

19th SSBP International Research Symposium

Early/late-life adversities and behavioural phenotypes: insight into metabolomics, genomics and connectomics

Programme Book 9th – 11th September 2016 • Siena, Italy



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20th SSBP International Research Symposium will be held in Leiden, the Netherlands, in September 2017

Registration and abstract submission open: 1st April 2017 Deadline for online abstract submission: 31st May 2017 Deadline for discounted early bird registration: 1st August 2017 Educational Day: 14th September 2017 Research Symposium: 15th – 16th September 2017

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The Society for the Study of Behavioural Phenotypes

9th – 11th September 2016

The 19th SSBP International Research Symposium

Early/late-life adversities and behavioural phenotypes:

insight into metabolomics, genomics and connectomics

Siena, Italy



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Welcome to Siena





This is the welcome ("Siena open you the hearth") that the City of Siena offers to all people arriving in the Middle Ages into the town from the "Porta Camollia", the North Door that was the Francigena way from the North Europe to Rome.

With the same feeling, we welcome all participants to this congress dedicated to "genomic, metabolomics and connectomic influence of human behavior in normal and pathologic conditions".

Siena is an old University with more than 700 years of history and we hope that your stay in Siena will be very fruitful for all scientific, relational and touristic and cultural aspects.

Welcome and enjoy Siena!

Antonio Federico University of Siena



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Siena Conference Organisers

Professor Antonio Federico

Professor Antonio Federico, is a full professor of Neurology at University of Siena since 1990. Here he was director of the Department of Neurological Sciences and of Postgraduate School of Neurology. He is Director of PhD Programme on Neurological and Behavioural Sciences, at University of Siena, and professor in the Tuscan PhD Program on Neurosciences in Florence. He was President of the Italian Society of Neurology and at present he is Chairman of the Scientific Committee of the European Academy of Neurology and Board Member. He is also the Italian representative in the UEMS (Union Europeen Medicin Specialists, section Neurology) and WFN (World Federation

of Neurology). He obtained laurea honoris causa in Medicine and Pharmacy, University Carol Davila, Bucharest. Currently he is vice-Rector of the University of Siena. He published more that 500 articles in the most important international Journal and he is in the editorial board of many of them. He is Editor in Chief of Neurological Sciences, Edited Springer. His main research interest is Neurometabolic, neurogenetic and neurodegenerative diseases of the central, peripheralnervous system and muscle.

Dr Annapia Verri

Annapia Verri was educated in Pavia. She took a degree cum laude in Medicine at Pavia University in 1970 and than moved to Milan University, where she obtained under the guide of Professor Guareschi Cazzullo a postgraduate degree in Child Neurology and Psychiatry in 1974. A second postgraduate degree in Neurology was obtained in 1976 at the Pavia University, with Professor Paolo Pinelli. She was assistant at the C Mondino Neurological Institute and consultant in the Pediatric Department headed by Professor GR Burgio, where she followed children with chronic diseases, and oncohematologic

conditions, before and after hematological stem cells transplantation. In 1990 she was entitled with a research project funded by Health Ministry about quality of life of families with intellectually disabled (ID) members. After that, she started a second project about causes of ID, in collaboration with Prof. Antonio Federico, and Pavia and Milan genetists. From 1990 to 2015 she was head of the Laboratory for Cognitive-behavioral Psychology at the C Mondino Institute and appointed professor of psychology of disability. Currently she is consultant in the same Institute and member of the committee of Unitask (Society for Klinefelter Syndrome). She was a contributor to different editions of the pediatrics Textbook." Pediatria Essenziale" (last edition 2012) and has published over a hundred articles.





