessed in 21 PKU patients during childhood (i.e. T1, mean age 10.4 years, SD=2.0) and again in adulthood (T2, mean age 25.8 years, SD=2.3). At T2 additional assessments of EF in daily life and mental health were performed.

Results: Childhood (i.e. o – 12 years) blood phenylalanine levels were significantly related to cognitive flexibility, executive motor control, EF in daily life and mental health in adulthood (i.e. at T2). Patients with a greater increase in phenylalanine levels after the age of 12 performed more poorly on EF-tasks at T2. Group-based analyses showed that patients with phenylalanine below 360 µmol/L in childhood and phenylalanine above 360 µmol/L from age 13 onwards (n=11) had better cognitive flexibility and executive motor control than those who had phenylalanine above 360 µmol/L throughout life (n=7), supporting the notion that phenylalanine should be below the recommended upper treatment target of 360 µmol/L during childhood for better outcome in adulthood.

Conclusion: Despite some results indicating additional influence of phenylalanine levels between 13 and 17 years of age, evidence for a continued influence of phenylalanine levels after childhood on adult outcomes was largely lacking. This may be explained by the fact that the patients in the present study had relatively low phenylalanine levels during childhood (mean: 330 μ mol/L, range: 219 – 581 μ mol/L) and thereafter (mean Index of Dietary Control at T2: 464 μ mol/L, range: 276 – 743 μ mol/L), which may have buffered against transitory periods of poor metabolic control during adolescence and early adulthood.

Keywords: Phenylketonuria, executive functioning, executive motor control, mental health, adults, longitudinal.

TALK 12: Mental Health and Quality of Life and Their Relation to Metabolic Control in NTBC Treated Tyrosinemia Type 1 Patients

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Background: Treatment with 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) and dietary restriction of phenylalanine and tyrosine largely improved outcome in Hereditary Tyrosinemia type 1 (HT1). This study aimed to investigate mental health and quality of life (QoL) in NTBC-treated HT1 and to relate this to phenylalanine and tyrosine concentrations.

Methods: 22 HT1 patients were studied (sixteen males; mean age 13.5 \pm 5.2 years). Mental health was assessed with the Achenbach System of Empirically Based Assessment (ASEBA). QoL was assessed with the TNO AZL Children's and Adults QoL (TACQOL; TAAQOL). Furthermore, lifetime and first-year-of-life phenylalanine and tyrosine concentrations were collected.

Results: Impaired mental health and QoL were found in several domains, particularly attentional, social, thought and somatic problems. In addition, impaired QoL on scales such as independent daily functioning, cognitive functioning and school performance, social contacts with parents and peers, and motor functioning were observed. Low phenylalanine and high tyrosine concentrations were partly associated with these issues. **Conclusion**: HT1 patients show several mental health problems and a lower QoL, which could partly be associated with measures of metabolic control. This suggests the need to keep phenylalanine and tyrosine concentrations between the target ranges in NTBC-treated HT1 patients.

Keywords: Tyrosinemia type 1, mental health, behaviour, QoL, metabolic control.

KEYNOTE 11: An Expanding Genetic Spectrum Causing Hyperphenylalaninemia and Central Monoamine Neurotransmitter Deficiency

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Objective: Phenylketonuria (PKU, phenylalanine hydroxylase deficiency), an inborn error of metabolism, can be detected through newborn screening for hyperphenylalaninemia (HPA). Most individuals with HPA harbour mutations in the gene encoding phenylalanine hydroxylase (PAH), and a small proportion (2%) exhibit tetrahydrobiopterin (BH4) deficiency with additional neurotransmitter (dopamine and serotonin) deficiency. Here we report six individuals from four unrelated families with HPA who exhibited progressive neurodevelopmental delay, dystonia and a unique profile of neurotransmitter deficiencies without mutations in *PAH* or BH4 metabolism disorders related genes.

Methods: In these six affected individuals, whole-exome sequencing was performed after exclusion of mutations in the known genes associated with HPA (*PAH, GCH1, PTS, QDPR* and *PCBD1*) or biogenic amine neurotransmitter defects (*SPR, TH, DDC, DAT* and *VMAT2*).

Results: Biallelic mutations in *DNAJC12*, which encodes a heat shock co-chaperone family member that interacts with phenylalanine, tyrosine and tryptophan hydroxylases respectively catalyzing the BH4-activated conversion of phenylalanine into tyrosine, tyrosine into L-dopa, the precursor of dopamine and tryptophan into 5-hydroxytryptophan, the precursor of serotonin. The *DNAJC12* protein was undetectable in fibroblasts from the individuals with null mutations. PAH enzyme activity was reduced in the presence of *DNAJC12* mutations. Early treatment with BH4 and/or neurotransmitter precursors had dramatic beneficial effects and resulted in the prevention of neurodevelopmental delay especially in the one individual treated before symptom onset who remained asymptomatic at 2 years of age.

Conclusion: DNAJC12 deficiency is a novel preventable and treatable cause of intellectual disability that should be considered in the early differential diagnosis when screening results are positive for HPA. Sequencing of DNAJC12 may resolve any uncertainty and should be considered in all children with unresolved HPA.

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KEYNOTE 12: Behavioural Phenotypes in Adults with Inherited Metabolic Disease

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Inherited metabolic disorders (IMDs) are disorders of pathways: they involve the processing of molecules. Most are caused by enzyme deficiencies, but activators and co-factors (and their metabolism) can also be involved. In other cases, transport mechanisms which carry molecules in and out of the cell, or from one part of the cell to another, are involved. The result is that a metabolic pathway becomes blocked, with accumulation of some molecules and deficiency of others. These imbalances are what eventually produce the disease phenotype. Clinical presentations are due to intoxication, storage, or deficiency.

In general, IMDs are considered to be rare, genetic, biochemical diseases of childhood. This is a dangerous misconception. Although individually rare, IMDs have a collective incidence of at least 1 in 1000. Although mortality rates are still high for some conditions, and prevalence in infants is higher than in adult populations, with improved treatment more patients with IMDs are surviving longer. Moreover, not all IMDs present in early life. Disorders of intermediary metabolism classically present with a metabolic crisis in infancy but in organellar disorders, such as the lysosomal storage disorders (LSDs), disease burden accumulates gradually. The most severe forms of these conditions can present soon after birth and be rapidly fatal, but in others progressive storage does not lead to significant clinical disease until adulthood.

The brain is affected in the majority of IMDs. Patient's behaviour can be affected acutely by intoxication, or chronically by permanent and progressive neurological damage. Many patients suffer the consequences of learning difficulties or epilepsy, but many conditions are also associated with specific and characteristic neuropsychology. In some conditions the initial presentation can be with psychiatric symptoms. In others, accumulated neurological damage can result in characteristic neuropsychological features. Various chronic illness behaviours can be superimposed on this.

The aim of this presentation is to introduce the problems we see in an adult IMD clinic and to stimulate research that might lead to a better understanding of the underlying pathology and improved management in the future.

TOM OPPÉ DISTINGUISHED LECTURE: Transgenic Non-Human Primate Research: Prospects And Ethical Issues

James C. Harris

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Background: The recent development of programmable nuclease gene editing tools (ZFNs, TALENs and CRISPRcas9) has led to the prospect of transgenic non-human primate (NHP) models of neurogenetic syndromes with behavioural phenotypes. Such preclinical research in non-human primates is an essential precursor to human trials. Germline transmission of a transgene is documented in marmosets and is underway in rhesus macaques. The marmoset genome is sequenced and complete marmoset brain mapping is underway in Japan. Ethical NHP research must consider moral standing, cognitive capacity, complexity of social behaviours, and capacity to feel pain and experience stress.

Methods: Programmable nuclease gene editing tools, especially CRISPR-cas9, target specific genomic nuclei and generate double-stranded breaks in the DNA based on sequences of unique base pairs; an RNA guide is constructed to target specific genes for editing for knock out and knock in models. Challenges include off-target genome-editing, low efficiency of homologous-directed repairs, and mosaicism.

Results: Rett syndrome, Fragile X syndrome and autism NHP research is underway in the US and internationally. High efficiency gene editing using CRISPR-cas9 in NHP zygotes has been documented with no detected offtarget effects at selected off-target loci. An immunodeficient marmoset has been created by gene targeting in embryos with blastomere splitting to reduce mosaicism. Cell based therapies for neurological disease in NHP models are ongoing.

Conclusion: Gene editing and cell based therapies in NHPs are progressing and syndromes with behavioural phenotypes are beginning to be studied. Ethical guidelines are needed as methodological enhancements provide opportunities for developing new knock out and know in models for human genetic diseases. Peer review will be required to prioritize genetic lines most likely to lead to breakthroughs in understanding human brain disorders. An infrastructure will be needed to facilitate dissemination of primate lines to individual research institution

Keywords: Gene Editing, CRISPR-cas9, Non-human primates, ethics.

KEYNOTE 13: Interventions for Cognitive Impairment in Children with Neurofibromatosis Type 1 (NF1): What Works and Future Directions.

Belinda Barton

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Neurofibromatosis type 1 (NF1) is one of the most common dominantly inherited genetic disorders with a birth incidence of approximately 1 in 3,000 individuals. The disorder is caused by a mutation in the NF1 gene encoding neurofibromin, which is a negative regulator of the Ras signalling cascade. NF1 is characterized by multiple caféau-lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, and iris Lisch nodules. However the most common complication of NF1 in childhood is cognitive impairment. While there is a slight lowering of intelligence, specific learning disabilities affect 20% to 65% of children with the disorder. Specific impairments in attention, visuospatial skills and executive functioning also commonly occur.

Mouse models of NF1 ($nf_1+/-$) have assisted in identifying the mechanisms underlying the cognitive deficits found in humans with NF1. Study findings indicate that the learning and memory deficits observed in $nf_1+/-$ mice are associated with excessive Ras, which leads to abnormally high GABA-mediated inhibition and impairments in synaptic plasticity. Pharmacological reduction of Ras activity with lovastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor appear to reverse the cognitive deficits observed in $nf_1+/-$ mice.

These findings subsequently led to a number of clinical trials to assess the efficacy of statins in treating cognitive deficits in humans with NF1. This presentation will summarise the findings of these clinical trials, as well as other interventions for children with NF1, highlighting 'what works'. Future directions for the treatment of cognitive deficits in children with NF1 will also be briefly outlined.

Keywords: neurofibromatosis type 1, cognitive impairment, children, treatment.

KEYNOTE 14: The GABA Hypothesis in NF1: From Animal Models to the Human Disease

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Understanding the aetiology of cognitive deficits in Neurofibromatosis type 1 (NF1) is critical to develop targeted treatments. Alterations in the excitation/inhibition balance might hold a pivotal role in the cognitive alterations observed in NF1. Studies in animal models revealed a mechanism by which GABAergic neurotransmission results in behavioural impairments. However, human patients have shown a complex pattern of GABA alterations, involving reduced GABA levels and GABAA receptor density, thus highlighting the difficulty in bridging the translational gap between the bench and clinically relevant therapies.

In order to understand how the GABA system is altered in NF1 and how this relates to the cognitive phenotype, a twofold approach is necessary: 1) To perform studies that can provide a mechanistic understanding of the role of the GABA system in behavioural and cognitive functions in humans and; 2) To reconcile the difference between the human and animal phenotypes from the neurochemical and functional points of view by employing, in the animal model, the same techniques that are available in humans.

Over the past years we have employed multimodal techniques to address these two approaches. I will discuss the implications of these studies and address the following questions: How is the GABA system related to cognitive deficits in NF1? Can measures of GABA function be used as a cognitive biomarker in NF1?

Keywords: Neurofibromatosis type 1 (NF1), GABA, cognition

TALK 13: Disease Burden and Symptom Structure of Autism in Neurofibromatosis Type 1 - A Study of the International NF1-ASD Consortium Team (INFACT)

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Background: Recent reports have demonstrated a higher incidence of autism spectrum disorder (ASD) and substantially elevated autistic trait burden in individuals with neurofibromatosis type 1 (NF1). However, important discrepancies regarding the distribution of autistic traits, sex predominance, and association between ASD symptoms and attentional problems have emerged, and critical features of the ASD phenotype within NF1 have never been adequately explored.

Methods: Using anonymized, individual-level primary data from 6 tertiary referral centres in the United States, Belgium, United Kingdom, and Australia, the distribution of ASD and attention-deficit/hyperactivity disorder (ADHD) traits, ASD symptom structure, latent structure, base rate derived from mixture modelling, and familiality were determined.

Results: Of the 531 patients included in the analysis, 247 were male (46.5%); median age was 11 years (range, 2.5 – 83.9 years). QAT scores were continuously distributed and pathologically shifted; 13.2% (95% Cl, 10.3%-16.1%) of individuals scored within the most severe range (i.e. above the first percentile of the general population distribution) in which the male to female ratio was markedly attenuated (1.6:1) relative to idiopathic ASD. Autistic symptoms in this NF1 cohort demonstrated a robust unitary factor structure, with the first principal component explaining 30.9% of the variance in SRS-2 scores, and a strong association with ADHD symptoms (r=0.61). Withinfamily correlation for QAT burden (intraclass correlation coefficient, 0.73 in NF1-affected first-degree relatives) exceeded that observed in the general population and ASD family samples.

Conclusion: This study provides confirmation that the diversity of mutations that give rise to NF1 function as quantitative trait loci for ASD, and the within-family correlation implicates a high-degree of mutational specificity for this ASD-associated disorder. Reproduced with permission from JAMA Psychiatry. 2016. 73(12): 1276 – 1284. Copyright © (2016) American Medical Association. All rights reserved.

Keywords: Autism Spectrum Disorder, Neurofibromatosis Type 1, Attention-Deficit/Hyperactivity Disorder, Genetics.

TALK 14: Adaptive and Maladaptive Functioning in Kleefstra Syndrome Compared to Other Rare Genetic Disorders with Intellectual Disabilities

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Background: Detailed neurobehavioural profiles are of major value for specific clinical management, but have remained underexposed in the population with intellectual disabilities (ID). This was traditionally classified based on IQ level only. Rapid advances in genetics enable etiology based stratification in the majority of patients, which reduces clinical heterogeneity. This paper illustrates that specific profiles can be obtained for rare syndromes with ID. Our main aim was to study (mal)adaptive functioning in Kleefstra Syndrome by comparing and contrasting our findings to three other subgroups: Koolen-de Vries Syndrome, GATAD2B-related syndrome and a mixed control group of individuals with ID.

Methods: In total we studied 58 individuals (28 males, 30 females) with ID; 24 were diagnosed with Kleefstra Syndrome, 13 with Koolen-de Vries Syndrome, 6 with the GATAD2B-related syndrome and 15 individuals with undefined neurodevelopmental disorders. All individuals were examined with a Vineland Adaptive Behavior Scale, mini PAS-ADD interview and an Autism Diagnostic Observation Schedule to obtain measures of adaptive and maladaptive functioning.

Results: Each of the three distinctive genetic disorders showed its own specific profile of adaptive and maladaptive functioning, while being contrasted mutually. However, when data of the subgroups altogether are contrasted to the data of Kleefstra Syndrome, such differences could not be demonstrated.

Conclusion: Based on our findings, specific management recommendations were discussed for each of the three syndromes. It is strongly suggested to consider the genetic origin in individuals with congenital neurodevelopmental disorders for individual based psychiatric and behavioural management.

Keywords: Kleefstra syndrome, Koolen de Vries syndrome, GATAD2B syndrome, adaptive functioning, intellectual disabilities, psychopathology.

TALK 15: Identification of Molecular Biomarkers Predictive of Response to Targeted Treatment in Fragile X Syndrome and Autism Spectrum Disorder

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Background: Both, serotonergic and inflammatory pathways play a role in the pathogenesis of autism spectrum disorder (ASD) and fragile X syndrome (FXS) and are considered potential targets for therapeutic interventions. A number of clinical trials have been carried out at the MIND Institute using sertraline to target the serotonergic pathway and lovastatin to target the inflammatory pathway in both children with ASD and FXS. The focus of this study was to identify molecular biomarkers to monitor disease progression and predict efficacy of response to targeted treatment.

Methods: We have been conducting a double-blind, randomized, 6-month placebo-controlled clinical trial of low-dose sertraline in young children with ASD and a clinical trial of Lovastatin in adolescents with FXS. Genotype analyses of candidate genes were carried out using single-nucleotide polymorphism arrays. Plasma levels of brain-derived neurotrophic factor, amyloid precursor protein, and matrix metallopeptidase 9 were measured by enzyme-linked immunosorbent assay while plasma cytokine/chemokine expression profiles were conducted using multiplex assays at both time-points (before and after treatment). Associations between genotypes and changes from baseline in primary and secondary clinical outcome measures were modelled using linear regression models.

Results: Significant associations were observed between different polymorphisms in candidate genes and improvements in several clinical measures, including the Clinical Global Impression scale (P= 0.008) and the Cognitive T Score (P= 0.017) in the group of children with FXS treated with sertraline compared to the placebo group. Additional analyses including lovastatin data are ongoing and preliminary results will be presented. **Conclusion**: Preliminary data from this study shows that polymorphisms/activity of genes involved in the serotonergic pathway and the chemokine and cytokine profile involved in the inflammatory pathway, could play a potential role in predicting response to targeted treatments in young children and adolescents with ASD and FXS.

Keywords: ASD, FXS, Targeted Treatment, Biomarkers, Sertraline, Lovastatin.

TALK 16: Differential Effects of Anxiety and Autism on Social Scene Scanning in Males with Fragile X Syndrome

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Background: Existing literature draws links between social attention and socio-behavioural profiles in neurodevelopmental disorders. Research has identified atypically reduced social attention in autism spectrum disorder (ASD; behaviourally associated with social withdrawal), and atypically prolonged social attention in Williams syndrome (associated with hyper-sociability). The socio-behavioural profile of fragile X syndrome (FXS) includes social motivation alongside heightened anxieties and ASD symptomatology. However, studies investigating social attention to naturalistic scenes in FXS are scarce. Furthermore, insight into the role of anxiety and autistic features is important to understand the potential mechanisms underlying social attention, and to guide interventions. This study compares social attention in males with FXS to typically developing (TD) children, and investigates the relationships between social attention, anxiety and ASD symptomatology.

Methods: Eleven males with FXS ($M_{age} = 26.29$) and 11 TD children, matched on gender and receptive language ability ($M_{age} = 6.28$), participated in an eye-tracking task where 20 colour photographs of naturalistic social scenes were displayed. Dwell times to the background, body, and face regions of the stimuli were analysed. The relationships between social attention, anxiety and ASD symptomatology were investigated using the Spence Child Anxiety Scale and the Social Communication Questionnaire, respectively.

Results: There were no between-group differences for dwell time to the background, body or face regions of the stimuli. Increased looking at faces was associated with both heightened anxiety and fewer social communication impairments in the FXS group only.

Conclusion: These results suggest that whilst social attention to naturalistic social scenes may be developmentally 'typical' in males with FXS, anxiety and autism symptomatology are differentially related to social attention in this population. These results offer novel insights into the mechanisms associated with social attention in FXS, and paves the way for future investigations of the relationship between clinically-relevant, sociobehavioural phenotypes and social attention in neurodevelopmental disorders.

Keywords: fragile X syndrome, social attention, eye-tracking, anxiety, autism

TALK 17: Metformin is a New Targeted Treatment for Individuals with FXS

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Background: Metformin hydrochloride is a biguanide drug that is FDA approved for individuals with type 2 diabetes and/or obesity ages 10 through adulthood. It has also been used successfully to treat atypical antipsychotic induced obesity in children ages 6 to 17y0 with ASD. Most recently, metformin rescued abnormalities of the circadian rhythm and short and long term memory problems in the Drosophila fragile X fly model. Recent studies of the fragile X knock out (KO) mouse demonstrated the rescue of social deficits, grooming abnormalities and dendritic spine abnormalities in addition to improvements in ERK signalling, EIF4E phosphorylation and lowered expression of MMP9 with metformin. We recently reported the clinical benefit in 7 individuals with fragile X syndrome (FXS) with metformin treatment (Dy et al 2017 Clinical Genetics). **Methods**: Clinical data on 17 individuals with FXS treated with metformin (2 - 60y0) included baseline and follow-up Aberrant Behavior Checklist-Community (ABC) both before and after treatment lasting >3 mo. Those with obesity including the PWP of FXS were prioritized for treatment. However, our cohort also included young children (>2y0) and those who were not obese. The starting dose ranged from 50 mg to 500 mg once a day at dinner.

Results: The great majority of patients with FXS demonstrated benefits with metformin treatment including weight loss and behaviour improvements noted on the ABC. Specifically improvement in the irritability subscale and language improvements were noted by the families. Usually HgbA1c improved, and one patient had type 2 diabetes at baseline. No hypoglycemia was seen and loose stools were the most common side effect. **Conclusions**: This clinical trial suggests benefits from metformin treatment in FXS. A multicentre controlled trial has now been initiated to document efficacy in behaviour and cognition and this will be outlined in this presentation.

Keywords: metformin, treatment, fragile X syndrome.

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TALK 18: Using Pharmacogenomics in Clinical Treatment of Children with Fragile X Syndrome and Sex Chromosome Aneuploidy

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Background: There is increasing recognition of the role of genetic polymorphisms on individual response to psychopharmacologic medication. New commercially available pharmacogenomic (PG) panels analyse genes involved in medication response and metabolism, leading to individualized medication recommendations based on results. Given the complexity of neurodevelopmental differences in FragileX syndrome (FXS) and sex chromosome aneuploidy (SCA), it is unclear if PG results are useful for informing treatment. The goal of this study is to evaluate the impact of clinical PG testing in genetic conditions of FXS and SCA.

Methods: Chart review was performed on 41 patients who had a pharmacogenomic panel (Genesight) collected as part of clinical care during medication management visits in specialty clinics for fragile X syndrome (n=27) and sex chromosome aneuploidy (SCA) (n=14). Records were reviewed for 6 months prior to and 6 months following the PG testing. Medication class, number of medications, frequency of medication changes (initiation, discontinuation, and dose adjustments), and adverse effects were recorded. Clinical Global Impression of improvement (CGI-I) was assigned after review of clinical records following any changes.

Results: There were significantly more instances of medication initiation, medication changes, and dose adjustments following PG testing, especially in the Fragile X group. Improvements on CGI-I were not significantly different before and after PG testing (61.0% before and 68.3% after, NS).

Conclusion: Pharmacogenomic testing may lead to more frequent initiation of medications, medication adjustments and fewer adverse effects in both FXS and SCA. However, PG testing did not lead to marked benefits to the rate of improvement of behavioural symptoms following a medication change. Further analyses of specific polymorphisms in pharmacodynamic and pharmacokinetic genes and individual response to specific medications is important in a larger cohort of individuals with FXS and SCV

Keywords: Pharmacogenomic testing, fragile X, sex chromosomes. XXY.

TALK 19: Socio-Emotional Functioning of Children and Adults With 47,XXY: A Focus on Underlying Mechanisms

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Background: Approximately 1 in 650 boys are born with an extra X chromosome. Boys and men with 47,XXY (Klinefelter syndrome) are at risk for neurobehavioral problems and cognitive impairments. Socio-emotional dysfunctioning seems to be among the core areas of vulnerability, which calls for the study of underlying mechanisms driving this risk. In this study we focused on social anxiety, and how social cognitive deficits, emotion regulation problems and testosterone deficiencies might play a role in this.

Methods: Several groups of boys and men with 47,XXY were compared to non-clinical controls, with samples size ranging from 25 to 70 participants per group. Cognitive tests measuring the labelling of facial expressions and Theory of Mind were administered. Eyetracking was used to assess social attention. Emotion regulation and anxiety were measured using autonomic nervous system measures (skin conductance) as well as self-report questionnaires. Testosterone was measured in saliva.

Results: Individuals with 47,XXY show more difficulties in social attention, facial expression understanding and Theory of Mind, and increased levels of social anxiety. Within the 47,XXY group, more emotion regulation problems and lower levels of salivary testosterone were significantly associated with higher levels of social anxiety. In contrast, salivary levels of testosterone were uncorrelated to social cognitive skills.

Conclusion: These findings suggest that emotion regulation problems and deficits in social cognition may help explain the observed increased social anxiety in individuals with 47,XXY. Also, lower circulating testosterone levels might contribute to high social anxiety in 47,XXY. As social anxiety is often seen in individuals with 47,XXY, this knowledge may help in directing therapeutic interventions, such as testosterone supplements, targeted at alleviating social anxiety. In contrast, circulating testosterone levels were not associated with social cognitive functioning, suggesting that lower social anxiety is likely not mediated by better social cognitive skills, and that other mechanisms are involved.

Keywords: Klinefelter syndrome, XXY, emotion regulation, testosterone, social cognition, social anxiety.

TALK 20: Early Childhood Development of Rare X and Y Chromosomal Disorders (XYD) 49,XXXXY and 49,XXXYY

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Background: 49,XXXXY occurs 1: 85,000 – 100,000 births while there have been less than 10 reported cases of 49, XXXYY. We present the early neurodevelopmental history of an unreported international sample of 49,XXXYY and 49,XXXYY boys.

Methods: 14 previously undescribed cases (13 49,XXXY and 1 49,XXXYY) from Italy/the UK underwent comprehensive evaluations within immunology, neurocognition, neurogenetics, physical therapy, speech and language.

Results: The 49,XXXYY case resulted from a 35-week uncomplicated pregnancy with inverted pinna, exotropia, fifth-finger clinodactyly, feeding difficulties, cat-like cry, truncal hypotonia, ventricular septal defect (VSD), apnea and asymmetric congenital cryptorchidism. First steps were taken at 29 months and 2-word combinations occurred at 36 months. At 9 years, he has moderate dysfluency, strabismus, visuospatial difficulties, GERD, molluscum contagiosum and keratosis pilarus. Receptive vocabulary was a standard score (SS) of 57 and behavioural issues prevented completion of nonverbal IQ (NVIQ) testing. The 49,XXXXY boys were, on average, 38 week pregnancies, second born with birthweight of 2.3kg. They walked at 40 months and spoke in 2-word combinations at 45 months. They had a frequency of URIs, and cardiac defects including CHD, atrial septal defect, systolic murmur, and VSD (2). Dysmorphic features included flat noses, high arched brows, fifth finger clinodactyly, congenital cryptochordism, tremors, and NG tubes. Receptive vocabulary skills were a mean SS of 77 (N=8). NVIQ were a mean score of 74 (N=4).

Conclusion: This is a large sample size for these rare variant disorders and suggests 49,XXXY displays increased incidence of congenital cardiac defects and immunological vulnerability related to the additive X chromosomes not previously described. The 49,XXXYY was distinct in presentation but behaviourally complex. This suggests that phenotype may be influenced differently based on the additive X or Y chromosome.

Keywords: Sex Chromosome Disorders X and Y Chromosomal Variations Neurodevelopment 49, XXXYY 49, XXXYY.

KEYNOTE 15: Stress Reactivity, Cortisol Levels and Experience Sampling in Adults with 22q11DS

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Background: 22q11 deletion syndrome (22q11DS) is a genetic disorder associated with anxiety and mood disorders, and increased risk for psychosis. Cortisol levels and stress reactivity reflect hypothalamic-pituitary-adrenal (HPA)-axis activity and are believed to be altered in subjects that often experience daily life stress, depression and psychotic symptoms. However, it is unknown whether patients with 22q11DS have an altered stress reactivity.

Methods: We included 27 adults with 22q11DS (age: 34.4 years, 66.7% female) and 24 healthy controls (HC) (age: 36.5 years, 68.6% female). The experience sampling method (ESM) was used and at every assessment a saliva cortisol sample was taken. Cortisol samples were averaged and compared between groups using an independent t-test and a multilevel regression model was used to analyse the ESM data.

Results: Cortisol was significantly lower in the 22q11DS group (t(57)=11.1, p<.001) compared to healthy controls. In addition event-related-stress reactivity scores were a negative predictor for average self-reported negative affect in both 22q11DS patients and healthy controls, respectively R^2 =0.130, F(2,1155)=87.62, p<.001 and R^2 =0.0578, F(2,1120)=35.4, p<.001 and significantly higher in 22q11DS compared to healthy controls (z=-2.430, p<.05).

Conclusion: These preliminary results indicate that people with 22q11DS may experience higher self-reported negative affect to small stressors in daily life, whilst showing lower mean cortisol levels than HC, possibly resulting from an over sensitization of the HPA-axis, which gives rise to hypocortisolism in posttraumatic stress disorder and psychotic major depression. This could imply a permanent long-term effect of stress and possibly be present in adults with 22q11DS too.

TALK 21: Maternal Origin of Familial 22q11.2 Deletions Negatively Impacts FSIQ Scores

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Background: Familial 22q11.2 deletions have a negative impact on FSIQ in affected offspring, thought to be the result of cognitive deficits in the affected parent/assortative mating, but no study has examined the impact of parent of origin.

Methods: We examined data on 211 Philadelphia subjects from 89 families comparing the mean FSIQ of those with familial v. de novo deletions and maternally v. paternally inherited familial deletions. We then compared our findings to those from Leuven, Belgium (N=26). Finally, we compared both datasets to those of de novo cases where parent of origin studies were complete (POOS) (N=57).

Results: CHOP cohort: N=26 children from 23 families; 65% maternally inherited; MFSIQ score (71.3) - statistically lower (p=.o2) than de novo deletions (N=342, M=76.6). MFSIQ for maternal deletions (M=68.3) was statistically lower (p=.o3) than paternal deletions (M=76.3). Leuven cohort: N=26 children from 22 families; 73% maternally inherited; MFSIQ score (M=61.4) lower than de novo (M=76.6). MFSIQ for maternal deletions (M=59.8) lower than paternal deletions (M=65.9). Combined Analyses: 67% of familial deletions were maternally inherited; MFSIQ (M=66.4) was much lower than de novo deletions. MFSIQ for children with maternal deletions (M=63.7) remained statistically lower (p=.o3) than paternal deletions (M=72.0). NY cohort: N=57 children with POOS; MFSIQ for maternal deletions (N=37, M=73.41) was no different (p=0.68) than for paternal deletions (N=20; M=73.41). **Conclusions**: Our findings confirm the association of lower FSIQ in familial versus de novo deletions, however, we observed the novel association of lower FSIQ's in maternally inherited familial deletions in contrast to de novo deletions. Thus, a maternally inherited familial deletion is a significant risk factor for poorer cognitive outcome in our combined American and Belgian cohorts. Confounding factors could include maternal comorbidities, socioeconomics, mitochondrial effects, level of engagement of the unaffected parent, etc. to explain this important finding.

TALK 22: High Prevalence of Fatigue in Individuals with 22q11.2 Deletion Syndrome: An Update

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Background: Fatigue is a very frequent complaint in the life of individuals with 22q11.2 DS. Clinical observations suggest that many suffer from fatigue. A pilot study confirmed the presence of higher levels of fatigue compared to the norms. Here we present an update in a larger sample of individuals with 22q11.2 DS thereby focusing on the relation between fatigue and psychiatric symptoms.

Methods: 50 individuals with 22q11.2DS with a mean age of 25.5 years (age range: 15 – 49y) completed the multidimensional fatigue inventory (MFI). The results of the study group were compared with a group of 28 healthy controls and with published population norms. Cross-sectional associations were examined between fatigue and depression (Beck Depression Inventory- BDI), anxiety (State and Trait Anxiety questionnaire-STAI), quality of life (QoL-WHO) and Resilience (Resilience Scale-NI- Rs-NI).

Results: Subscales and total MFI scores were significantly higher in 22q11.2DS compared to controls. A positive linear relationship was found between fatigue and anxiety as well as depressive symptom scores. Looking at QoL, fatigue was strongly associated to the perceived psychological health score. No association was found between resilience and fatigue. A subgroup of 13 adults with 22q11.2DS (26%) had no psychiatric diagnosis and still scored significantly higher on general, physical and total fatigue scores.

Conclusion: These findings confirm the high prevalence of fatigue in 22q11.2DS. Although psychiatric symptoms related to anxiety and depression show a strong relationship with fatigue, psychiatric causes alone do not appear to explain all the problems with fatigue in this population. Future research should also investigate possible underlying somatic disorders. Given the multisystem nature of 22q11.2DS, we recommend that investigation of fatigue should be part of the clinical examination in 22q11.2DS.

Keywords: 22q11.2 DS, fatigue.

TALK 23: Developmental Trajectories of Socio-Communicative Abilities in Children with 22q11.2 Deletion Syndrome

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Background: Considering the increased risk of psychiatric disorders in children with 22q11.2 deletion syndrome (22q11.2DS) from middle school-age onwards, follow-up of socio-communicative behaviours is very valuable. This study aimed to contribute to the delineation of syndrome-specific phenotypic changes in social-communicative development of children with 22q11.2DS.

Methods: Parental concerns regarding socio-communicative development were investigated by means of the Childrens Communication Checklist-2-NL and the Social Responsiveness Scale Dutch edition. Reports of about 20 monolingual Dutch-speaking children with 22q11.2DS were followed-up after 18 to 24 months. The longitudinal changes in the socio-communicative profiles were compared to the developmental course of children with idiopathic intellectual disability (IID) and children with IID and comorbid autism spectrum disorder (IID+ASD). All groups were matched for nonverbal fluid reasoning, structural language skills and chronological age. **Results**: Parents of children with 22q11.2DS indicated limited progress primarily in the appropriate use of language in changing contexts (pragmatics). In a subgroup, a growing into deficit trajectory was demonstrated.

Differences with children with IID were noted. In the 22q11.2DS group, overall social responsiveness significantly declined over time, whereas in the IID group no significant change was observed. Although some sociocommunicative characteristics of children with 22q11.2DS mirrored features reported by parents of children with IID+ASD, less profound impairments were demonstrated.

Conclusion: Socio-communicative profiles of children with 22q11.2DS are likely to change over time. Recommendations should be fine-tuned to the changing individual needs and environmental demands.

Keywords: 22q11.2 deletion syndrome, socio-communicative development, cross-syndrome comparison.

KEYNOTE 16: SSBP into the future

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This presentation will review briefly the past history of the Society for the Study of Behavioural Phenotypes (SSBP) and highlight how research into neurodevelopmental disorders has changed significantly over recent decades. Since the chromosomal anomaly causing Down syndrome was first identified in the 1950's, knowledge about the genetic abnormalities underlying other disorders associated with intellectual disability has expanded greatly. Transformations in molecular biology and gene sequencing and mapping techniques have now led to the identification of many genes associated with a wide range of developmental disorders, including those, such as autism, that were once considered to have no genetic basis. However, while exploration of genotype–phenotype associations has been crucial for understanding the fundamental causes of neurodevelopmental disorders, the practical impact of these findings has often been limited. Thus, genetic knowledge has not necessarily led to significant improvements in the lives of individuals with intellectual disability, or their families. In this talk I will consider how far genetic knowledge has affected approaches to intervention and what more might be done to enhance progress.

Keywords: SSBP; neurodevelopmental disorders; genetics; intervention.

Abstracts for Poster Presentations

(in alphabetical order of primary author)

POSTER 1: What Do Parents of Children with Angelman and Prader-Willi Syndrome Think About Potential Clinical Trials?

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Background: The rapid growth in genomic medicine has led to advances in potential treatments for a number of rare syndromes associated with intellectual and developmental disabilities. However, little is known about what parents of children with rare genetic syndromes think about such advances and their hopes or fears relating to clinical trials and gene therapy. This is important in order to identify what information they may need or want before deciding whether to participate.

Methods: Two focus groups were undertaken with mothers of children of rare genetic syndromes; one with mothers of children with Angelman syndrome and one with mothers of children with Prader-Willi syndrome. The focus groups were audiotaped and the transcriptions were subjected to a thematic content analysis. Results: A number of similar themes were raised within both groups including the combination of a positive interest in the potential for genetic treatments with a limited knowledge of levels of evidence or stages of trials for new treatments. Although the participant's children were of differing levels of ability, there was a strong recognition of the difficulties with standardised assessment in a clinic setting. Some syndrome-specific themes were also identified.

Conclusion: It is hoped that by furthering our knowledge in this area, future trials can consider parental beliefs and to some extent, preferences (for example, in areas such as methods of data collection) and proactively address any unhelpful or incorrect beliefs, therefore maximising the chance of parents making a fully informed choice.

Keywords: Angelman syndrome, Prader-Willi syndrome, treatment, therapeutics, intellectual disability.

POSTER 2: The Important Role of Histone Deacetylase 6 (HDAC6) in Behavioral Phenotypes of Neurological Disorders

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Background: Cognitive impairment, learning and memory deficits are the most common phenotypes of neurological disorders. One of the underlying reasons is the alteration of gene expression regulated by epigenetic modifications of histones. Histone deacetylase (HDAC) family is a group of enzymes, which dynamically modify chromatin and have a pivotal role in synaptic function in the brain. Amongst them, HDAC6 is highly expressed in the central nervous system and its aberrant expression has been shown to have several behavioral consequences including cognitive decline and memory disturbances. HDAC6 has recently been shown to be upregulated in Rett (RTT) syndrome. RTT is caused by mutation in X-linked gene methyl-CpG binding protein 2 (MECP2). Targeting HDAC6 with histone deacetylase inhibitors as a novel therapeutic approach has provided promising results for neurological disorders including Alzheimer's disease, Parkinson disorder, Huntington disease, Autism, and Rett syndrome. However, despite the efficacy of HDAC6 inhibitors, their molecular interactions are still poorly understood. The focus of this work was to summarize and visualize the known interaction pathways and to identify the gaps.