Scientific Committee

Antonio Federico (Chairman)

Full professor of neurology Director Unit Clinical Neurology and Neurometabolic Diseases Medical School, University of Siena, Italy

Annapia Verri (Co-Chair)

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Leopold Curfs

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Alexander Von Gontard (Saarland)

Chair for Child and Adolescent Psychiatry Saarland University Director of the Department of Child and Adolescent Psychiatry Saarland University Hospital

The SSBP

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

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

The SSBP Executive Committee :

Life President	<i>Dr Martin Bax</i> (London) (m.bax@imperial.ac.uk)	
President	Professor Patricia Howlin (London) (patricia.howlin@kcl.ac.uk)	
Chairman	Professor Petrus de Vries (Cape Town) (petrus.devries@uct.ac.za)	
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	Global – Pat Howlin (London) (patricia.howlin@kcl.ac.uk)	
Administrator	Elizabeth Walmsley (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	17t ^h International
2015	London, UK	18 th International

Forthcoming Meetings of the SSBP

2016	Siena, Italy	19 th International
2017	Leiden, The Netherlands	20 th 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

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

2016 Tom Oppé Distinguished Lecturer: Dr André Strydom

Dr André Strydom (MRCPsych, MSc, PhD) is a Reader in Intellectual Disabilities at UCL's Faculty of Brain Sciences (Division of Psychiatry) and a Consultant Psychiatrist in Developmental Disabilities. His research is focused on the epidemiology and genetic aetiology of mental disorders in adults with neurodevelopmental conditions, and the development and evaluation of interventions to reduce associated morbidity. He is particularly interested in ageing-related conditions such as dementia in adults with

Intellectual Disability and Down syndrome. Dr Strydom is the chief investigator of the LonDownS consortium which is exploring the neurobiological aetiology of Alzheimer's disease in Down syndrome. He is also involved in developing and evaluating complex interventions in adults with ID such as health checks for people with intellectual disabilities in primary care.



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Patricia Howlin and the Patricia Howlin Prize Lecture



Patricia Howlin

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

Pat Howlin Prize Lecture: Area of Research:

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

Eligibility of applicants:

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

Award Procedure:

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

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

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

Patricia Howlin Lecturers

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

2015 Pat Howlin Lecturer: Dr Shruti Garg

Institute of Brain, Behaviour & Mental Health, University of Manchester..

Shruti Garg studied medicine at the University of Mumbai, India. She trained in psychiatry in Oxford and Leeds, and in child psychiatry in Manchester. After completing her training, she was appointed as a clinical senior lecturer in Translational Child Psychiatry at the University of Manchester and Honorary Consultant in Child & Adolescent Psychiatry at the Royal Manchester Children's Hospital. Her research is focused on identifying causes of autism by studying syndromic models particularly



Neurofibromatosis type 1 and other Rasopathies. Her research is supported by awards from the Manchester Biomedical Research Council, Action for Medical research and the Newlife Foundation.

Sponsors

The SSBP is extremely grateful to the following organisations for their sponsorship of SSBP 2016 in Siena.

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19th International SSBP Research Symposium

Keynote Speaker Profiles

(in order of presentation)

Dr Sakkubai Naidu

Dr Naidu is a Prof of Neurology and Pediatrics at the Johns Hopkins School of medicine She is also a Pediatric Neurologist in the Hugo Moser Research Institute at the Kennedy Krieger Institute, Baltimore MD.

She has been involved in Rett syndrome research since 1985 when Hugo Moser initiated the first Rett syndrome meeting in the USA.

Her work also includes the study of leukodystrophies.



Professor Alessandra Renieri

Alessandra Renieri was born in 1965 and graduated in Medicine in 1989 at the University of Siena. She has a PhD in Human Genetics and an MS in Medical Genetics. She is currently Full Professor of Medical Genetics at the School of Medicine of the University of Siena. She is the director of the Medical Genetics Unit of the General Hospital of Siena. Since 2001 she has coordinated as director of the Medical Genetics Unit more than 10,000 genetic counselling.