Methods: We systematically analyzed direct and regulatory interactions of HDAC6 with other proteins, especially with MECP2, by using BioGRID and ENCODE, two molecular interaction databases, and reviewing the literature. **Results**: A possible connection between MECP2 and HDAC6 was identified via two different transcription factors. The results are visualized on a WikiPathways pathway. (www.wikipathways.org/instance/WP3987).

Conclusion: Given recent findings, which has implicated a role for HDAC6 in RTT, the underlying biological mechanisms linking this protein to MECP2 requires more investigation. Using molecular pathways to visualize molecular interaction data, we provide a better understanding of the interactions by which HDAC6 exerts its function after being regulated by MECP2. Such combined targets could be evaluated further as possible new biomarkers for therapeutic applications.

Keywords: Rett syndrome, MECP2, HDAC6, Behavioral phenotype, Molecular interaction data.

POSTER 3: Lack of Sleep is Related to Symptoms of ADHD in Angelman Syndrome

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Background: Sleep problems, overactivity and distractibility are common problems in individuals with Angelman syndrome (AS), but the association between these areas of difficulty is uncertain. This study explored the relation between sleep problems and ADHD-symptoms in individuals with AS; the impact of epilepsy and developmental level was also investigated.

Methods: Assessment of sleep difficulties was based on parental ratings on five statements about sleep behaviour; (maximum score 5 on each question). The Strengths and Difficulties Questionnaire (SDQ) hyperactivity/inattention subscale (maximum score 10) was used to assess ADHD symptoms. Information about epilepsy was based on medical records. The number of signs used to communicate was used as a proxy measure of developmental level. Forty individuals aged 4 years or older (mean= 20.2yrs; range 4 – 57) were included; 33 had epilepsy.

Results: Mean score on the SDQ hyperactivity/inattention subscale was 7.4 (range 2 – 10). Two of 5 sleep questions were related to the SDQ score in the following ways; 'When my child wakes up during night, s/he often takes a long time to go back to sleep' (r=.34; p=.034); 'My child sleeps less than his/her peers' (r=.38; p=.020). SDQ hyperactivity/inattention were also related to age of onset of epilepsy (r=-.46; p=.01), but not with developmental level. Linear regression analysis with SDQ hyperactivity/inattention as the dependent variable and 'age of epilepsy onset' and 'sleeping less than peers' as covariates was significant (R2=.35; F=6.9; p=.004) with both variables having an independent contribution.

Conclusion: Lack of sleep seems to be related to degree of symptoms of hyperactivity/inattention in AS, even when controlling for age of epilepsy onset. This is interesting because lack of sleep is known to impact ADHD-symptoms in typically developing children and treating sleep problems may improve behaviour. More details about the sleep problems in AS will be presented at the time of the meeting.

Keywords: Angelman syndrome, sleep problems, ADHD.
POSTER 4: Emotion regulation and language in children with an extra X chromosome (47,XXX and 47,XXY)

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Background: Many boys and girls with an extra X chromosome (47,XXX and 47,XXY) are at risk for social difficulties, such as shyness, social withdrawal and social anxiety. It is thought that language impairments that are commonly found, may contribute to this risk. However, there is now evidence to suggest that impaired emotion regulation may also play a role. This refers to regulation of specific emotions such as anger or fear, along with global mood states, and stress. The present study of boys and girls with an extra X chromosome aimed to gain more insight in emotion regulation strategies, the association with language skills and behavioral problems. **Methods**: 53 children with an extra X chromosome (23 girls and 30 boys) and 91 typical developing children (50 girls and 41 boys) participated in the study. Emotion regulation strategies were measured using the Cognitive Emotion Regulation Questionnaire (CERQ). Language skills were measured with the Clinical Evaluation of Language Fundamentals (CELF). Behavioral problems were assessed with the Childhood Behavior Checklist (CBCL).

Results: As for emotion regulation, when compared to typical developing children, children with an extra X chromosome ruminated more, concentrated less on positive or pleasant matters instead of the actual event, and were more inclined externalize negative experiences. Refocusing on positive matters was significantly associated with better expressive language skills. Problems in emotion regulation strategies were associated with various behavioral parameters.

Conclusion: Besides insight in the various emotion regulation strategies of children with an X chromosome, the present study may also contribute to getting a better understanding of the relatively higher levels of stress, and emotional and behavioral problems in children with an extra X chromosome.

Keywords: Klinefelter syndrome, Trisomy X, emotion regulation, language, behavior, X chromosome

POSTER 5: Sluggish Cognitive Tempo in Children with Klinefelter Syndrome

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Background: There has been an increased focus on the construct of sluggish cognitive tempo (SCT). A recent meta-analysis by Becker and colleagues shows that SCT is a distinct symptom dimension that is separable from ADHD, other dimensions of psychopathology such as anxiety and depression, and daytime sleepiness. Since most studies of SCT have been done in children with ADHD, there is a need to study this construct in other clinical samples. The goal of this study was to examine the utility of the SCT symptom dimension in predicting executive and adaptive functioning in children with Klinefelter (47, XXY) syndrome.

Methods: Thirty-six boys with XXY, ages 10 – 15, were recruited as part of a larger randomized clinical trial testing the effects of testosterone. Baseline neuropsychological evaluation included measures of IQ, attention, executive functioning (EF), internalizing and externalizing symptoms, and adaptive skills. A SCT composite was derived from parent questionnaire items that measured 9 of the key SCT domains identified in Becker *et al.* Hierarchical linear regression analyses were conducted predicting EF and adaptive skills from SCT, ADHD, and mood symptoms. **Results**: SCT and ADHD symptoms each uniquely and significantly predicted metacognitive skills, even after controlling for IQ and processing speed (R-square =.76, p<.001). SCT also contributed significant unique variance in the prediction of adaptive functioning skills, after controlling for externalizing and internalizing symptomatology, and ADHD (overall R-square =.577, p<.001; SCT R-square change =.08, p<.05).

Conclusion: These results provide support for the internal validity of the SCT symptom dimension in a clinical disorder with a broad spectrum of deficits. SCT is distinguishable from ADHD in XXY and adds explanatory variance in predicting both metacognitive and adaptive functioning skills. Further research on SCT in this population is warranted to understand its relationship with academic outcome and as a target of intervention.

Keywords: Klinefelter, sluggish cognitive tempo, ADHD, executive function.

POSTER 6: High Prevalence of Movement Disorders and Related Abnormalities in Adults with 22q11.2 Deletion Syndrome

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Background: An increasing number of reports suggest that 22q11.2 deletion syndrome (22q11.2DS) may be associated with movement disorders and abnormalities in adulthood, in addition to other more well-known neuropsychiatric manifestations such as schizophrenia and anxiety disorders. In this study, for the first time, we investigated the spectrum and prevalence of movement disorders and abnormalities in adults with 22q11.2DS. Methods: In 92 adults with 22q11.2DS (47 male), we recorded the history of clinician-reported movement disorders and abnormalities using available lifetime medical records.

Results: At median age of 26.0 years (range 17 – 65), we found the following prevalence of movement-related problems: tremors 30.4%, dystonia 10.9% rigidity 10.9%, generalized shakiness of unknown etiology 7.6%, myoclonic jerking 6.5%, bradykinesia 5.4%, adult tic disorders 4.3%, tardive dyskinesia 4.3%, akathisia 3.3%, and Parkinson's disease 1.1%. Restricting to the subset of 35 subjects with a history of antipsychotic medication use, the prevalence of the three most commonly observed movement disorders were tremors 51.4%, rigidity 22.9%, and dystonia 20.0%.

Conclusion: The results indicate that movement disorders and abnormalities are common manifestations observed in adults with 22q11.2DS by clinicians. Even ahead of systematic study of movement disturbances, the findings have potential implications for monitoring and management of 22q11.2DS. Given the fact that about one in every four individuals with 22q11.2DS develops schizophrenia, a particularly high degree of vigilance for motor side effects would be recommended when prescribing antipsychotic medications in patients with 22q11.2DS.

Keywords: 22q11.2 deletion syndrome; Parkinson disease; parkinsonism; movement abnormalities; dystonia; antipsychotics.

POSTER 7: Neurodevelopmental Risks in Young Children with an Extra X or Y Chromosome: The TRIXY Study

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Background: About 1 to 2 in 1000 children are born with an extra X or Y chromosome (Sex Chromosome Trisomies; SCT). Children with SCT are at increased risk for neurodevelopmental problems. However, the number of studies on SCT is limited and the majority of publications (75%) are focused on physical problems. The aim of the TRIXY (TRIsomy of X and Y chromosome) Study is to understand risks for psychopathology by focusing on social adaption and underlying (neurocognitive and neurophysiological) mechanisms in children with SCT. Methods: The population of the pilot study consisted of 38 typical developing children, aged 1 to 6 years old. Methods included eye tracking (fixation duration, first fixation), heart-rate and skin conductance measures, (neuro)psychological tests, questionnaires, behavioral observations, and structured parental interviews. Results: The eye tracking results showed that fixation duration towards social cues was not correlated with IQ or gender. Significant associations were found between time spent looking at social cues (eyes and faces) and initiating and responding to behavioral requests during a structured social behavior observation measure. Looking times were also correlated with expressive and receptive communication as measured with the Vineland Interview, and with daily life social behaviors as measured with the Social Responsiveness Scale. Conclusion: Social attention is associated with expressive and receptive communication skills, and with daily life social behaviors of children. Children with SCT are at increased risk for problems in language, communication, and social behavior, which calls for further investigation of early social attention development in this population. Knowledge on the early development in these domains is needed to learn more about early risk factors in development, and to improve clinical care.

Keywords: Sex Chromosome Trisomies, early development, social behavior, communication, social attention, eye tracking.

POSTER 8: Emotional Self-Regulation in Rasopathies

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Background: Emerging research indicates that gene mutations within the RAS-MAPK signaling cascade, which cause Noonan syndrome (NS) and related disorders, affect the activity of inhibitory brain circuits on prefrontal cortex and striatum leading to attention and executive function impairment. Other evidences showed that alteration in the striatum might be related to affective problems too, like depression and mood dysregulation. Several studies have highlighted the presence of depressive, anxious and ADHD symptoms in NS assuming a possible role of affective problems such as emotional instability, impulsivity, agitation, anxiety and mood disorders. Emotion regulation can be defined as the ability to inhibit inappropriate behavior related to strong negative or positive emotion, self-soothe any physiological arousal that the strong affect has induced, refocus attention and organize for coordinated action in the service of an external goal. The aim of the present study is to investigate the presence of deficient emotional self-regulation in RASopathies.

Methods: Parents of 72 individuals with RASopathy were asked to fill out the Child Behavior Checklist for identifying children with deficient emotional self-regulation (DESR). DESR profile is characterized by a elevation, between 1 and 2 Standard Deviation (SD), of scores in 3 syndrome subscales (Anxiety/Depression, Aggression, Attention).

Results: Children with NS and Cardiofaciocutaneous syndrome (CS) have higher and more often clinically significant DESR scores than children with LEOPARD syndrome (LS) and Costello syndrome (CS). Moreover children with NS, compared to typical children's development, show significant different scores in all CBCL subscales and the syndrome scale of Attention is the strongest factor in distinguishing the two groups.

Conclusion: Our findings indicate that gene mutations within the RAS-MAPK signaling cascade mark a possible increased psychopathological risk of highlighting deficient emotional self-regulation.

Keywords: emotional self-regulation, ADHD, RASopathies, Noonan Syndrome.

POSTER 9: Exploring Neuropsychological Skills and Emotion Recognition in Males with XXYY Syndrome

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Background: XXYY syndrome is a rare sex chromosome aneuploidy commonly associated with IQ deficits, ADHD, social-behavioral difficulties, and autism. This study aimed to expand upon the XXYY behavioral phenotype to further describe behavioral profiles, executive function domains, and emotion recognition (ER) using standardized assessments.

Methods: Participants (Ss) with confirmed XXYY syndrome were included. A large sample (N=92) completed the BASC-2. A subset of 45 Ss completed the following protocol: brief cognitive assessment (WASI), computer-administered ANT (tasks: processing speed (PS), attention regulation (AR), EF (inhibition (IN) and mental flexibility (MF)), and ER (happy, sad, angry, fear)).

Results: BASC-2 scores (N=92; M=11.65 years, SD=5.98) fell in the at-risk range in all domains, except aggression, anxiety and somatization which were in the average range. Of the forty-five males (M=18.1 years, SD=7.6 [6 – 35]) included the ANT protocol, mean FSIQ was in the borderline range (M=79.3, SD=16.3). About half of the Ss' scores fell in the average range for PS (46.7%) and AR (51.1%) scores (z=1.5 or below) with the remaining Ss falling in the borderline-impaired or impaired range. There were significant deficits in both MF (mean z=4.7, p=.001) and IN (mean z= 2.2, p=.03) scores. Ss' ability to recognize happy was in the average range (N=37; mean z=1.03), but significantly lower for other emotions (sad z=2.53; angry z=2.35; and fearful z=2.54) (ANOVA F(3.31)=11.3, p <.001). ANT scores were not correlated with age or FSIQ. ADHD symptoms and daily life EF were both significantly predicted by AR. Adaptive behavior was significantly predicted by MF and ER.

Conclusion: Results highlight deficits in both EF and ER not been previously described in XXYY syndrome. Deficiencies in EF skills, which present independent of IQ, are important for counseling families regarding expectations for overall daily and academic functioning, and may be potential targets for interventions.

Keywords: XXYY; executive function; behavior; emotion recognition; neuropsychological features.

POSTER 10: Indicative Evidence That Developmental Dyscalculia May Be Part of the Down Syndrome Behavioural Phenotype

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Background: Developmental dyscalculia has been proposed as a potential aspect of the behavioural phenotype of Down syndrome. This hypothesis is based on the observed difficulties in arithmetic with which students with Down syndrome present, along with accumulating evidence that other aspects of mathematics, such as algebra and coordinate geometry, are able to be learned.

Methods: Data were collected from 209 individuals with Down syndrome from age 4 to 31 years, with a number of participants contributing data on multiple occasions (total occasions = 545). In order to avoid problems associated with inordinate contributions from some individuals, we created three groups in which there was no overlap between participants. These age groups were: 6 - 8 years (n = 41); 13 - 15 years (n = 70); and 20 - 22 years (n = 40). The data used for the analysis presented here were scores on the Quantitative and Pattern Analysis subscales of the Stanford-Binet Fourth Edition. The quantitative subscale measures a range of mathematical skills while the Pattern Analysis subtests is a test of fluid intelligence where individuals are asked to copy a model, using coloured blocks. While standard scores are available we used mental age scores for the analysis as they provided more variation across the samples.

Results: Paired t-tests were used to compare performance on the two subscales for the three age groups. Differences were significant for each group, with performance on the Pattern Analysis subtest being significantly better than performance on the Quantitative subscales in each analysis. Approximately 66% of the participants had a higher age equivalent on the Pattern Analysis subscale than on the Quantitative subscale.

Conclusion: Preliminary evidence is sufficient to suggest that developmental dyscalculia is worthy of further investigation to determine if it contributes to the behavioural phenotype of Down syndrome.

Keywords: Down syndrome; developmental dyscalculia, behavioural phenotype; mathematics, numeracy.

POSTER 11: Sleep Disorders Expand the Non-Epileptic Phenotype of Patients with Dravet Syndrome

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Background: Patients with Dravet Syndrome (DS), a refractory epilepsy syndrome associated with mutations in *SCN1A*, often display non-epileptic features. Sleep disorders are mentioned frequently by caregivers but no studies have been performed in this field. In this study we explored the sleep behaviour and incidence of sleep problems in a large cohort of DS patients.

Methods: An online questionnaire, based on the *Sleep Behavior Questionnaire by J.F. Simonds & H. Parraga (SQ-SP)*, was distributed amongst Dutch speaking parents (or caregivers) between December 2016 and April 2017. Patients above the age of 6 months with a confirmed clinical diagnosis of DS could participate. With the SQ-SP questionnaire a multitude of sleep related aspects from the last month were assessed. Completed questionnaires were evaluated by: total SQ-SP score, factor scores and Composite Sleep Index (CSI). A CSI \geq 4 was defined as aberrant sleep behaviour.

Results: In total 66 responses were recorded of which 59 could be used. The mean age was 13,79 (range 1 – 48y) with 51.7% males. The CSI ranged from 0 – 9 with a mean of 2,1 (StDev 2,1, n=59), of which 22% had a CSI of \geq 4. Sleep problems were mainly related to night awakening. A negative correlation was seen with the age. No correlation was seen with gender, overall or nocturnal seizure frequency. Sleep disorders were mainly reported in patients living at home and led to a decrease in the sleep quality of parents or siblings. Most parents did not receive any (treatment) advice concerning the sleep problems of their child.

Conclusion: Sleep problems are frequent in patients with DS and are influenced by age and living arrangement. A causative relationship has yet to be established.

Keywords: Dravet Syndrome, Sleep behaviour, epilepsy syndrome, SQ-SP questionnaire.

POSTER 12: Autism Spectrum Disorder in an Unselected Cohort of Children with Neurofibromatosis Type 1 (NF1)

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Background: Recently, studies have started to focus on the prevalence and profile of Autism Spectrum Disorders (ASD) in children with neurofibromatosis type 1 (NF1), and prevalence rates of ASD symptoms ranging between 13 – 30 % have been reported. However, these estimates are often based on screening instruments and preselected samples of children with NF1 with an initial suspicion of autism spectrum problems, and are most likely not representative for the general pediatric NF1 population. We aimed to examine the prevalence of ASD in an unselected sample of children with NF1 without a presumption of ASD. Additionally, we assessed the predictive value of a screening- and clinical observational instrument in relation to clinical DSM-IV ASD diagnosis in a pediatric NF1 population, and we examined possible correlates.

Methods: In 128 children, aged 2 – 10, the Autism Diagnostic Observation Schedule (ADOS; a clinical observational instrument for ASD assessment) was administered, and 103 parents also completed the Social Responsiveness Scale (SRS; a screening instrument for autism symptoms). All children were clinically assessed by a child psychiatrist.

Results: A prevalence rate for clinical ASD of 10.9% was found. The positive predictive value in relation to the DSM-IV ASD diagnosis was highest when the screening- and observational instrument were combined. An ASD diagnosis was associated with gender and age; more boys were diagnosed with ASD and the group of children with an ASD diagnosis was older.

Conclusion: This ASD prevalence rate is clearly higher than in the general population, but lower than has been previously reported in NF1 studies using pre-selected samples of children with a presumption of ASD. Furthermore, our results highlight the importance of using both the ADOS and SRS for the identification of ASD in children with NF1.

Keywords: Neurofibromatosis type 1 - Autistic traits - Autism spectrum disorder - Prevalence - Autism Diagnostic Observation Schedule - Social Responsiveness Scale.