Her main research interest has always been the study of the genetic basis of rare diseases, including Rett syndrome and other conditions with intellectual disabilities (ID), Alport syndrome, retinoblastoma and other rare cancers. She identified two new genes disease: FACL4 gene for X-linked ID and FOXG1 gene for Rett syndrome. Her laboratory was among the first in Italy to introduce the technology of array-CGH and of Next Generation Sequencing. Since 2002 she directs the Genetic Biobank of Siena (GBS, http://www.biobank.unisi.it), one of the few in Italy certified SIGU-CERT and ISO9001. GBS is the Italian Partner of BBMRI (Biobanking and Biomolecular Resources Research Infrastructure), member of EuroBioBank and RD-Connect. Her laboratory is a referral center for Rett in Italy and, since 2009 Alessandra Renieri coordinates the international Rett Networked Database (www.rettdatabasenetwork.org).

Research activities of Prof. Alessandra Renieri are substantiated by 196 original publications in international journals with a total IF of 874,543. She is author of 3 book chapters, 8 reviews made by request, and one N&V in Nat Genet. She has an H-index of 35, with a number of total citations of 4,605 and has published 129 articles in the last 10 years.

Professor Dafin Muresanu

Professor of Neurology, Senior Neurologist, Chairman of the Neurosciences Department, Faculty of Medicine, University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca, President of the Romanian Society of Neurology, President of the Society for the Study of Neuroprotection and Neuroplasticity (SSNN), member of the Academy of Medical Sciences, Romania, secretary of its Cluj Branch. He is also member of 13 scientific international societies (being member of the American Neurological Association (ANA) -Fellow of ANA (FANA) since 2012) and 7 national ones, being part of the executive board of most of these societies.



Professor Dafin F. Muresanu is a specialist in Leadership and Management of Research and Health Care Systems (specialization in Management and Leadership, Arthur Anderson Institute, Illinois, USA, 1998 and several international courses and training stages in Neurology, research, management and leadership). Professor Dafin F. Muresanu is coordinator in international educational programs of European Master (i.e. European Master in Stroke Medicine, University of Krems), organizer and co-organizer of many educational projects: European and international schools and courses (International School of Neurology, European Stroke Organisation summer School, Danubian Neurological Society Teaching Courses, Seminars - Department of Neurosciences, European Teaching Courses on Neurorehabilitation) and scientific events: congresses, conferences, symposia (International Congresses of the Society for the Study of Neuroprotection and Neuroplasticity (SSNN), International Association of Neurorestoratology (IANR) & Global College for Neuroprotection and Neurology (CONy), Danube Society Neurology Congresses, World Academy for Multidisciplinary Neurotraumatolgy (AMN) Congresses, Congresses of European Society for Clinical Neuropharmacology, European Congresses of Neurorehabilitation).

His activity includes involvement in many national and international clinical studies and research projects, over 350 scientific participations as "invited speaker" in national and international scientific events, a significant portfolio of scientific articles (134 papers indexed on Web of Science-ISI, H-index: 15) as well as contributions in monographs and books published by prestigious international publishing houses. Prof. Dr. Dafin F. Muresanu has been honoured with: the Academy of Romanian Scientists, "Carol Davila Award for Medical Sciences / 2011", for the contribution to the Neurosurgery book "Tratat de Neurochirurgie" (vol.2), Editura Medicala, Bucuresti, 2011; the Faculty of Medicine, University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca "Octavian Fodor Award" for the best scientific activity of the year 2010 and the 2009 Romanian Academy "Gheorghe Marinescu Award" for advanced contributions in Neuroprotection and Neuroplasticity.

Dr Massimo Filippi

Massimo Filippi was born in Monza on 31/08/1961, took his Graduation in Medicine in 1986 and his Post-Degree Graduation in Neurology in 1990 and in Neurophysiology in 1994. He is currently Full Professor of Neurology at Vita-Salute San Raffaele University, Milan, Italy; Director of the "BrainMap" (Human BRAin IN-vivo MAPping with Neuroimaging) Scientific Interdepartmental Program and Director of the Neuroimaging Research Unit (NRU), Department of Neurology, Institute of Experimental Neurology, Scientific Institute San Raffaele, Milan.