POSTER 13: How Do We Engage Parents In Programs Targeting Behavioural Phenotypes?

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Background: Stepping Stones Triple P (SSTP) is a program designed to prevent and treat the emotional and behavioural problems of children with developmental disabilities. The SSTP project is a public health strategy that was rolled out to parents of children with disabilities aged o – 12 years across three states in Australia. The project provided an opportunity to examine the barriers and facilitators of parent engagement in programs targeted toward specific genetic syndromes.

Methods: The SSTP project trained 300 practitioners to provide parenting programs to all parents of a child with a disability aged 2 – 12 years. In addition to the general disability programs, some practitioners hosted syndrome specific programs for the following disabilities: Down Syndrome, 22q11.2 Deletion Syndrome and Fragile X Syndrome.

Results: We will describe how the following factors influenced parent engagement in the syndrome specific programs. 1. severity of the behavioural phenotype 2. how well families are engaged with the syndrome organisations 3. The medium used to reach families (e.g. flyers, word of mouth from a professional. **Conclusion**: Understanding the barriers and facilitators to engagement in parenting programs will help improve the development and delivery of future programs. Increasing participation in parenting programs will significantly reduce the burden of emotional and behavioural problems associated with genetic developmental

disabilities.

Keywords: Parent engagement, Stepping Stones Triple P, developmental disabilities.

POSTER 14: A Population Based Profile of Prader-Willi Syndrome in Ireland

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Background: PWS, a complex multisystem genetic disorder, is characterised by developmental abnormalities leading to somatic and psychological symptoms. Symptoms of PWS include infantile hypotonia and failure to thrive followed by life-long hyperphagia, obesity, developmental delays and several physical problems that impact health. Associated with the syndrome are a number of behaviours that are sufficiently distinctive that the syndrome is considered to have a specific "behavioural phenotype".

Methods: The results of the study are based on a paper survey designed by experts in the field of PWS in Ireland and carers of people with PWS. The survey was completed by 61 primary carers for people with PWS across the country. This represents around 60% of all individuals with PWS living in Ireland today.

Results: The most commonly reported PWS related behaviours included self-injury, in particular self-scratching (58%), repetitive questioning (63%), hyperphagia (72%), obsessions/compulsions (53%) and non-compliance (48%). Over 40% of respondents reported that they found these behaviours relatively difficult to manage. **Conclusion**: The findings of this study reveal the multiple physical, developmental, and behavioural issues

associated with PWS and how these issues require families and carers to devote considerable time and effort to care for a person affected by this condition.

Keywords: Prader-Willi Syndrome, Behavioural Phenotype.

POSTER 15: Barriers and Facilitators to Participation in an Evidence-Based Behavioural Family Intervention for Parents of Children with Autism Spectrum Disorder

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Background: The high rate of behaviour and emotional problems in children with ASD and other developmental disabilities is well established, along with the associated psychosocial distress within families. Parent training programs have been shown to be effective in reducing problem behaviour and improving child and parent outcomes. Despite this, parental engagement is traditionally low. There is therefore a need to understand the barriers and facilitators to engagement in parenting programs in order to improve parental engagement and improve outcomes.

Methods: Prior to implementing a statewide (Victoria, Australia) parent training program (Stepping Stones Triple P; SSTP) for parents of children with ASD and other developmental disabilities, a community survey (MySay) was conducted with parents to ascertain service need. The MySay survey revealed high rates of child behaviour and emotional problems and parent psychosocial distress, and low rates of participation in parenting programs. SSTP was then made available for two years; free to all families in Victoria who had a child with a developmental disability aged 2 – 12 years. Of those families who participated in the MySay survey, only a small proportion participated in the SSTP parenting program. A further survey (MySay2) was conducted with the MySay participants in order to better understand barriers to participation in SSTP.

Results: 373 families who participated in MySay reported that their child had received a diagnosis of Autism Spectrum Disorder (ASD). 309 of these families participated MySay2. Of these, 15.8% had completed an SSTP program in the previous two years. The most frequently reported reasons for non-participation were inconvenience (date, time, location), lack of awareness of programs, high family stress levels, no access to child care, additional costs, and work commitments.

Conclusion: The results of this survey will be reviewed, along with factors potentially influencing engagement, within the framework of public health implementation of programs.

Keywords: ASD, parenting program, engagement, barriers, facilitators.

POSTER 16: A Genetic Perspective on Self-Injurious Behaviour

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Background: Self-injurious behaviour (SIB) is a common behaviour in individuals with intellectual disabilities (ID), but pathogenesis remains a puzzle. SIB in genetic syndromes can be characterized by prevalence, age of onset and topography. What are the differences in these characteristics across genetic syndromes? To what hypotheses on pathogenesis may these differences lead?

Methods: We performed a comprehensive literature review on SIB characteristics in twelve genetic entities in which phenomenological SIB data were available: Angelman Syndrome (AS), Cornelia de Lange Syndrome (CdLS), Cri du Chat Syndrome (CdCS), Down Syndrome (DS), fragile X Syndrome (fraX), Lesch-Nyhan Syndrome (LNS), Lowe Syndrome (LS), Prader-Willi Syndrome (PWS), Rett Syndrome (Rett), Smith-Magenis Syndrome (SMS), Tuberous Sclerosis Syndrome (TSC), and Williams-Beuren Syndrome (WBS).

Results: SIB rates in several genetic syndromes are noticeably higher than in individuals with ID in general. Highest prevalence rates have been reported in LNS, SMS, PWS, CdCS and CdLS. Generally SIB starts in early childhood, but age of onset differ widely across syndromes. Pulling, scratching, hitting, banging, biting are most prevalent topographies. Topographies also vary across syndromes and some topographies are typical for specific syndromes. Particularly in CdLS and SMS involvement of several body parts frequently occurs.

Conclusion: SIB characteristics in genetic entities caused by mutations in different genes show considerable differences. Our hypotheses are that there may be a single common metabolic pathway that each time is influenced by the function of the genes causing the various syndromes, or there may be different pathways involved that each in themselves can cause SIB. Understanding the different causes and pathogenetic mechanisms by studying SIB from a genetic perspective will likely be an important step towards targeted early intervention and prevention.

Keywords: Self-injurious behaviour, intellectual disability, genes, genetic syndromes, Cornelia de Lange Syndrome, pathogenetic pathways.

POSTER 17: Assessing Mental Age in Children with Intellectual Disability: Can a Picture Paint a Thousand Words?

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Background: Evaluation of the mental age (MA) of children with intellectual disability (ID) in a clinical context is problematic. Standardised measures of cognitive ability are time-consuming and may be unsuitable for children with very low attention or behavioural problems. In the IMAGINE ID study, a national cohort of children with ID of genetic aetiology, we aimed to compare parental estimates of their children's MA with MA estimates derived from the Draw-a-Person (DAP) test (Goodenough, 1926).

Methods: A national sample of children (N=273) from the IMAGINE ID cohort (4 – 19 years) completed the adapted DAP test at home. A further 142 children did not complete the task. They were asked to draw their 'best picture' of a man, without assistance. Drawings were returned by post. Scoring was undertaken by two independent raters, according to the original methodology, which discriminated ability in 3-month intervals over the age range 3 years 3 months - 15 years 9 months. Inter-rater reliability (Bland-Altman) was excellent. **Results**: Children reportedly enjoyed the task. Reasons for failure to complete included visual impairment, but there appeared to be no correlation with the degree of motor impairment (as described by the parents). Parental estimates of MA were correlated with DAP-estimated MA (r=0.5, p<0.05). Mean DAP estimated delay (Chronological - Mental age) was significantly lower than the parental estimates: 37 months delay vs. 47 months delay, p<0.05.

Conclusion: The DAP test is an acceptable measure of MA in an ID population, which can be rated according to a standardized protocol, with a high degree of reliability. It correlates reasonably well with parental estimates of mental age, although consistently indicates higher ability, perhaps because parents consider a wider range of functioning. Validation with standardized IQ measures is required.

Keywords: Intellectual disability, mental age, Draw-a-Person.

POSTER 18: Recurrence Quantification Analysis (RQA) of Resting State EEG as Risk Biomarker for Autism Spectrum Disorder

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Background: Premutation carrier mothers of children with Fragile X Syndrome (FXS) are reported to have more anxiety and mood disorders compared to controls. The role of cognitive and emotional dysregulation (CED) in increasing the risk of developing and maintaining mood and anxiety symptoms has been highlighted in studies of different populations. However, there are limited studies exploring CED in FMR1 premutation carriers. This study aims to explore emotional and cognitive regulation strategies used by female premutation carriers of the FMR1 gene, and to compare these to those used by mothers of children with Down Syndrome (DS), in order to control for the psychological and environmental stresses of raising a child with special needs and possible challenging behaviours. We also aim to explore the association between dysfunctional cognitive emotional strategies and the presence of depressive and anxiety symptoms in this population.

Methods: Premutation carrier mothers of children with FXS will be recruited from records of the Fragile X Syndrome Society (UK). Mothers of children with DS will be the comparison group. Scores on the Cognitive and Emotion Regulation Questionnaire (CERQ), Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) will be compared.

Results: We postulate that premutation carrier mothers of children with FXS use more dysfunctional cognitive emotional regulation strategies, which are associated with more anxiety and depressive symptoms compared to those in the control group.

Conclusion: Identification of the patterns of cognitive and emotional dysregulation in this population will have important therapeutic and remedial implications to meet the needs and improve the quality of life of these mothers.

Keywords: Premutation carriers, Fragile X, Emotional Dysregulation, Depression, Anxiety.

POSTER 19: Social Attention in Young Children with Sex Chromosome Trisomies: A Case Study

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Background: The most common sex chromosome trisomy (SCT) in females is the presence of an extra X chromosome (47, XXX), known as Trisomy X, and occurs in 1 in 1000 female births. Children with Trisomy X and other SCT are at increased risk for language, communication, and social problems. One of the aims of the TRIXY (TRIsomy of X and Y chromosome) Study at Leiden University is to understand these risks by focusing on social attention development in children with SCT aged 1 to 6 years. This abstract will focus on the presentation of a Trisomy X case study in comparison to 23 typically developing children, to test the hypothesis that difficulties in language and social communication are accompanied by impaired social attention.

Methods: The pilot study sample included 23 typically developing (TD) children and one 3.5-year-old girl with Trisomy X. Methods included eye tracking (fixation duration, first fixation), questionnaires, and structured parental interviews (Vineland).

Results: The results showed that the girl with Trisomy X displayed substantial deficits in social functioning and language, both expressively and receptively. As hypothesized, her social attention abilities were deviant and in the clinical range, as expressed in less social orienting, lower accuracy in following gaze shifts, and more difficulties in following pointing gestures than the control group.

Conclusion: This is the first study to report weaknesses in the social attention profile of young girl with SCT. Children with SCT are at increased risk for problems in language, communication, and social behavior, which calls for further investigation of early social attention development in this population. Knowledge on the early development in these domains is needed to learn more about early risk factors in the development of young children with SCT, and to improve clinical care.

Keywords: Sex Chromosome Trisomies, case study, early development, social behavior, social attention, eye tracking.

POSTER 20: 47,XXY in Two Siblings and Their Varying Neurodevelopmental Presentation (NP)

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Background: 47,XXY is the most commonly occurring X and Y Chromosomal variation (1:660 males) and is associated with varying degrees of disruption in endocrine systems, neurodevelopment, brain morphology and musculoskeletal structure. We report siblings in which SiblingA (10 years) is affected with 47,XXY and a terminal deletion on 14q31.1(65kb) and SiblingB (7 years) is affected with 46,XY/47,XXY (60% of cells are 46,XY). Methods: Multidisciplinary evaluation was completed encompassing immunology, neurogenetics, speech and language, physical therapy, and neurodevelopment. The Childhood Behavior Checklist (CBCL) and standardized assessment were completed to assess receptive vocabulary (RV) and nonverbal intelligence (NVIQ). Results: SiblingA presented with global deficits in cognition, truncal hypotonia with scoliosis and a possible connective tissue disorder. Severely delayed speech with first words at 5 years and no 2-word combination supports the high probability of childhood apraxia of speech (CAS). Multiple physical differences noted at birth with diagnosis at 3 years. RV is a standard score of 57 and NVIQ of 65. SiblingB was diagnosed prenatally and has congenital hypothyroidism, truncal hypotonia and delayed speech. RV is standard score of 126 with NVIQ of 108 with dyslexia and dysgraphia. Internalizing, ADHD and social problems are present in both boys. Conclusion: This is a rare occurrence of two siblings with 47, XXY who are not the result of a twin gestation with complex but different ND presentations. Further testing is underway to determine if either parent has the chromosomal deletion of SiblingA. These two different ND further expand our understanding of the

heterogeneity of 47,XXY. The potentially confounding factors impacting on the mosaic form of 47,XXY include familial learning disorders, and complex family dynamics secondary to two children with neurodevelopmental issues.

Keywords: Neurodevelopment 47, XXY Sibling Report Copy Number Variant Developmental Delay.

POSTER 21: Sleep Difficulties in Children with Intellectual Disability of Known Genetic Aetiology

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Background: Sleep disturbances are common in children with intellectual disability (ID). Despite research showing that disturbed sleep impacts negatively upon both the child and their caregiver, sleep problems have not been investigated specifically in children with ID with a known genetic cause. This study aims to investigate sleep difficulties and their association with child psychological wellbeing and parental stress within IMAGINE ID, a national cohort study of children with ID of a genetic aetiology recruited through Regional Genetics Centres. **Methods**: Psychiatric interviews were conducted online with the caregiver of 1097 children aged 4 – 19 years with ID of genetic aetiology (Pathogenic CNVs assessed by array CGH). Sleep was measured using the Eating, Sleeping and Toilet training section of the Development and Wellbeing Assessment (DAWBA). The Strengths and Difficulties Questionnaire (SDQ) assessed the psychological wellbeing of the children and the Everyday Feelings Questionnaire (EFQ) measured parental stress.

Results: 37% of children in our cohort had insufficient sleep, slightly higher than other reported prevalence rates of sleep problems in children with ID (range 25.5% - 36.2%). 42% had difficulties falling asleep, 66% were not settling in their own bed and 23% were reported to have night terrors or nightmares. Caregiver EFQ total scores were significantly higher in those who reported their children as having insufficient sleep (p=0.00) and SDQ total scores were significantly higher in children reported to have insufficient sleep (p=0.00), falling in the 'very high' category. Sleep difficulties had a significant impact on daily living (p=0.00).

Conclusion: Children with ID of known genetic aetiology had sleep difficulties which were associated with higher parental stress and poorer psychological wellbeing of the children. Given this association, a better understanding of the interaction between psychological wellbeing and sleep is important in improving outcomes for these families.

Keywords: Sleep, parental stress, intellectual disability.

POSTER 22: The effectiveness of the Self-management Training: the impact of cognitive-behavioral intervention on executive functioning and behavior regulation in men with 47,XXY (Klinefelter syndrome)

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Background: One in 500 – 600 males have an extra X chromosome (Klinefelter syndrome, 47,XXY), which is associated with difficulties in social interaction and adaptation. Although individuals with Klinefelter syndrome are at risk for developing psychopathology, so far there have been no studies evaluating psychosocial therapeutic interventions in individuals with Klinefelter syndrome. In order to meet this therapeutic need a Social Management Training tailored to the specific vulnerabilities in Klinefelter syndrome was developed. The SMT aimed to increase the ability of individuals to regulate their emotions and behavior in ways that are socially adaptive.

Method: Sixteen adolescents and men with Klinefelter Syndrome participated in the SMT. This novel group treatment program consists of 10 sessions and includes psychoeducation, cognitive-behavioral skills training, home-assignments and mindfulness exercises. There were pre- and posttest evaluation (5 months apart) of behavioral problems by means of informant and self-report and cognitive assessments of executive function including sustained attention, inhibition, cognitive flexibility and working memory.

Results: Informant reports showed a significant decrease in attention problems (effect size 0.69), aggression (effect size 0.52), rule breaking behavior (effect size 0.54) and internalizing problems (effect size 0.69). Self-reports showed a significant decrease in anxiety and depression (effect size 0.40), and a trend for reduced social distress (effect size 0.36). Significant pre- to posttest improvements were found in inhibitory control (performance test) and metacognition skills (self-report), with effects sizes of 1.3 and 0.5 respectively. No effects of intervention were found on sustained attention, cognitive flexibility and working memory.

Conclusion: These findings suggest that the SMT tailored to the behavioral and cognitive profile of males with Klinefelter syndrome, may be a promising and potential efficacious treatment approach for improving self-control and behavior regulation, and reducing behavioral symptoms.

Keywords: Sex chromosome aneuploidy, social functioning, intervention, psychosocial treatment.

POSTER 23: Comparisons of the Brief Parental Report and Neuropsychological Clinical Tests of Executive Function in Fetal Alcohol Spectrum Disorders: Data from the UK National Specialist Clinic

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Background: Extant literature is somewhat sparse with regards to the relationship between parent reports and neuropsychological tests of executive functioning in Fetal Alcohol Spectrum Disorders (FASD). The goal of this paper was determining the clinical utilities of executive functioning measures used in the UK National Specialist FASD clinic, by examining relationships between outcomes on the Behaviour Rating Inventory of Executive Function (BRIEF) and the Delis-Kaplan Executive Function System (D-KEFS), as part of an ongoing service evaluation. Profiles of executive function from the BRIEF and the D-KEFS were also reported to contribute to delineating a profile of executive dysfunction in FASD.

Methods: Caregivers of 51 people with FASD completed the Parent BRIEF, and 72 people with FASD completed the D-KEFS. Raw scores were converted into scaled T-scores before analysis, and compared to normative means. Results: Pearson's Correlation between all eleven BRIEF scales and the eighteen selected D-KEFS subscales found little to no relationship. The BRIEF showed a profile of clinically significant elevations on all three index scores and seven out of the eight scale scores. The D-KEFS showed below average executive functioning in several scales compared to the normative mean.

Conclusion: The findings highlight that both executive function measures have separate clinical utility in demonstrating executive function deficits, and can be used in conjunction for a wider profile of executive function. However, parent reports display little relationship to neuropsychological tests, despite executive dysfunction being exhibited on both measures from people with FASD. These measures therefore likely monitor different aspects of executive functioning in different settings, and do not have similar clinical utilities. Future research should focus on identifying tests that better correlate findings from clinical settings to that of real world behaviour, and recognising factors that affect discrepancies between parental rating and objective clinical tests.

Keywords: Fetal Alcohol Spectrum Disorders (FASD); Executive Function; Neuropsychology; Behaviour Rating Inventory of Executive Function (BRIEF); Delis-Kaplan Executive Function System (D-KEFS); Parent Report.