His research activity has always been focused on the definition of the mechanisms leading to progressive accumulation of irreversible physical disability and cognitive impairment in various neurological conditions. As Director of the NRU, he coordinated the MRI acquisition and analysis of several large-scale international MRI-monitored trials of MS. He is member of various national and international Scientific Societies and Boards and, in some of them, he covered or is covering institutional roles. Prof. Filippi is author of over 900 papers published on peer-reviewed journals, he edited several international volumes; he is member of the Editorial Boards of many international scientific journals and acts as a reviewer on a regular basis for several others in the neurology and neuroimaging fields, and for many Governmental Organizations and private Foundations. He is

Editor-in-Chief of the Journal of Neurology. He has been and is very often requested as speaker and/or chairman in national and international neurological congresses. He is also Visiting Professor at the University of Belgrade (2006) and at Heinrich-Heine University Duesseldorf (2008). In 2001, Prof. Filippi was awarded the "Rita Levi Montalcini" Prize for his outstanding contributions to the study of MS.

Dr Antonio Giorgio

Antonio Giorgio is Neurologist and Researcher at the UOSA Experimental Neurology and Quantitative Neuroimaging Laboratory (both directed by Prof. Nicola De Stefano), Department of Medicine, Surgery and Neuroscience, University of Siena and Azienda Ospedaliera Universitaria Senese.

He graduated in Medicine in 1999 and specialized in Neurology in 2004 at the University of Siena. He was visiting PhD student at the Centre for Functional Magnetic Resonance

Imaging of the Brain (FMRIB), University of Oxford, from 2006 to 2009 and obtained the Doctorate in Applied Neurological Sciences at the University of Siena in 2010. From 2010 he is teacher at the course of Advanced Neurology, Medical Biotechnology degree, University of Siena.

In 2013 he received from the Italian Society of Neurology the Award for the best scientific publication on the clinical research in multiple sclerosis.

In 2014 he was awarded from the Italian Ministry of Health as Principal Investigator for the Young Researcher project. His main scientific interest is in the application of various brain magnetic resonance imaging methods (lesion mapping and quantification, volumetry, magnetization transfer imaging, magnetic resonance spectroscopy, diffusion tensor imaging and tractography, functional connectivity) to clinical neurology and in particular to multiple sclerosis. He is author of 70 articles published on international peer-reviewed journals, 4 book chapters on multiple sclerosis. He was invited speaker in 17 national conferences, courses, seminars and workshops. He gave 18 platform presentations at international and national scientific conferences, congresses and workshops. He serves as reviewer for 18 international scientific journals. He was tutor for 15 Italian and foreign medical students and neurologists.

Professor Stefano Cappa

Stefano F. Cappa is a neurologist and cognitive neuroscientist with an extensive experience in the development and application of behavioural testing and advanced neuroimaging to neurodegenerative disorders. His present position is professor of neuroscience at the IUSS institute in Pavia and scientific director of the IRCCS Centro S. Giovanni di Dio, Fatebenefratelli, Brescia, Italy. His main areas of expertise are disorders of language, memory and social cognition. He is the past president of the Federation of European Neuropsychological Societies and president of the Italian Neurological Society for the study of dementia (SINDEM). He has published more than 300 papers in refereed journals.



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Professor David Zee

Dr. Zee began his scientific career at The Johns Hopkins University in 1965 as a medical student and then completed his neurology residency there. For half a century, Dr. Zee has been a member of the Johns Hopkins Medical community, with a special interest in vision and eye movements, cerebellar function and motor learning, and vestibular disorders. His research combines studies in experimental models of disease, and in human patients and normal subjects, all aimed at understanding brain function and neurological disease.

He has been Professor since 1985. Among his accomplishments has been coauthor of

the textbook, The Neurology of Eye Movements with Dr. R. John Leigh, with the fifth edition published in 2015. He is an author on more than 400 publications. Among his honors he received the Ottorino Rossi prize from the University of Pavia in Italy, the Koetser Foundation for Brain Research Prize in Zurich, the Hallpike-Nylen Medal of the Barany Society in Uppsala Sweden and he gave the Lord Adrian lecture at Cambridge University in England. His academic pursuits include several short research sabbaticals in Paris and in Marseilles, and a 22 year, close collaboration with the departments of Otolaryngology and Neurology at the University of Siena in Italy.

Dr. Andreas Chiocchetti

Dr. Andreas G. Chiocchetti graduated in Genetics and Biotechnology at the University of Salzburg, Austria, and joined the German Cancer Research Center in Heidelberg, Germany for his PhD studies in 2008. There, he studied die genetic architecture of Autism Spectrum Disoders and investigated the functional impact of autism associated genetic variants of ribosomal proteins at experimental and systems-network level.

Since October 2008 he is head of the Molecular Genetics Laboratory of the Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy at the University Hospital in Frankfurt am Main, Germany and is active member in the Autism Genome

Project and the Autism Sequencing Consortium. During 2014/15, he was a visiting scientist at the University of California, Los Angeles, investigating prenatal neuronal development and differentiation in primary human tissue at transcriptomic level to further understand how genetic variants act within a network to modulate a complex clinical phenotype.

Currently, he continues this work in Frankfurt focusing on the system-wide characterization of genes and genetic variants in the context of neuropsychiatric disorders and neuronal differentiation. This year the University of Frankfurt awarded him the biannual price for early career investigators in medical sciences donated by the Dr. Paul and Cilli Weill Foundation for his work on the genetic and functional analysis of the autism risk gene CNTNAP₂.





Professor Ernesto Burgio

Professor Ernesto Burgio graduated in Medicine and Surgery (1977) at the University of Pavia - Italy (Final score 110/110 cum laude) and specialised in Pediatrics (1980) at the University of Florence-Italy (Final score 30 / 30 cum laude). He is the President of ISDE Scientific Committee (International Society of Doctors for Environment) since 2010; Coordinator of the Scientific Committee ISDE Italy since 2008; Member of the Environmental Health Committee of SIP (Italian Society of Pediatrics) 2009-2013; Scientific Coordinator of the Environmental Health Committee of the FIMP (Federazione Italiana Medici Pediatri); Member of the Scientific Committee of ARTAC (Association pour

la Recherche Therapeutique anti-Cancéreuse, Paris) since 2010; Member of ENSSER (European Network of Scientists for Social and Environmental Responsibility) 2009-2010; Member of EPH (Environment & Public Health) Panel - European Society for Research and Prevention on Environment and Health (European SREH) 2010-2013; Member of the Scientific Committee of ECERI (European Cancer and Environmental Research Institute, Bruxelles) since 2012.

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.

Dr Harris received his M.D. degree from George Washington University School of Medicine and completed pediatric, Neurodevelopmental Pediatrics, General Psychiatry and Child Psychiatry residencies at Johns Hopkins University. He served on the DSM-5 committee that wrote the new definitions of the Neurodevelopmental Disorders and was lead author for criteria for IDD and SMD. He is the recipient of the George Tarjan Award (AACAP), Agnes Purcell McGavin Award (APA), Leon Eisenberg Award (Harvard Medical School) and the Frank J. Menolascino Award (APA) awarded for contributions to the field of Intellectual Developmental Disorders and Developmental Disabilities.





Dr Shahid Zaman

I am an affiliated lecturer and consultant psychiatrist at the Department of Psychiatry, University of Cambridge and Cambridgeshire and Peterborough Foundation NHS Trust. I am interested in understanding the natural history of Alzheimer's disease in people with Down's syndrome, which is a population at a very high risk of developing the disease. We aim to develop means to detect the disease before it clinically manifests by developing measures to predict those who would most benefit from primary prevention interventions. In collaboration with colleagues, we use a number of techniques, including magnetic resonance imaging and spectroscopy, positron emission tomography, electroencephalography and blood analysis to achieve this.