POSTER 24: Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder Phenotypes in Fetal Alcohol Spectrum Disorders: Data from the UK National Specialist Clinic

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Background: The relationship between Fetal Alcohol Spectrum Disorders (FASD) and other neurodevelopmental outcomes continues to be explored. Prior publications have started to look into these relationships. This study, based on an ongoing service evaluation, continues to delineate the behavioural phenotype associated with FASD and other neurodevelopmental outcomes, as seen over 8 years in a national clinic.

Methods: Retrospective data was taken from consecutive patients seen in our FASD clinic since 2009. Descriptive analysis was carried out on the sample. Due to differences in clinical process over the 8 years, 128 people were assessed for Attention Deficit Hyperactivity Disorder (ADHD) and 106 for Autistic Spectrum Disorders (ASD). The measures used were all standard to each patient assessed.

Results: From the sample, 100 individuals (78.1%) met criteria for ADHD. 60 (46.9%) individuals had ADHD Predominantly Inattentive Type, 37 (28.9%) ADHD Combined Type, and 3 (2.3%) ADHD Predominantly Hyperactive/Impulsive Type. ADHD criteria were further delineated by DSM-V criteria, highlighting that predominantly an inattentive, impulsive subtype is seen. For ASD, 56 (53%) met criteria for ASD clinically using the Diagnostic Interview for Social and Communication Disorders (DISCO). Of this group, only 4 met more classic ASD descriptions of being aloof in their social functioning, with the majority 39 (37%) having a more prosocial style of functioning without true reciprocity.

Conclusion: FASD is a complex neurodevelopmental disorder. By applying careful evaluation and a behavioural phenotype approach, it is possible to understand its relationship to other disorders. This phenotype can help delineate it from other causes of ASD and ADHD and also help direct future management.

Keywords: Fetal Alcohol Spectrum Disorders; Autistic Spectrum Disorders; Attention Deficit Hyperactivity Disorder; ADHD; Autism; Neurodevelopmental Disorders.

POSTER 25: Assessing the Complexity of Adult ASD Cases Across 3 Areas in Southern England: A Service Evaluation

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Background: Multiple areas of functioning affected in individuals with ASD, co-occurring conditions may manifest. From subjective evaluation, differences in case presentations seen quantitatively in clinics between Surrey, Hampshire and Portsmouth through Surrey and Borders Partnership (SABP) NHS Foundation trust ASD services. Aim to evaluate the complexity of the cases and understand patient types seen in each area to shape future services. Establish the complexity of the presentations, service delivery issues, severity of autism and the effects of the quality of life.

Methods: 75 cases from each location, combining to 225 cases were scored using the modified Global Assessment of Functioning (GAF) as a measure of complexity. For a secondary descriptive the short sensory profile scores were recorded when available. Database statistical package for the social sciences (SPSS) Statistics 23 was used to allow effective data management and conduct in depth statistical analysis.

Results: Condensing of 5 groups of GAF achieved into 3 groups: Mild to Moderate, Serious and Major. 14.2% of total cases were mild to moderate, holding 13.3% of Surrey's cases, 10.7% of Hampshire's cases and 18.7% of Portsmouth's cases. 70.7% of total cases were serious, holding 78.7% of Surrey's cases, 72% of Hampshire's cases and 61.3% of Portsmouth's cases. 15.1% of total cases held the score of major, holding 8% of Surrey's cases, 17.3% of Hampshire's cases and 20% of Portsmouth's cases.

Conclusion: ASD cases show a wide range of complexity. Service development will need to bear this in mind when developing services for the ongoing care of people with ASD.

Keywords: Autism Spectrum Disorder, Complexity, Service Evaluation.

POSTER 26: Direct In-Person Neurodevelopmental Assessments Are Indispensable to Understand the Neurodevelopmental Phenotype in Individuals with SMC1A Variants

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Background: The neurodevelopmental phenotype in individuals with SMC1A variants includes intellectual disability (ID), autism spectrum disorder (ASD) and self-injurious behaviour (SIB). There is a reciprocal interaction between neurodevelopmental characteristics, physical phenotype and environment. To offer tailored care and support, direct in-person neurodevelopmental assessments are essential. We present results of direct in-person assessments in a sample of individuals with SMC1A variants.

Methods: After written consent, three authors (PAM, AL, SP) performed direct in-person assessments (N=8), including Autism Diagnostic Observation Schedule (ADOS), Autism Questionnaire (AQ), Bayley III, Wechsler Intelligence Scale (WPPSI-III and WAIS-IV), Vineland-2, and Short Sensory Profile (SSP).

Results: Three of eight patients had a profound ID, 2/8 moderate and 3/8 mild. Deficits in adaptive abilities were not in line with cognitive abilities (e.g. communication skills were poorer than expected based on developmental level). Three of eight patients with profound ID met ASD criteria. After careful analysis, two authors (PAM, AL) agreed that only two of these three patients were impaired by ASD in daily functioning when considering their developmental level. Severe difficulties in sensory information processing were present in most patients, more processing time was needed and shifting between tasks was delayed. Repetitive and restricted behavioural patterns were common.

Conclusion: From these direct assessments, a clearer picture of neurodevelopmental functioning has emerged. It is important to weigh results within the context of the developmental level of the individual. Autism may be assumed based on questionnaires, but behaviour should be considered within the developmental context. Direct in-person assessment provides valuable and specific information relevant to understanding the neurodevelopmental phenotype in individuals with SMC1A variants.

Keywords: neurodevelopment, phenotype, behaviour, autism, intellectual disability, SMC1A.

POSTER 27: Reversed Gender Ratio of Autism Spectrum Disorders in Smith-Magenis Syndrome

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Background: Substantial amount of research show higher rate of autistic type of problems in boys compared to girls. The 4:1 male to female ratio is one of the most consistent findings in autism spectrum disorders (ASD). Lately the interest in studying ASD in genetic disorders has increased, and research has showed a higher prevalence of ASD in some genetic disorders than in the general population. SMS is a rare, complex genetic syndrome caused by an interstitial deletion of chromosome 17p11.2, or a mutation on the retinoic acid induced 1 (RAI1). The disorder is characterized by intellectual disability, multiple congenital anomalies, obesity, neurobehavioral abnormalities, and a disrupted circadian sleep-wake pattern.

Methods: Parents of 26 persons with SMS between 5 and 49 years old participated in this study. 11 of the persons with SMS were above the age of 18 at the time of the study. 9 came from Sweden, 17 from Norway. We collected information about severity of autism spectrum symptoms using Social Communication Questionnaire (SCQ) and Social Responsiveness' Scale (SRS). Adapted behaviour was also measures using Vineland Adapted Behavior Scale II (VABS II). The level of intellectual disability (ID) was derived from journal review.

Results: We found significant gender differences in ASD symptomatology using SCQ and SRS questionnaires. We found 3.6 females per male above the SCQ cut off. The same differences were not found in intellectual level, adapted behaviour, or behavioural and emotional problems. Using linear regression gender had an independent contribution on SCQ scores, neither VABS or DBC had an independent contribution on the SCQ scores. **Conclusion**: We found a clear revised gender difference in autism spectrum disorders in persons with SMS.

Keywords: Gender, Autism symptomatology, Smith-Magenis syndrome.

POSTER 28: Sleep Assessment in Smith-Magenis Syndrome

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Background: SMS is a rare, complex genetic syndrome caused by an interstitial deletion of chromosome 17p11.2, or a mutation on the retinoic acid induced 1 (RAI1). The disorder is characterized by intellectual disability, multiple congenital anomalies, obesity, neurobehavioral abnormalities, and a disrupted circadian sleep-wake pattern. **Methods**: Patients with SMS between 5 and 49 years old participated in this study. The data collection is ongoing. The patients used an Actiwatch for a period of 12 – 18 days in their home. During the same period a sleep diary was filled out by parents/care takers. Parents also filled out Pittsburgh Sleep Quality Index is a 19-question questionnaire that measures the sleep quality during the previous month. ASD symptomatology and behaviour and emotional problems were assessed using Social Communication Questionnaire (SCQ), Sensory Responsiveness Scale (SRS), and Developmental Behavior Checklist (DBC).

Results: Data collection and analysis is in progress and results will be presented at the meeting. Preliminary analysis shows that patients with SMS in all ages has a shorter nightly sleep than recommended, and a high number of awakening episodes during the night. Correlations between sleep, ASD, and behavior will be presented at the meeting.

Conclusion: Patients with SMS in all ages has a substantial shorter nightly sleep than recommended, and a high number of awakening episodes during the night.

Keywords: Sleep, Actigraphy, Smith-Magenis syndrome.

POSTER 29: Cortisol Plasma Levels, In Vitro TNF-ALFA and IL-1BETA Production in a Group of Children with Obstrctive Sleep Apnea

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Background: Paediatric Obstructive Sleep Apnea (OSA) (prevalence 1.2 – 5,7%, peak between 2 and 6 years) is "characterized by prolonged partial and/or intermittent complete upper airway obstruction that disrupt normal ventilation and sleep pattern". The sleep fragmentation may alter the functioning of the Hypothalamic Pituitary Adrenocortical (HPA) axis, serum cortisol levels, increased TNF- α , IL1- β .

Methods: After an overnight PSG 43 non obese children (1- 15 years old, 22 F) were divided into 3 groups: mild OSA (m-OSA) 20, moderate-severe OSA (MS-OSA) 16 and controls (C) 7. At 2.00am and at 8.00am plasma cortisol levels (pg/mL) were assessed and in vitro 24 hours cultures of peripheral blood mononuclear cells (PBMC) from 7 children of every group, with PhytoHaemoAgglutinin (PHA+) or without (PHA-), were set up and the supernatant TNF- α and IL-1 β (pg/mL) assayed.

Results: At 2.00 am cortisol nadir (48.40 ± 47.11 ; m-OSA 36.42 ± 8.3 ; MS-OSA 53.75 ± 14.00) and higher levels at 8.00 am (163.82 ± 50.07 ; m-OSA 157.80 ± 10.3 ; MS-OSA 167.51 ± 10.82) (p=n.s.). In controls TNF- α in PHA- at 2.00 am and 8.00 am was 39.84 ± 40.12 vs 16.97 ± 16.52 (p=n.s.) similarly in PHA+ the values were 256.00 ± 123.58 vs 258.04 ± 85.17 (p=0.045). IL-1 β : no difference between PHA-, in PHA+ IL-1 β : at 2.00 am, 106.13 ± 137.81 vs 72.92 ± 63.39 (p=0.0083), at 8.00 am 252.48 ± 181.45 vs 318.84 ± 169.01 (p=0.0025). m-OSA vs MS-OSA vs C: at 2.00 am TNF- α in PHA- $57.96\pm63.94, 72.15\pm105.51$ (p= n.s.), in PHA+ m-OSA 336.73 ± 317.76 , MS-OSA 130.17 ± 124.23 (p=0.03), C 256.00 ± 123.58 (p=0.046). At 8.00 am PHA+ TNF- α in MS-OSA 127.18 ± 88.38 , m-OSA 395.65 ± 384.03 (p=0.03), C 256.00 ± 123.58 (p=0.046). No differences emerged for IL-1 β .

Conclusion: Nocturnal and arousal cortisol was not altered. The in vitro cytokines production was marginally affected in our OSA children. Differences between our data and some already published should be discussed.

Keywords: OSA, Paediatric OSA, Cortisol, TNF-α, IL-1β.

POSTER 30: Is There Phenotypic and Neurobiological Differentiation Between Schizotypal Disorder and Autism Spectrum Disorder in Children?

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Background: Children with Schizotypal Disorder (SDc) experience preoccupying fantasies but share some phenotypic features with Autism Spectrum Disorder (ASD), creating differential diagnostic challenges. We developed the Melbourne Assessment of Schizotypy in Kids to standardize assessment of SDc. Given their difficulty switching attention from an internal focus we aimed to (1) investigate executive functioning and sociopragmatic skills in SDc or ASD children and those co-morbid for SDc/ASD. (2) examine brain networks subserving internal to external switching mechanisms (Central Executive Network: CEN, Default Mode Network: DMN). **Methods**: Executive functioning and socio-pragmatic skills were investigated in 6 – 12 year old children with ASD (N=15), SDc (N=8), comorbid SDc/ASD (N=12), and typically developing (TD) children (N=32). To test DMN and CEN function, we developed a novel fMRI task isolating internal from external processes.

Results: Both ASD and SDc groups performed worse than the TD group on socio-pragmatic skills (p<.oo1) and had higher attrition at an extra-dimensional attention shifting task (p<.oo1), with the SDc group also making greater errors at intra-dimensional attention shifting (p=.o8). However, executive function of the comorbid (SDc/ASD) children was not significantly different from the TD group, and they were superior to ASD (p=.o19) and SDc (p=.o42) groups on socio-pragmatic skills. In the fMRI study the children (8 SDc, 4 ASD, 8 TD) engaged well (> 85% accuracy) with consistent fMRI activations in expected midline brain regions. Effect size estimates indicated medium-large group differences between SDc and TD in lateral prefrontal and parietal regions, and large-very large differences in widespread areas between SDc and ASD.

Conclusion: SDc is characterised by difficulty shifting attentional focus from internal thoughts probably reflecting abnormalities in switching between the DMN and CEN. This might represent a point of differentiation in diagnosis, prognosis and treatment. The novel findings for comorbid children suggesting normalization of attentional switching, require further investigation.

Keywords: Children, Schizotypal disorder, Autism Spectrum Disorder, Attentional Switching, Phenotype Differentiation.

POSTER 31: Communication Assessment and Intervention for Individuals with Rett Syndrome: How Our Understanding of the Communication Challenges and Possibilities Has Changed Over the Last 30 Years

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Background: Individuals with Rett Syndrome (RTT) demonstrate severe limitations in their ability to communicate. Historically, this has contributed to a universal assumption that they are severely intellectually impaired. In recent years this view has been increasingly questioned. This presentation gives an overview of research and practice in relation to communication and RTT spanning the past 30 years, culminating with the views and experiences of professionals and families around the world. It will identify changes in awareness and knowledge as well as current challenges and possibilities.

Methods: A systematic review of published research was recently undertaken as part of a project funded by Rettsyndrome.org, together with a review of grey literature. Surveys were also conducted online with communication professionals and families from over 30 countries in 16 languages, to capture real-life experiences. In the final stages of the project (fall 2017) international guidelines for the management of communication in individuals with RTT will be formulated through combining the available evidence with expert consensus. **Results**: The research literature is small but growing and signals an increasing awareness of the influence of apraxia on the communicative behaviours of individuals with RTT. Eye gaze offers the most reliable form of access for assessment and intervention/functional communication purposes, with more findings reported anecdotally than published as research paradigms. There is variability in clinical practice, availability of resources and professional knowledge/expertise between and within countries but a prevailing view amongst parents and professionals that individuals with RTT know and understand more than they can say and express by conventional means.

Conclusion: Increasing use of eye gaze technology is opening up possibilities for communication and participation but multiple challenges still exist in relation to assessment and intervention. The development of international guidelines will raise awareness and knowledge and promote consistency of practice across the field.

Keywords: Rett syndrome, communication, guidelines, challenges, possibilities.

POSTER 32: Developing International Clinical Guidelines for the Management of Communication in Individuals with Rett Syndrome

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Background: In February 2016 an international consortium (see authors), led by the Rett Expertise Centre Netherlands, began a two-year project to develop clinical guidelines for the assessment, intervention and longterm management of communication in individuals with RTT. The project is funded by Rettsyndrome.org.

Methods: To date, the project team have undertaken systematic reviews of published research and grey literature, an inventory of clinical practices - conducted via an online survey for communication professionals -, and an online survey for families which was globally available in 16 languages.

Results: More than 400 families and 120 communication professionals from over 30 countries have so far completed the online surveys. These responses are being analysed both quantitatively and qualitatively (using NVivo software) and will be added to the literature reviews to produce statements for draft guidelines. A consensus panel of experts drawn from professionals, parents and individuals with RTT will help shape the draft statements into final guidelines.

Conclusion: One of the challenges faced by the team was how to produce rigorous guidelines in the face of a large body of anecdotal evidence yet limited research evidence. The methodology adopted attempts to solve this by combining available evidence with expert consensus. A further challenge is in writing guidelines that need to be flexible and responsive to variations between countries in culture and language, and economic and political situations which influence and shape societal attitudes towards individuals with rare diseases and which determine differing national healthcare and education policies. Fundamental to the effective implementation of the final guidelines is the involvement of individuals with RTT, their family members and professionals who work in the field of communication and RTT. This project draws on such knowledge and experience from as many countries as possible and is firmly embedded in the lived experience of Rett syndrome.

Keywords: Rett syndrome, communication, surveys, guidelines, expert consensus.

POSTER 33: Changes in Conversational Behaviours in Children with Williams Syndrome

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Background: This study aimed to explore developmental courses of three conversational subskills (i.e. the ability to take into account listeners knowledge, topic management, and extending a topic by providing relevant information on a conversational partners turn in children with Williams syndrome (WS, n=8, ages 6 to 12). **Methods**: Conversational samples were elicited using the paradigm developed by Adams & Bishop (1989). Two types of analysis procedures were included: (1) a quantitative analysis after coding of conversational turns, and (2) a categorical analysis at a global level evaluating the conversation as a whole to characterise conversational shortcomings. We re-evaluated the conversational subskills after 18 to 24 months and compared them to same-aged children with idiopathic intellectual disability (IID), IID and comorbid autism spectrum disorders (IID+ASD) and children with 22q11.2 deletion syndrome (22q11.2DS).

Results: Children with WS showed greater difficulties with topic management compared to children with IID and 22q11.2 deletion syndrome. They overall rating of conversational impairments was not significant different from children with IID+ASD. However, there level of impairment seemed caused by different shortcomings. Over time taking account of listeners knowledge became challenging for children with WS.

Conclusion: Our results demonstrate that regular follow-up is needed to anticipate conversational challenges and suggest that support of conversational skill should be considered in children with WS.

Keywords: Williams syndrome, longitudinal follow-up, conversation, cross-syndrome comparison Reference: Van Den Heuvel, E., Botting, N., Boudewijns, I., Manders, E., Swillen A., & Zink, I. (accepted). Developmental course of conversational behaviour of children with 22q11.2 deletion syndrome and Williams syndrome. First Language.

POSTER 34: Executive Functions and Social Cognition in Transplanted Versus NTBC Treated Tyrosinemia Type 1 Patients

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Background: Tyrosinemia Type 1 (HT1) patients show neuropsychological deficits on executive functions (EF) and social cognition (SQ). It is hypothesized that these deficits could be related to NTBC treatment that causes high blood tyrosine concentrations. To assess the influence of any metabolic alterations, we compared liver transplanted patients with patients treated with NTBC.

Methods: All patients performed the Amsterdam Neuropsychological test battery (ANT). Nineteen patients were treated with NTBC (male: 15, mean age: 12.8 years) and six had liver transplantation (OLT) (male: 2, mean age: 16.4 years). Five of these six OLT patients received NTBC before the OLT. Different tasks measuring the percentage of errors and reaction time of core EF (inhibition, working memory and cognitive flexibility) and SQ (face recognition (FR) and identification of facial emotions (IFE)) were performed. Differences on the tasks were studied with Mann-Whitney U tests.

Results: Patients with OLT had a significant lower percentage of errors than patients still on NTBC with the easiest part of the FR task, presenting frontal pictures (p=0.003). The overall percentage of errors on this task was also lower in OLT patients (p=0.015). On the IFE task, OLT patients made significantly less mistakes when they had to identify persons who were happy (p=0.030). On the feature identification task, measuring working memory, NTBC treated patients had a significant longer reaction time (p=0.047). No significant differences on the other tasks were found.

Conclusion: Differences in results could be due to differences in treatment modality, although the results should be considered with caution due to the low number of patients and the difference in age between the two groups. Still, these data indicate that brain function in NTBC treated patients requires further study to investigate if this is associated with NTBC (and diet) related parameters.

Keywords: Tyrosinemia type 1, NTBC, liver transplantation, cognitive functioning.

POSTER 35: Growing Up with FXS; Concerns and Care Needs of Young Adult Males and Females with FXS

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Background: Fragile X syndrome (FXS) is an X-linked neurodevelopmental disorder and one of de most common heritable causes of intellectual disability (ID). The behavioral phenotype is generally milder in females compared with males, and includes autistic features, attention- and concentration deficits, anxiety, and self-injurious behavior. Little is known about the worries and the healthcare needs of young adult male and female FXS patients and their caregivers. More information on care needs will assist in providing optimal transitional and adult care for this vulnerable patient group.

Methods: A qualitative study was performed using semi-structured group and individual interviews with young adult patients aged 18 – 30, and parents of young adults. Concerns and healthcare needs in medical, psychological and socio-economic domains were discussed, with an emphasis on the transition from pediatric to adult care. Data were transcribed verbatim and analyzed by thematic analysis, using ATLAS.ti software. Themes were organized using the International Classification of Functioning, Disability and Health (ICF).

Results: In total, 33 parents (20 of males, 1 of female) and 5 patients (1 male, 4 females) participated. Fourteen ICF themes were identified after transcription and coding. Results indicated many and diverse worries, with different outcomes for males and females. Self-injurious behavior, anxiety and sexuality issues were widely discussed for males. For females, learning disabilities, in particular a deficit in mathematics, problems with social relationships, and problems planning and organizing stood out. In both groups parents reported high stress levels, difficulties with their parental role, and a lack of knowledge of FXS in care providers.

Conclusion: The concerns and care needs of young adults with FXS and their parents revealed concerns on various domains, requiring gender-specific, multidisciplinary transitional care and adult follow-up for patients with FXS. Additionally, parental stress requires more attention from care providers.

Keywords: neurodevelopmental disorders; Fragile X syndrome (FXS); qualitative research; transition; ICF classification.

POSTER 36: Defining Anxiety in Adults with 22q11.2 Deletion Syndrome (22q11.2 DS)

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Background: The 22q11.2DS is known for a high prevalence of anxiety disorders. In clinical practice, there is discussion if the anxiety symptoms in this population should be classified based on the categorical diagnosis, or if a dimensional approach could learn us more and alter our approach in the clinic.

Methods: 50 adults with 22q11.2DS and 28 healthy controls participated. A DSM-5 based psychiatric interview was conducted and combined with more specific psychiatric and more dimensional measures such as the positive and negative symptoms scale, CAARMS interview and the state-and trait anxiety questionnaire.

Results: 22 of the 50 adults with a 22q11.2DS fulfilled the criteria for a current anxiety disorder, including 9 with prodromal psychotic symptoms. Compared to healthy controls, self-reported anxiety scores were significantly increased, even in the subgroup of adults with 22q11.2DS with no current DSM-5 diagnosis (n=14). Anxiety scores were correlated with the positive and the general subscale of the PANSS. Interestingly, anxiety scores were only higher in the group of adults with prodromal symptoms (n=13). However, anxiety scores in the subgroup of adults with only an anxiety disorder and no prodromal symptoms (n=14) were not significantly higher than in the subgroup with no current psychiatric disorder.

Conclusion: This study confirms the clinical observation that almost all adults with 22q11.2DS have increased levels of anxiety. Anxiety levels do not seem to differ significantly between adults with and without the actual diagnosis of an anxiety disorder. Our findings also suggest that more severe self-reported anxiety might be predictive of the development of psychotic symptoms in adults with 22q11.2DS. Further research is necessary to confirm this and to investigate if strategies to decrease anxiety might be helpful for adults with 22q11.2DS and might help in the treatment or prevention of psychotic disorders.

Keywords: anxiety; DSM 5, dimensional approach, STAI, prodromal psychotic symptoms.

POSTER 37: CNVS in Intellectual Disability: Clinical Comorbidities

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Background: Intellectual disability (ID) is a heterogeneous disorder characterized by deficits in cognitive ability and adaptive skills. There's often an associated comorbidity with other neurodevelopmental disorders (ND) such as autism spectrum disorders (ASD) and other clinical conditions as epilepsy and psychotic disorder. Array-based comparative genomic hybridization (Array-CGH) is a useful tool to locate and identify copy number variations (CNVs) in genomic loci that can be associated with the development of specific phenotypes. Aim of this paper is to identify different CNVs in ID and describe more common comorbidities.

Methods: One hundred sixty-three ID patients (93 M; 70 F; mean age 33 yrs) without an etiological diagnosis were evaluated from the clinical and neurological point of view and with psychometric instruments (WISC). Psychiatric evaluation was performed with DSM5 criteria. All of them were tested with array-CGH. Statistical evaluation was performed using SPSS.

Results: Sixty-two patients/163(38%) were carriers of 76 CNVs, since multiple CNVs were detected in 10 subjects. 17/62 individuals (27.4%) have at least a CNV classified as pathogenic, in 7/62 (11,3%) patients the CNV is considered probably pathogenic, of unknown significance in 38/62 (61,3%). Out of all CNVs detected, duplications and deletions were equally represented. Mean IQ level was 59.10 in CNV+ group and 62.46 in CNV-. Duplications were associated with severe ID (59.4%) and with ASD (56.3%). ASD was also correlated with pathogenic (13.8%) and inherited (52.9%) CNVs. Comorbidity with epilepsy was detected in 20.6% of CNVs (19% partial,1.6% generalized). Inherited CNVs were detected in partial epilepsy (10%) and in generalized (1%). Comorbidity with psychotic disorder was present in the 14% of deletions and 31.3% of duplications.

Conclusion: CNVs contribute to the risk of developing a ND. Several developmental disorders may share the same genetic rearrangements.

Keywords: ID CNV comorbidity.

POSTER 38: Catatonia in Adults with Phelan-Mc Dermid Syndrome

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Background: Catatonia is a motor dysregulation syndrome co-occurring with a variety of psychiatric and medical disorders. Response to treatment with benzodiazepines (BZD) and electroconvulsive therapy (ECT) suggests a neurobiological background. BZD and ECT are agonists of the inhibitory function of the GABA-A receptor complex. Their therapeutic effect on catatonia suggests a dysfunctional neurotransmission as the underlying neurobiological mechanism. Despite the evidence of a role of disturbed neurotransmission involving different synaptic receptors, studies on the genetic etiology of catatonia are scarce.

Methods: In this study, we performed copy number analysis in 15 adults with intellectual disability and catatonia to identify chromosomal deletions and duplications.

Results: In 3 out of 15 patients (20%), the genetic etiology of catatonia was established: two adults were diagnosed with a 22q13.3 deletion, causing Phelan-McDermid syndrome, and one patient with trisomy 21. **Conclusion**: Two catatonic adults were diagnosed with a 22q13.3 deletion, causing Phelan-McDermid syndrome, SHANK3 has been identified as the critical gene in neurological and behavioual aspects of Phelan-McDermid syndrome. SHANK3 is a scaffolding protein, enriched in the postsynaptic glutamatergic excitatory synapses and interacting with various synaptic molecules. A major interaction partner of SHANK3 is the NMDAR complex well known for its role in anti-NMDAR-encephalitis. Interestingly, this non-infectious encephalitis has specific clinical features compatible with catatonia like catalepsy, stupor, mutism, posturing and stereotypical movements. This suggests dysfunction of the postsynaptic NMDAR-SHANK3 unit in at least some of the catatonic patients.

Keywords: SHANK3, Phelan-McDermid Syndrome, catatonia.

POSTER 39: Aberrant Sexual Behaviors in Two Intellectually Disabled Adults with the Recurrent 16p11.2 Deletion

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Background: Deletion of the recurrent circa 600 kb BP4-BP5 chromosomal region 16p11.2 has been associated with a wide range of neurodevelopmental and physical characteristics. An increased frequency of autism spectrum disorder, intellectual and learning disabilities, behavioral difficulties and psychiatric disorders has been observed. However, the description of this behavioral phenotype remains vague and incomplete.

Methods: From 2005 up to 2015, 284 intellectually disabled adults, admitted to the inpatient psychiatric unit, were selected for genetic examination, consisting of a clinical examination and molecular karyotyping (Comparative Genomic Hybridization). Two patients (0.7 %) were diagnosed with the same recurrent 16p11.2 deletion. Medical files were analyzed retrospectively to collect data on their cognitive functioning, psychiatric diagnosis, environmental factors and behavior.

Results: Both patients were diagnosed with moderate intellectual disability and presented with similar aberrant sexual behavior with pedophilic tendencies. Neither of them had a history of possible provoking environmental factors such as a history of sexual abuse.

Conclusion: To our knowledge, this is the first report of severe aberrant sexual behavior in adults with the recurrent 16p11.2 deletion. Although the etiology of pedophilia and hypersexual disorder remains unknown, recent studies have suggested a possible genetic contribution toward pathological sexual interest and behavior. The fact that out-of-control sexual behavior has not been reported before in adults with 16p11.2 deletions may be explained by the fact that hypersexual disorder and pedophilia are not included in the standardized psychiatric questionnaires used in most studies. Another explanation may be that the diagnosis of aberrant sexual behavior may be missed in 16p11.2 deletion adults with normal or borderline intelligence. Although these results have limited value by the small sample and are exploratory, evaluation of sexual behavior in adolescents and adults with 16p11.2 deletion is recommended.

Keywords: recurrent 16p11.2 deletion, aberrant sexual behavior.
POSTER 40: Intellectual Disability and Coexisting Autism and ADHD in Down Syndrome - a Population-Based Study

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Background: This study, aiming at identifying Autism spectrum disorder (ASD), ADHD and level of ID in Down syndrome (DS), was based on the total population of children and adolescents with DS (5 – 18 years) in the Swedish county of Uppsala.

Methods: The diagnosis of ASD, ADHD and ID was assessed in accordance with clinical praxis.

Results: A high proportion of ASD was found. For the study cohort, the rate was 41%. The proportion of children with ADHD was 34%. The level of Intellectual Disability (ID) was analysed. ID was found to be more profound than reported earlier. A majority (57%) of the teenagers had severe or profound ID. The corresponding figure in the younger age group (5 – 12 years) was 35%. ID was more severe when ASD was present.

Conclusion: The more severe ID, compared to earlier reports, could possibly be due to the population-based design, with 100% participation, thereby including also children with the most profound ID. We cannot explain the lower levels of IQ among the teenagers with DS, i.e. whether this is a sign of early intellectual decline or if the age groups differ in other aspects. The population-based design should empower the results. In Uppsala County, there is a centralized follow-up program, including all children (o – 18 years) with DS, which means that all patients with DS in the targeted age group have been reached. A limitation of the study is that only two thirds of the cohort took part in the ASD-ADHD assessment. The ID-study was based on the total population of 60 children. In conclusion, our cohort had a more profound ID than that reported in earlier studies. This is most prominent for the teen-agers. More than half of the children have another developmental disorder in addition to ID. Children with DS and ASD generally have a more severe level of ID.

Keywords: Down syndrome, Intellectual Disability, Autism, ADHD.

SSBP Syndrome Sheets 2017

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.

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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 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 nonverbal 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) Copyright ©2014 M. Heald & C. Oliver

Classification

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

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

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

Associated conditions

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

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

Genetics

The risk of ASD in siblings of probands is significantly increased and there is a high concordance rate in monozygotic twins. Family studies indicate that the "Broader Autism Phenotype" (i.e. having problems related to social, language and/or cognitive functioning) occurs in up to 20% of first-degree family members. Although ASD is highly heritable there is wide genetic heterogeneity, with multiple modes of inheritance including high rates of de novo mutations and a wide range of possible rare and common copy number variations (CNV's; i.e. submicroscopic chromosomal deletions or substitutions). Diverse clinical phenotypes and limited sample sizes add to the challenges of identifying the specific genes involved and currently only around 10% to 15% of cases of ASD appear to be associated with a known genetic mutation (Bourgeron, 2016; Krishnan, *et al.*, 2016).

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

Prevalence

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

CHARGE Syndrome

First Description

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

Genetics/aetiology

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

Incidence/prevalence

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

Physical phenotype

The acronym was suggested by Pagon and colleagues (1981) based on common features: C – coloboma of the eye (missing part of iris and/or retina); H – heart defects; A – atresia of the choanae (bony or membranous blocking of nasal passage); R – retardation of growth and/or development; G – genitourinary anomalies; E – ear anomalies and/or deafness. While all six features may appear, there is wide variation in both occurrence and severity. This has led to a more refined diagnostic system (Blake et al, 1998) with four major features (coloboma, choanal atresia, cranial nerve dysfunction, characteristic CHARGE ear) and a number of minor anomalies. Diagnosis is based on 3 major or 2 major and 2 minor. Other diagnostic systems have since been proposed (i.e., Verloes, 2005). Diagnosis is difficult because there is great variability in presence and severity of the features.

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

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

Behavioural and psychiatric characteristics

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

Neuropsychological characteristics

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

Useful websites/associations for more information

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

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Timothy S. Hartshorne, May, 2015

Coffin-Lowry Syndrome

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

Genetics and molecular biology

The *RPS6KA*₃ gene encodes a growth factor regulated serine-threonine protein kinase, Rsk2 (alternate names: p90^{RSK2}, MAPKAPK1B, ISPK-1), which acts at the distal end of the *Ras*-Erk1/2 signalling cascade. Mutations in the *RPS6KA*₃ gene are extremely heterogeneous and lead to premature termination of translation and/or to loss of phosphotransferase activity of the RSK2 protein. For the vast majority of mutations so far reported, no consistent relationship has been observed between specific mutations and the severity of the disease (Delaunoy *et al.*, 2006). However, expression of some features was found to be associated with particular truncating mutations in a few patients (Nakamura *et al.*, 2005).

Incidence / Prevalence

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

Physical features and natural history

The typical facial aspect in adult male patients includes a prominent forehead, orbital hypertelorism, downward-slanting palpebral fissures, epicanthic folds, large and prominent ears, thick everted lips, and a thick nasal septum with anteverted nares. Orodontal findings include typically a high narrow palate, a midline lingual furrow, hypondontia, and peg-shaped incisors. Skeletal malformations appear progressively in most patients and may include delayed bone development, spinal kyphosis/scoliosis, and pectus carinatum or excavatum. Radiographic changes include cranial hyperostosis, abnormal shape and end plates of the vertebral bodies, delayed bone age, metacarpal pseudoepiphyses, and tufting of the distal phalanges. Uncommonly associated manifestations include epileptic seizures and sensorineural hearing loss, which can be profound. Stimulus-induced drop episodes, with onset typically from mid-childhood to the teens (unexpected tactile or auditory stimuli or excitement triggers a brief collapse but no loss of consciousness), and cardiac involvement, usually in the form of mitral valve dysfunction, are often present. Reduced total brain volume, with a particular effect on cerebellum and hippocampus, has been reported in some patients. Affected newborn males often show only hypotonia and hyperlaxity of joints. However, broad, tapering fingers may also be present at birth. The typical facial appearance is usually apparent only by the second year of life and shows progressive coarsening thereafter with increasing prominence of the glabella and protrusion of thelips. Retardation of growth and psychomotor development become apparent gradually in the first years of life. Other possible early signs are sensorineural hearing deficit and microcephaly. The age of walking is delayed, and difficulties in ambulating may persist with a clumsy gait.

Female heterozygotes show variable involvement that can range from short stubby digits with normal appearance to quite marked facial dysmorphism. Ventriculomegaly has been observed in several affected males and females. Although accurate information is not available the paucity of reports of older affected males suggests that their life expectancy is reduced in contrast to that of females who can survive well into old age. Reported causes of death in affected males include myocarditis, pneumonia and inhalation during a convulsion. Several males have succumbed to complications following general anaesthesia for correction of orthopaedic problems or dental extraction (Hanauer & Young, 2002, Hunter, 2002).

Behavioural characteristics

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

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

Available guidelines for behavioural assessment/ treatment/management

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

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André Hanauer, June 2010 Revised Stewart Einfeld, 2015

Coffin Siris

First description and alternative names

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

Genetics and molecular biology

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

Studies have examined the candidate region for Coffin Siris. An infant with findings consistent with Coffin Siris syndrome was reported to have an apparently balanced translocation with breakpoints at 1q21.3 and 7q34 (Mcpherson *et al.* 1997). Other research suggested a candidate region for Coffin Siris at 7q32->34 (McGhee *et al.* 2000). A partial trisomy 9p gene change has also resulted in a Coffin Siris phenotype (Temtamy *et al.* 2007). Coffin Siris investigations continue.

Incidence/prevalence

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

Physical features and natural history

Minimal clinical criteria for the diagnosis of Coffin Siris syndrome include developmental delay, hirsutism, coarse facies, feeding problems, and hypoplasia or aplasia of the distal fifth digits and nails. Additional characteristics of Coffin Siris syndrome include feeding or sucking difficulties, wide mouth, thick lips, hypotonia, flat nasal bridge with broad nose, sparse scalp hair, thick and laterally placed eyebrows, microcephaly, abnormal ear placement, abnormal or delayed dentition, high arched palate, delayed bone age, coxa valga, frequent otitis media, and respiratory infections (Fleck *et al.* 2001). Head circumference-forage 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.

Behavioural and psychiatric characteristics

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

Neuropsychological characteristics

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

Available guidelines for behavioural assessment/ treatment/management

Frequent infections have been reported for individuals diagnosed with Coffin Siris syndrome. Respiratory infections may be related to hypotonia, poor sucking, and aspiration besides increased susceptibility. Consultation with feeding clinics, G tube placement, fundoplication, thickened infant feedings, and careful positioning post-feeding may be helpful. Early cardiac evaluation is suggested. Indications for surgical or medical treatment of congenital heart disease are managed the same as the general population. CNS imaging and GI evaluation may be considered. Renal ultrasound evaluation is suggested to investigate for infrequently reported renal abnormalities. Hernias and tear duct occlusion are treated as medically indicated.