Dr Sophie van Rijn

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Sophie van Rijn has a PhD in Neuropsychology, and for the last 14 years her line of research has focused on the neurocognitive and behavioral phenotype of individuals with 47,XXY and 47,XXX. She is currently appointed as an Associate Professor at the department of Clinical Child and Adolescent Studies at Leiden University, where she has set up a research lab for the study of neurodevelopmental risks in children with these conditions. Using techniques from the field of neuroscience, such as neurocognition, neuroimaging, eyetracking, and neurophysiological parameters, she has contributed to the understanding of neurodevelopmental mechanisms driving risk for social problems

and psychopathology in children and adults with an extra X chromosome. As the Scientific Director of the national TRIXY expert center in the Netherlands, her aim is to integrate knowledge from scientific research with clinical care.

Professor Randi Hagerman

Randi Hagerman, MD, FAAP is a Distinguished Professor of Pediatrics at the University of California Davis Medical Center and Director of the Fragile X Research and Treatment Center at the MIND Institute and holds an Endowed Chair in Fragile X Research. She and her husband and team have published extensively regarding fragile X premutation disorders including the first description of FXTAS in 2001. She co-founded the National Fragile X Foundation in 1984 and has been involved in targeted treatments for fragile X syndrome and FXTAS for several years. Dr Hagerman has written over 300 peer-reviewed articles and several books on fragile X. Her most recent book is R. Hagerman and R

Hendren (eds) (2014) Treatment of Neurodevelopmental Disorders: Targeting Neurobiological Mechanisms published by Oxford University Press.







Conference Programme

Venue: Aula Magna, Rectorate of the University of Siena

Educational Day

Day One: Friday 9 th September 2016		
13:00-14:00	Registration	
14:00–14:15	Welcome from the SSBP and the Conference Organisers	
Friday Sessio	n 1: Update on Rett Syndrome (Chair: Leopold Curfs, Maastricht)	
14:15–14:55	Keynote 1: Sakkubai Naidu – Rett syndrome: from Discovery to Treatment.	
14:55–15:35	Keynote 2: Alessandra Renieri – Dissecting the genomic complexity underlying Rett spectrum disorders.	
15:35–15:45	General Discussion	
15:45 - 16:00	Refreshments	
Friday Sessio (Chair: Anto	n 2: Brain connectomics in behavioural phenotypes and neurodegenerative diseases onio Federico, Siena; Maria Dotti, Siena)	
16:00–16:30	Keynote 3: <i>Dafin Muresanu</i> – From molecules to large scale networks in brain protection and recovery after stroke.	
16:30–17:00	Keynote 4: <i>Massimo Filippi</i> – The "vegetarian brain": behind our dietary habits and ethical beliefs	
17:00–17:30	Keynote 5: Antonio Giorgio – Brain connectivity during development of the human brain.	
17:30–17:45	Refreshments	
17.45–18.15	Keynote 6: <i>Stefano Cappa</i> – Brain connectivity in neurodegenerative diseases – from phenotype to proteinopathies	
18:15–18:30	General Discussion	
18:30-19:00	Keynote 7: David Zee – Eye movements in neurodegenerative diseases	
19:00–19:15	Discussion	
19:15–20:30	Welcome Reception. University of Siena	