Myringotomy and adenoidectomy when indicated may decrease recurrent otitis. Regular audiological screening for hearing loss is recommended because of frequent otitis media. Ophthalmologic evaluations are suggested because of reported vision problems. Paediatric dental evaluation is appropriate; primary teeth are potentially retained long term.

Useful Websites

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

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Judith Hiemenga, Srinivasan Sathyanarayanan & Joann Bodurtha, 2010 Revised Stewart Einfeld, 2015

Cornelia de Lange Syndrome

First description and alternative names

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

Incidence/prevalence

CdLS has an estimated prevalence of 1 in 50,000 live births (Beck & Fenger, 1985), although this is thought to be an underestimate, with more mildly affected individuals increasingly being identified.

Genetics

CdLS is caused by a deletion in the NIP-BL gene on chromosome 5 (locus 5p13) in 20% to 50% of cases (Gillis *et al.*, 2004; Krantz *et al.*, 2004; Miyake *et al.*, 2005; Tonkin *et al.*, 2004). Additional mutations on the SMC3 gene on chromosome 10 (Deardorff *et al.*, 2007), X linked SMC1a and HDAC8 genes (Deardorff *et al.*, 2012a; Musio *et al.*, 2006) and more recently identified RAD21 mutations (Deardorff *et al.*, 2012b) are reported to account for a smaller proportion of cases. All genes are involved in the structure and regulation of the cohesin complex which is crucial for neural maintenance and repair (Deardorff *et al.*, 2012b; Lui & Krantz 2009). It is probable that there are further unidentified mutations relevant to the cause of CdLS.

The NIP-BL gene is expressed in the developing skeleton and soft tissue of the limbs, hands, spinal column, face and head including the ear canal, the atrial and ventricular areas of the heart, oesophagus, trachea and lungs (Tonkin *et al.* 2004). Individuals with NIP-BL mutations show large variability in presentation but a larger proportion of these individuals appear to be more severely affected by the syndrome with more severe intellectual disability and limb abnormalities (Gillis *et al.* 2004; Bhuiyan *et al.* 2006). In contrast, mutations in SMC1A and SMC3 have currently been found to result in a milder presentation of the CdLS phenotype with less severe intellectual disability and fewer physical abnormalities (Deardorff *et al.* 2007).

Physical features and natural history

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

Little is known about the life expectancy of individuals with CdLS, although recent research studies have included participants aged 40 years and above (Cochran *et al.*, 2015; Moss *et al.*, 2009; Nelson *et al.*, 2013; Oliver *et al.*, 2011). Gastro-intestinal disorders associated with CdLS create an increased risk of early mortality due to aspiration, leading to pneumonia in some cases. Early assessment and intervention of gastro- intestinal difficulties is of utmost importance in individuals with CdLS.

Behavioural characteristics

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

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

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

An association between CdLS and autism spectrum like characteristics has been consistently reported (Basile et al., 2007; Berney et al., 1999; Bhyuian et al., 2006; Moss et al., 2008; Nakanishi et al., 2012; Oliver et al., 2011; Strivastava et al., 2014). This association with ASD is not solely accounted for by associated intellectual disability (Moss et al., 2008), although the profile of ASD characteristics appears to be different to that of idiopathic ASD (Moss et al., 2012; Moss et al, 2013). Extreme shyness and social anxiety are characteristic of many individuals with CdLS and an unusually high number of individuals with CdLS are reported to show characteristics of selective mutism. These difficulties may become more prominent with age (Goodban, 1993; Nelson et al., 2014; Richards et al., 2009).

There is emerging evidence indicating broad agerelated changes in CdLS including increased anxiety, low mood, social withdrawal and challenging behavior (Berney *et al.*, 1999; Cochran *et al.*, 2015; Nelson *et al.*, 2014; Oliver *et al.*, 2011; Sarimski, 1997) alongside the early onset of physical signs of ageing (Kline *et al.*, 2007). Biological processes that occur downstream from the genetic mutations responsible for CdLS have been implicated in these reported changes with age (Gimigliano *et al.*, 2012; Kline *et al.*, 2007).

Neuropsychological characteristics

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

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

Useful websites/associations for more information

- CdLS Foundation UK and Ireland: www.cdls.org.uk
- CdLS World: www.cdlsworld.org
- FIND resources: www.findresources.co.uk

Available guidelines for behavioural assessment/ treatment/management

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

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 5psyndrome 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 $5p_{15.1} - 5p_{15.3}$, using cytogenetic analysis (Niebuhr, 1978). More recent work has mapped specific critical areas within this region as being responsible for the expression of the core clinical features of the syndrome. For example, the characteristic high pitched 'cat-like' cry from which the syndrome derives its name has been mapped to the proximal part of 5p15.3, the speech delay to the distal part of 5p15.3 and severe intellectual impairment to 5p15.2 (Overhauser et al., 1994). This distinctive cry is considered the most prominent clinical diagnostic feature of the syndrome (Mainardi et al. 2006). Though relatively rare, CdCS represents the most common deletion syndrome in humans (Cornish et al, 2001).

Physical features and natural history

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

Behavioural characteristics

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

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

Down Syndrome

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

Incidence/prevalence

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

Genetics

The presence of a complete or partial third copy of human chromosome 21 (Hsa21) is the cause of DS. Partial copy should include all or part of the long arm of Hsa21. This excess of genetic material leads to a dysregulated expression of certain genes. The functional impact of these changes could be a direct result of the action of the proteins expressed in excess by the Hsa21 genes, or indirectly, through the proteins that they regulate. In any case the effect will be different according to the protein involved (Fillat, 2014). The nuclear compartments of trisomic cells undergo modifications of the chromatin environment influencing the overall transcriptome, and gene expression dysregulation domains may therefore contribute to some trisomy 21 phenotypes (Letourneau, 2014).

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

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

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

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

Physical features

Two types of phenotypes are observed in trisomy 21: those seen in every patient and those that occur only in a fraction of affected individuals. For example, cognitive impairment is present in all patients with DS, so as muscle hypotonia and Alzheimer disease neuropathology after 35 years (Antonarakis, 2004). Motor dysfunction is highly prevalent among individuals with DS, who exhibit clumsy sequences of movements, and poor control in programming motor sequences, their timing and force. Motor dysfunction in DS is accompanied by hyporeflexia and reduced muscular strength and tone (Dierrsen 2012) On the contrary, congenital heart defect occurs only in ~40% and atrioventricular canal in ~16% of patients. Duodenal stenosis/atresia, Hirschsprung disease and acute megakaryocytic leukemia occur 250-, 30- and 300-times more frequently, respectively, in patients with DS than in the general population. In addition, for any given phenotype there is considerable variability (severity) in expression. DS is also associated with an increased incidence of autoimmune disorders, such as autoimmune thyroiditis, primary sclerosing cholangitis, insulin dependent diabetes mellitus, celiac disease and alopecia areata. On the other hand, DS seems be protective against other conditions, such as multiple sclerosis, Crohn disease, neuroblastoma and the development of most solid tumors, which are rarely reported in association with DS.

Most adults with DS are of short stature (70%), with a characteristic facial appearance. The eyes seem to slope upwards and outwards as a result of alterations in the structure of the surrounding tissues. The nose has a wide bridge, and the head an unusual shape ("brachycephaly"). Protruding tongue is present in 45%. Limb abnormalities include a single transverse crease on the palm (85%), a large cleft between the first and second toes, and relatively short upper arms. People with DS are prone to disorders of the thyroid gland (15% develop hypothyroidism during childhood or adolescence). Ninety percent of all DS syndrome patients have a significant hearing loss, usually of the conductive type. Sight problems (44 - 71%) are common in DS of advanced age, and in a large percentage of the general population.

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

Life expectancy

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

Behavioural characteristics

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

17.6 % of individuals with DS aged less than 20 years have a psychiatric disorder, most frequently a disruptive behaviour disorder such as attention deficit hyperactivity disorder (6.1%), conduct/oppositional disorder (5.4%), or aggressive behaviour (6.5%). Twenty five % of adults with DS present a psychiatric disorder, most frequently a major depressive disorder (6.1%) or aggressive behaviour (6.1%). The dual diagnoses of DS and autism has gained much attention; although the association has always been appreciated, recent reports suggest a frequency as high as 7% and great delays in diagnosis. The stereotype of people with DS as happy, placid individuals with a gift for mimicry is not borne out by recent behavioural research. "Stubbornness" and obsessional features seem to be over-represented, and many people with DS react adversely in situations involving conflict.

No significant associations between age and the range or severity of any behavioural and emotional items were found in adult DS subjects without dementia. This suggested a more positive pattern for ageing adults with DS than has been previously described (Makary 2014). 129

Cognitive characteristics

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

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

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

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

Clinical signs and symptoms of Alzheimer's disease are noted in 75% of DS individuals over 60 years of age, and are most frequently seizures (58%), change in personality (46%), focal neurological signs (46%), apathy (36%), and loss of conversational skills (36%). Seizures appear to be associated with rapid cognitive decline in demented individuals with DS. In any adult for whom the diagnosis of Alzheimer's disease is being considered, a complete medical assessment should be done to detect any treatable disorders such as thyroid disease or depression.

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Foetal Alcohol Syndrome/ Alcohol Related Neurodevelopmental Disorder

First description and alternative names

FAS was first observed in Nantes by paediatrician 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 guidelines for those with neurodevelopmental disorders associated with prenatal alcohol exposure (NDDPAE 315.8) but without facial features. It requires features to be ruled into a diagnosis with other factors ruled out. This was the first time this was included in an international diagnostic manual.

Genetics and molecular biology

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

direct apoptotic damage, interneuruonal signaling deficits and damage to scaffolding proteins interfering with neural migration (18).

Incidence/ prevalence

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

Physical features and psychiatric characteristics

Characteristic facial features include short palpebral fissures, thin (flat) upper lip, flattened philtrum, flat midface. Growth retardation less than the 10th percentile for height and weight. Low birth weight for gestational age, decelerating weight over time not due to nutrition, disproportional low weight-toheight ratio. FAS has the classic facial features, ARND does not have the facial features. Gross and fine motor delays as in Developmental Coordination Disorder. Alcohol Related Birth Defects (ARBD) with eye, renal, cardiac and/or skeletal anomalies. FAS is the much less common, but most recognisable form of FASD (3,8,9,10).

Infants can demonstrate Primary Regulatory Disorders characterized by difficulties in tolerating environmental stimuli (i.e. habituation problems), coordinating basic motor movements (i.e. sucking), or interacting with parents or care-providers. Secondary psychiatric disorders appear due to environmental stressors such as PTSD after physical or sexual abuse, or Reactive Attachment Disorder of Infancy or Early Childhood related to separation from birth mother or multiple foster home placements. FASD increases the vulnerability to many common psychiatric disorders, such as ADHD, Mood Disorder, Anxiety Disorder, Alcohol or Drug Dependence, PDD, Autism and Schizoaffective Disorder. Personality Disorders seen are, Avoidant, Dependent, Schizoid, Passive/Aggressive and Borderline. Presence or absence of facial dysmorphology or growth features do not clinically correlate with the psychiatric presentation or structural brain damage in FASD (5,8, 11, and 12).

Neuropsychological Deficits

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

Brain structural abnormalities

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

Brain neurotransmitter and neurophysiological abnormalities

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

Available guidelines for behavioral assessment/ treatment/management strategies

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

Useful websites /associations for more information

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

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Raja Mukherjee, Kieran D O'Malley, May 2015

Fragile X Syndrome and Fragile X-associated Disorders

First described

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

Genetic aspects

There is sex-linked transmission because the *FMR1* gene is on the bottom end of the X chromosome (Xq27.3), so males are affected more severely than females. There is an expansion of the CGG repeat in the promotor region of the *FMR1* gene through the generations but progression to a full mutation (>200 CGG repeats) only occurs when it passes through a woman to the next generation. Ninety percent of males with a full mutation (>200 CGG repeats) have intellectual disability and the rest have learning and or emotional problems. When the CGG repeat in the promotor region of *FMR1* is greater than 200 there

is typically methylation of the FMR1 gene. However, those males with fragile X syndrome who are high functioning (IQ>70) are mosaic (some cells with the premutation (55 to 200 repeats) or partially/ completely unmethylated so that some FMRP is produced. In females with fragile X syndrome there is one X chromosome that is normal and the second X chromosome with the full mutation. In these females approximately 25% have intellectual disability and an additional 60% have learning difficulties particularly in math, attention and impulsivity in addition to emotional problems. The diagnosis of fragile X syndrome is made by FMR1 DNA testing. Cytogenetic studies may also show the fragile site in folate deficient media, but DNA studies are essential for diagnosis and to identify the CGG repeat expansion number.

Carriers have a premutation and are typically unaffected cognitively, although in approximately 10 to 20% intellectual disability or autism can occur. Carriers have an elevation of their FMR1 mRNA level of 2 to 8 times the normal range. This elevation of mRNA leads to a gain-of-function toxicity that can be associated with developmental delay at times but more commonly causes emotional difficulties, such as anxiety or depression in about 30 to 40%, primary ovarian insufficiency in 20% and neurological problems in a subgroup of aging male and female carriers. Additional medical problems that can occur in carriers includes hypertension, migraine headaches, insomnia, sleep apnea, hypothyroidism, gastroesophageal reflux, immune mediated problems, chronic fatigue, fibromyalgia and neuropathy. Additional neurological problems include autonomic dysfunction, intention tremor and ataxia, and the combination of these problems is called the fragile X-associated tremor ataxia syndrome (FXTAS). FXTAS occurs in approximately 40% of older male carriers and 8% to 16% of older female carriers. Brain atrophy and white matter disease are seen on MRI in those with FXTAS. The premutation disorders including FXTAS and the fragile X-associated primary ovarian insufficiency (FXPOI) typically do not occur in those with a full mutation because they usually do not have elevated FMR1 mRNA levels. However, a rare individual

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

Incidence/Prevalence

The allele frequency of the full mutation is 1 in 4000 to 6000 in the general population, however some individuals with the full mutation especially females do not have intellectual disability, although their learning difficulties and emotional problems still constitute fragile X syndrome. The premutation is more common and 1 in 130 – 250 females and 1 in 250 – 800 males in the general population have the premutation.

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

Physical

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

Life expectancy/Natural history

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

Behavioural characteristics

Intellectual impairment is variable and correlates with the molecular findings. Those with higher levels of FMRP, such as females and those with an unnmethylated full mutation or mosaic status (some cells with the premutation and some with the full mutation), will have a higher IQ. Verbal intelligence exceeds performance abilities in both affected males and non-learning disabled female carriers, although about 10% of patients will be non-verbal or will have very low verbal abilities. Particular difficulties with numeracy and visuospatial skills are common. The rate of intellectual development diminishes with age, particularly after puberty.

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

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

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

Treatment

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

Resources

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

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Randi Hagerman MD, August 2015

Klinefelter Syndrome (47,XXY)

First description and alternative names

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

Genetics and molecular biology

The vast majority of KS is due to the numerical chromosome aberration 47,XXY; some cases may have 46,XY/47,XXY mosaicism, or structurally abnormal X chromosomes. 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 paternal origin. The cause of the non-disjunction in not known.

Incidence/prevalence

The prevalence of 47,XXY is currently estimated at approximately 1/650 males. It is the most common chromosomal aneuploidy and the most common cause of male hypogonadism. It is frequently unrecognized. A large Danish study found that only 10% were recognized before puberty (Boisen et al, 2005) while a US study estimated that nearly 2/3 of cases remained undiagnosed (Abramsky & Chapple, 1997).

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 can vary widely. Prior to puberty physical differences can be minimal, including increased height and proportional leg length. These are thought likely related to dosage effects of the additional chromosome. Studies of testosterone levels during the perinatal period have had mixed results. During adolescence and adulthood physical features related to hypogonadism become more prominent, including small, firm testes; gynaecomastia, low testosterone levels and other abnormalities in endocrine response. Testicular histology may appear normal until puberty, but then demonstrates increasing hyalinization of the seminiferous tubules, disappearance of Sertoli cells, hyperplasia of Leydig cells, with loss of spermatogenesis. Islands of normal testicular tissue may remain in some individuals. Other areas of increased risk developing over adulthood include low energy and libido; osteoporosis; thromboembolic disease, obesity, and diabetes mellitus. Individuals with a mosaic form are usually less affected and may have normal fertility.

Behavioural and psychiatric characteristics

Individuals with 47,XXY are at increased risk for behavioural problems and psychiatric disorders. School aged children frequently show problems with anxiety and mood disorders, self-esteem, and socialization. Socialization problems frequently relate to inhibition and anxiety, and may become more pronounced during adolescence. Adults are at greater risk of depression related to low testosterone. 47,XXY individuals are considered to be at greater risk for psychosis. Brain imaging data has shown abnormal brain activation patterns and decreased brain volumes, particularly in frontal and temporal regions.

Neuropsychological characteristics

The effects on neurocognitive function widely, with many 47,XXY individuals having normal or above average cognitive capacity. On a group level mean IQ values fall within the normal to low normal range, and are depressed approximately 10 points below what would be expected based on siblings. Verbal ability may be more severely affected than nonverbal. 70 – 80% of 47,XXY individuals across several studies have had identified language problems. There may be difficulties with articulation, phonemic processing and word retrieval, in addition to more generally delayed expressive language and verbal fluency skills

Some studies have reported relatively more pronounced deficits in verbal IQ than performance

IQ, although this is not universal. Executive function capacities such as attention and impulse control may be impaired, although available studies are sparse. Several studies have reported impairments in both fine and gross motor skills. Cognitive features are thought to be a consequence of lack of fetal androgen.

Brain imaging may demonstrate significant changes in brain volumes but this does not clearly correlate with cognitive features. Underactivity of brain centres serving social cognition is evident.

Available guidelines for behavioural assessment/ treatment/management

Treatment trials are minimal and formal guidelines are not currently available. Current recommendations usually include neuropsychological assessment and early intervention for learning disorders or behavioural problems; monitoring endocrine status closely around puberty, institution of testosterone supplementation beginning in the pubertal period if levels are low, and monitoring of metabolic indices such as glucose tolerance.

Useful websites/associations for more information

- The American Association for Klinefelter Syndrome
 Information and Support (AAKSIS), www.aaksis.org
- Klinefelter's Syndrome Association UK, www.ksa-uk.co.uk
- KS & A (Knowledge, Support and Action), www.genetic.org

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Rhoshel K Lenroot, 2010 Revised: Stewart Einfeld, 2015

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 behaviour 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 behaviours. 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 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 overproduction 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 behavioural 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 behaviours 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 behaviour.

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).

Behavioural aspects

The behavioural phenotype of Lesch-Nyhan Disease, physical and emotional self-injury, including severe self-mutilation and aggressive behaviour, are generally involuntary in nature. The self-injurious behaviour is not under the patient's control nor does the patient desire it. These self-destructive behaviours 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 selfinjury 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 selfinjury include eye-poking, head banging, fingers in wheelchair spokes, and extension of arms in doorways. Emotional self injury, or outwardly directed aggressive behaviours, include hitting, kicking, headbutting, 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 behavioural manifestations of LND is multi-modal and should include: 1) judicious use of protective devices, 2) utilization of a behavioural technique commonly referred to as selective ignoring with redirection of activities, and 3) occasional use of medications.

The use of medications for treating the behavioural 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 behaviours', either motor or behavioural. Selective ignoring is a methodology that is designed to extinguish self-

destructive emotional or physical behaviour in the LND patient. It requires the caretaker to ignore such behaviour by the LND patient towards said caretaker so that the behaviour 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 behavioural 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 behaviour; 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 consequence of an unexplained neurological event. Certainly, as the accompanying clinical conditions are managed a longer life expectancy can be anticipated.

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Mowat-Wilson Syndrome

First description and alternative names

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

Incidence/prevalence

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

Genetics

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

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

Physical features and natural history

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

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

- Hypertelorism (wide set eyes)
- Deep set but large eyes
- Open mouth
- M shaped upper lip
- High arched palate
- Full or everted lower lip
- Fine, sparse hair
- Large uplifted ear lobes with a central depression

 arguably the most recognisable feature of
 MWS. The uplifted lobes remain with age but the
 depression becomes less marked.
- Flat feet and long, tapering fingers and toes are common, as is short stature.
Behavioural characteristics

A recent study (Evans *et al.*, 2012) reported that the behaviors associated with MWS include a very high rate of oral behaviors (in particular, chewing or 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/
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Updated by Liz Evans, Meredith Wilson and David Mowat, March 2014.

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 CBLassociated 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, 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, obsessivecompulsive disorders, and mood disorders. In adults, alexithymic traits seem to be present more often, as well as elevated levels of psychological and social distress (Verhoeven et al., 2008; Wingbermühle et al., 2009; 2012a). In comparison with women with Turner syndrome alexithymia and impairments in emotion recognition seem to be less pronounced (Roelofs et al., 2015).

Neuropsychological characteristics

Neuropsychological findings show intelligence scores in a wide range, with a mildly lowered average intelligence. Language and motor development are often delayed. In children, a highly variable cognitive profile has been found, with indications for impairments in visual processing and language development, weaknesses in memory function (inconclusive results mention problems in working memory, long-term verbal memory and immediate visual memory), mild deficits in selective and sustained attention, and suboptimal planning and organisational skills (Wingbermühle *et al.*, 2009; Alfieri *et al.*, 2011a,b; Pierpont *et al.*, 2010; 2013; 2015). These cognitive impairments may explain learning problems and an increased need for special education.

While extensive cognitive problems seem to be present in childhood, cognition in adults with NS is mainly characterised by a lowered speed of information processing. As described above, social cognitive functions (recognising and expressing emotions) may be impaired as well (Wingbermühle *et al.*, 2012b).

Available management guidelines

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

More information

For information on NS in OMIM, online database of human genes and genetic disorders, see: http://www.ncbi.nlm.nih.gov/omim/163950. For details on the Noonan syndrome support group, see: www.noonansyndrome.org.

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Renée Roelofs, Ellen Wingbermühle, Willem Verhoeven, Ineke van der Burgt, Jos Egger. June 2015

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

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

Prevalence

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

Genetics

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

Physical features

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

Behavioural characteristics

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

Cognitive characteristics

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

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Laurie Powis, Jane Waite and Chris Oliver (updated August, 2014)

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 seeminglynormal development in the early months of life following which there is a stagnation and regression of skills, beginning between 6 and 18 months of age ^[16, 17]. Recent retrospective studies have, however, shown that early development does not follow quite as typical a trajectory as supposed ^[18–20].

One of the first noticeable signs is a deceleration in head growth following which individuals with RTT demonstrate a loss of motor and communication skills, namely the loss of verbal language and purposeful hand use, accompanied by stereotypic hand movements (the handwashing/clapping noticed 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/eyetracking technologies can offer to individuals with RTT ^[26]. This has led to calls for the development of more objective eye gaze/eye-tracking based cognitive and receptive language assessments which can be used to validate parental reports [23, 27]

Differential Diagnosis

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

Historically, individuals with RTT were labelled as having an "autism spectrum disorder" (ASD)^[29], however, RTT was removed from the umbrella of ASD in the 2013 publication of DSM-V. While individuals with RTT pass through an autistic-like phase during regression, many regain social awareness and are especially noted for their sociability. Those with milder atypical forms of RTT (e.g. PSV) may continue to display features of ASD ^[30].

Management

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

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

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

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 latereplicating 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).

Behavioural 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 an unstable family (Netley 1986). The triple-X girls seem to be less able to cope in a stressful environment. After leaving school, most of the girls will find a job that reflects their non-verbal abilities (Robinson *et al.* 1990).

There seems to be a higher prevalence of psychiatric illness in general, especially in (mildly) mentally retarded cases, although we should be careful for there is 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 behavioural 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%20 Trisomy_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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Maarten Otter, 2015

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 multisystem nature of the disorder. The abbreviation TSC is used (Kwiatkowski *et al.*, 2010).

Genetics and Molecular Biology

Occurs as a spontaneous mutation in 70% of cases. Autosomal dominantly inherited in the remaining 30% of familial cases. The disorder is associated with mutations in one of two genes, TSC1 (on 9q34) or TSC2 (on 16p13.3). The TSC1 – 2 protein complex acts as an intracellular complex that links a number of intracellular signalling pathways including the AMPK pathway, the MAPK pathway and the PI₃K pathway. The TSC1 – 2 complex functions upstream of mTOR (mammalian Target Of Rapamycin). TSC mutations causes mTOR overactivation, leading to dysregulation of cell growth, proliferation and various other fundamental neurobiological processes (de Vries, 2010, Kwiatkowski et al., 2010). mTOR inhibitors have been approved by the FDA and EMA for the treatment of SEGA and angiomyolipoma associated with TSC. Clinical trials are underway of neurological and neuropsychiatric features of TSC (Curatolo, Moavero & de Vries, 2015)

Incidence/prevalence

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

Physical features and natural history

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

TSC is not an inevitably declining condition and any deterioration in physical, neurocognitive and behavioural profile should be further investigated. Life expectancy is influenced by the degree of physical and neurological involvement. Intractable seizures, brain tumours (SEGAs – subependymal giant cell astrocytomas) and renal failure secondary to angiomyolipomas may be causes of death.

Behavioural and psychiatric characteristics

Tuberous Sclerosis is associated with a wide range of behavioural, psychiatric, intellectual, academic, neuropsychological and psychosocial difficulties. The term TAND (TSC-Associated Neuropsychiatric Disorders) has been introduced as a summary term for all the bio-psycho-social aspects of the disorder (de Vries et al., 2015) and a TAND Checklist has been developed to aid clinical teams to screen for TAND (de Vries et al., 2015; Leclezio et al., 2015) TSC is associated with high rates of various disruptive behaviours, sleep problems and self-injurious behaviours. Developmental disorders including autism and autism spectrum disorders (ASD) in 40 - 50%, ADHD and attention-related disorders in 30 - 50% and intellectual disability in ~50% of individuals. TSC is one of the medical conditions most commonly associated with ASD. In adolescents and adults, very high rates of anxiety and mood-related disorders are reported. Psychotic disorders should raise the possibility of seizure-related psychopathology (de Vries et al., 2015; Kwiatkowski et al., 2010).

Neuropsychological characteristics

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

Available guidelines for behavioural assessment/ treatment/management

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

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

Targeted treatments using mTOR inhibitors are currently in clinical trials for the neurocognitive and neurodevelopmental features of TSC (Curatolo, Moavero & de Vries, 2015), but these are not at present recommended outside clinical trials. The diagnostic criteria and management guidelines for TSC were revised in 2012 and were published in 2013 (Northrup, Krueger *et al.*, 2013; Krueger, Northrup *et al.*, 2013).

Useful websites/associations for more information

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

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Petrus J de Vries, (updated 2015)

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

Behavioural and psychiatric characteristics

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

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

Neuropsychological characteristics

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

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

Available guidelines for behavioural assessment/ treatment/management

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 Care of girls and women with Turner syndrome:
 A guideline of the Turner Syndrome Study Group.
 J Clin Endocrinol Metab 92(1), 10 25.
- Gravholt C.H.(2009) "Turner know your body!"
 Editor –Published by Novo-Nordisk. Available as a free web-publication
 http://np.netpublicator.com/netpublication/
 n75088268

Useful websites/Associations for more information

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

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David H Skuse, 2014

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

First descriptions and alternative names

As is so often the case, chromosome 22q11.2 deletion syndrome (22q11.2DS) was first described independently by several perceptive clinicians back in the 1950s to 1970s. As these clinicians were experts within different specialties and therefore not focussing on the same medical problems, several constellations of features were described as separate conditions. The first person to describe children who most likely had 22q11.2DS was the otolaryngologist (i.e. ear nose and throat specialist) Eva Sedlačková who already in 1955 described children with hypernasal speech associated with a congenitally shortened soft palate, facial dysmorphology and intellectual impairments ^[1-4]. She was later to show that many of these children also had cardiac malformations and submucous clefts. Following Sedlačková's observations, other clinicians such as the endocrinologist Angelo DiGeorge (first English publication) described children with presentations of immunodeficiency, hypoparathyroidism and congenital heart disease [5], the physician Kinouchi described children with cardiac abnormalities and a typical face ^[6] and the speechlanguage 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 22g11.2DS it is the most common cause of syndromic palatal anomalies and also one of the most common causes of congenital heart defects and developmental delay ^[12]. It is also likely that the prevalence of the syndrome will rise as mortality decreases and reproductive fitness increases ^[13, 14]. The syndrome affects individuals of both sexes and of different ethnic background equally ^[15] although it has been suggested that there are sex differences in the expression of the syndrome [e.g., 16, 17].

Physical characteristics

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

Behavioural characteristics

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

Cognitive characteristics

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

Available guidelines for behavioural assessment/ treatment/management

- Practical guidelines for managing adults with 22q11.2 deletion syndrome ^[28]
- Practical guidelines for managing patients with 22q11.2 deletion syndrome ^[12]
- Towards a safety net for management of 22q11.2 deletion syndrome: guidelines for our times [29]
- Consensus Document on 22q11 Deletion Syndrome (22q11DS), MaxAppeal http://www.maxappeal.org.uk/downloads/ Consensus_Document_on_22q11_Deletion_ Syndrome.pdf

Useful websites/associations for more information

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

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Linda Campbell : June 2016

Williams Syndrome (also known as Williams-Beuren Syndrome)

First descriptions

The syndrome was first described by Williams, Barrett-Boyes and Lowe (1961) in four patients with supravalvular aortic stenosis (SVAS) in association with intellectual disability and an unusual facial appearance, and by Beuren, Apitz and Harmanz (1964). Black and Carter (1963) associated this characteristic facial appearance with that found in idiopathic infantile hypercalcaemia, a name initially used for the syndrome.

Genetic aspects

Williams syndrome is a genetically determined neurodevelopmental disorder caused by a heterozygous deletion of about 1.6 Mb (approx. 25 – 28 genes) on chromosome 7 (7q11.23). A deletion of the elastin gene (ELN) which occurs in >99% of individuals with WS) is associated with congenital heart disease and connective tissue abnormalities e.g. hernias and premature ageing of the skin. Several genes are also associated with the intellectual disabilities and cognitive deficits observed in WS, including GTF2l, LIMK1 and CYLN2 (see Skwerer & Tager-Flusberg, 2011, for review) Transmission is autosomal dominant and although most cases are de novo occurrences, some instances of parent to child transmission have been reported (Donnai & Karmiloff-Smith, 2000).

Incidence

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

Physical phenotype and natural history

The condition typically presents in infancy with difficulties in feeding, irritability, constipation and failure to thrive. The principal physical characteristics are well summarised by Donnai and Karmiloff-Smith (2000) and Skwerer and Tager-Flusberg (2011). The main features include: endocrine and growth abnormalities (pre- natal growth deficiency, failure to thrive in infancy, infantile hypercalcaemia, hypercalciuria, hypothyroidism, early puberty); cardiovascular disease (mainly supravalvular aortic stenosis) and renal abnormalities; connective tissue abnormalities (hoarse voice, inguinal/umbilical hernia, bowel/bladder diverticulae, rectal prolapse, joint and skin laxity) and distinctive facies (broad brow, short nose, long philtrum, bitemporal narrowness, periorbital fullness, full lips, wide mouth, malocclusion, small jaw and prominent earlobes).

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

Behavioural and psychological characteristics

Most individuals have moderate to mild intellectual impairments, although some may be of low-average to average IQ (Howlin, Elison, Udwin & Stinton, 2010; Porter & Coltheart, 2005). Visuo-spatial skills are often thought to be more severely impaired than language related skills, but, in fact, the cognitive profile of WS consists of a complex, and often subtle, pattern of peaks and valleys within each of these domains. Research into the nonverbal abilities of individuals with WS has highlighted particular deficits, e.g. number skills, planning, problem solving and spatial cognition. In contrast, face processing and some aspects of social cognition are seen as relative strengths. Within the verbal domain, auditory rote memory and receptive vocabulary are viewed as strengths, while spatial language (e.g. using spatial terminology), expressive vocabulary, syntax, semantics and grammatical comprehension are generally delayed (see Martens, Wilson & Reutens, 2008; Skwerer & Tager-Flusberg, 2011, for reviews).

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

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Further Information

www.williams-syndrome.org.uk

Patricia Howlin, 2014

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.

Behavioural and Neuropsychological characteristics

Attention deficits are observed in all subjects and adaptive behaviour levels were extremely limited. Children with WHS are more severely impacted [~ 65% are profoundly ID] in both general cognitive ability and overall adaptive behaviour 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 behaviour, 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

XYY Syndrome

First description and alternative names

XYY syndrome (47, XYY); YY Syndrome; Jacob's syndrome. The first case of XYY syndrome was reported as an incidental finding by Adam Sandberg and colleagues in 1961.

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. As it is typically not associated with marked phenotypic characteristics it is frequently underdetected. Most people with XYY are not diagnosed or diagnosed late.

Physical features and natural history

Physical phenotypic differences associated with XYY syndrome are usually mild. Hypertelorism, macrodontia, pes planus, central adiposity, clinodacty have been described (Bardsley, 2014, Lalatta, 2012). Speech delay is common. Delayed development of motor skills (such as sitting and walking), weak muscle tone (hypotonia), hand tremors or other involuntary movements (motor tics), and behavioral and emotional difficulties are also frequent. Boys have increased growth velocity during childhood, and adult height is usually increased approximately 7cm above what is expected . The tall stature is explained by the presence of additional copies of the SHOX gene (and possibly also other genes related to stature) in subjects with 47,XYY. A severe cystic acne may develop during adolescence. Asthma prevalence is significantly greater in XYY than in the general population (Bardsley, 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.

Behavioural and psychiatric characteristics

Individuals with XYY syndrome are at increased risk for behavioural problems and psychiatric disorders. There is a high rate of diagnosis of Attention Deficit Disorder, (more marked than in KS) and increased risk of problems with distractibility, impulsivity and 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. Prenatal diagnosis was associated with higher cognitive function and less likelihood of an ASD diagnosis (Ross, 2013). Further, expression of NLGN4Y , a gene that may be involved in synaptic function, is increased in boys with XYY vs. XY controls, and the level of expression correlates with more severe autism symptom score (Ross, 2015)

The prevalence of XYY syndrome among psychiatric patients is approximately **3 times** that of the general population prevalence. Psychiatric diagnoses are more common in boys diagnosed postnatally and are often the reason these boys had karyotype evaluation (Bardsley, 2013). Risk for psychosis is high in XYY men (Verri, 2008).

Jacob(1965) described that the XYY chromosome abnormality was about 20 times greater in frequency in the inmate population than in non-incarcerated population-.Recently a large study in persons with KS and 47,XYY covering all diagnosed individuals in Denmark demonstrates that persons with 47,XYY and KS are convicted of a number of specific offenses more frequently than the back, however the increased crime rate may be partly or fully mediated by poor socioeconomic conditions (Stockholm et al 2012).

Neuropsychological and neurological characteristics

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. XYY males underachieve despite their social background. Many boys require speech therapy and special education. Reading may be particularly affected. Educational performance may be more adversely affected than what would be expected based on IQ measures alone. Difficulties with attention and impulse control are frequently reported.

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

Neuroimaging

Male with XYY show increased total gray matter (GM) and white matter(WM) volume (Bryant,2012)-

Increased grey matter may be the result of reduced synaptic pruning, leading to altered synaptic function and perhaps increased seizure risk.(Bardsley, 2014).

Voxel MRI documented recently that boys with XYY have lesser WM in the frontal region combined with an increase in GM in the right insula, whereas increased WM and reduced GM were observed in the superior parietal, postcentral and occipital regions (Lepage, 2014). These results may be due to overexpression of genes either in the homologous region on the X and Y chromosome or alternatively of male specific genes located on the Y chromosome (ibidem)

Available guidelines for behavioural assessment/ treatment/management

Current recommendations usually include neuropsychological assessment and early intervention for learning disorders or behavioral problems.

Suggested Readings

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Annapia Verri, April 2016

Venues



2

Educational Day

The Educational Day sessions will be held in the Oranjerie at the Hortus Botanicus Leiden, Rapenburg 73, 2311 GJ Leiden



Conference Reception

The Conference Reception will be held in Burgerzaal at Leiden City Hall (Stadhuis), Stadhuisplein 1, 2311 EJ, Leiden (Entry at steps on Breestraat)



Research Symposium

The Research Symposium will be held in the **Theaterzaal** at **Scheltema, Scheltemaen Marktsteeg 1, 2312 CS Leiden**



Conference Dinner

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- SSBP Trustees and Executive Committee
Notes

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The 21st SSBP International Research Symposium Research Symposium 28th – 29th August 2018 • Educational Day 30th August 2018 • Melbourne, Australia

Translating knowledge of phenotype towards improved outcomes in neurodevelopmental disability

The International Society for Behavioural Phenotypes will be holding their 21st Research symposium in Melbourne on the 28th and 29th August 2018. The theme will be *Advancing the knowledge and translation of phenotypic understanding towards better outcomes for individuals with neuro-developmental disability.* The Education Day will be held in conjunction with the Neurodevelopmental Paediatric Society of Australia on the 30th August 2018.

Melbourne in Victoria, Australia has recently been voted one of the most liveable cities in the world and is a fabulous city for city and country (Wine region) escapes. Come and stay for a while.

Registration and abstract submission open: 12th March 2018 Deadline for online abstract submission: 22nd April 2018 Deadline for discounted early bird registration: 16th July 2018

For further information see www.ssbpconference.org



The SSBP is a charity registered in England (No. 1013849

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