Research Symposium

Day Two: Saturday 10 th September 2016		
07:30-08:30	Registration	
08:30	Welcome from the SSBP and the Conference organisers	
Session I: Aut	ism and related neurodevelopmental disorders. (Chair: Patricia Howlin, London)	
08:30–09:00	Keynote 8: Andreas Chiocchetti – Autism Spectrum Disorders: Complex disorders with a complex genetic architecture	
09:00–10:00	Talk 9: <i>Terje Nærland</i> – Autism Symptoms and Gender Ratios Across Different Disorders, - The Role of Aetiology and Degree of Intellectual Disability	
	Talk 10: <i>Stephan Huijbregts</i> – Executive Functioning and the Hypodopaminergic State in Adults with Phenylketonuria	
	Talk 11: <i>Friederike Ehrhart</i> – Biological Pathway Analysis of Rett Syndrome Transcriptomics Data from Published Studies.	
10:00–10:20	Talk 12: Pat Howlin Prize Lecture: <i>Shruti Garg</i> – A Randomised Controlled Trial of Simvastatin in Neurofibromatosis Type 1 Autism	
10:20–10:30	Short Break	
10:30–11:00	Keynote 13: Ernesto Burgio – The rise of Neurodevelopmental Disorders (NDS): from genetics to epigenetics	
11:00–11:30	Refreshments	
Session II : Behavioural phenotypes in genetic neurometabolic disorders. (Chairs: Petrus de Vries, Stellenbosch; Randi Hagerman, California)		
11:30–12:00	Keynote 14: James Harris – Lesch Nyhan Syndrome - A Quarter Century of Progress	
12:00–12:40	Talk 15: <i>Petrus de Vries</i> – Adjunctive Everolimus Therapy for the Treatment of Refractory Seizures in Patients with Tuberous Sclerosis Complex	
	Talk 16: <i>Stacey Bissell</i> – Comparing Difficult Behaviours in Younger and Older Children with Tuberous Sclerosis Complex	
12:40–13:10	Keynote 17: Antonio Federico – Genetic and metabolic consequences in brain function and dysfunctions and phenotypic presentations	
12,10 14.20	Lunch	
13:10-14:30	Poster viewing	

Day Two: Saturday 10th September 2016

Session III: Down Syndrome and other behavioural phenotypes (Chair: Stewart Einfeld, Sydney)	
14:30–15:00	Keynote 18: Shahid Zaman – Approaches to evaluating the earliest manifestations of Alzheimer's disease in Down syndrome
15:00–17:00	Talk 19: <i>Inês Pote</i> – The Developmental Trajectory of Glutamate in the Human Brain: From Neonatal Life to Early Infancy
	Talk 20: Rosalyn Hithersay – Executive Functioning in Adults with Down Syndrome: An Exploration of Frontal Cortical Activity using Functional Near Infrared Spectroscopy
	Talk 21: Jessica Penhallow – Long Term Predictors of Quality of Life for Adults with Genetic Syndromes
	Talk 22: Anne Basset – The Neurocognitive Profile of 22q11.2 Deletion Syndrome and Implications for Functioning
	Talk 23: <i>Kate Woodcock</i> – Towards Better Measurement of Cognitive Control in Individuals with Genetic Neurodevelopmental Disorders
	Talk 24: <i>Kate Wolfe</i> – Characterisation of Rare Pathogenic Cnvs At 2q13 And 4p16.3 in Intellectual Disabilities and Co-Morbid Psychiatric Disorders
17:00–17:15	Refreshments
17:15–18:00	Keynote 25: Tom Oppé Distinguished Lecture: André Strydom – Cognitive Decline and Dementia in Down Syndrome
18:30	Visit to the City Hall and Museum, walk to the Piazza Duomo, the Santa Maria della Scala Hospital and Museum, visit to a Contrada
20:30	Gala Dinner

Day Three: Sunday 11th September 2016

Registration before 1st session - for new arrivals only Session IV: X-related disorders and other behavioural phenotypes: (Chairs: Flora Tassone, California; Annapia Verri, Pavia) Keynote 26: Sophie Van Rijn - Social, Emotional and Behavioral problems in individuals 08:30-09:15 with an extra X chromosome (47,XXX and 47,XXY): A focus on underlying neurocognitive mechanisms 09:15-10:15 Talk 27: Paul Hagerman – The Pathogenic Mechanism(s) of Fragile X-Associated Tremor/Ataxia Syndrome Talk 28: Flora Tassone – Altered Molecular Phenotypes in 22q Deletion Syndrome Talk 29: Carole Samango-Sprouse – Large Prospective Study of the Neurodevelopmental Outcome in Prenatally Diagnosed Males with 47,XXY A short presentation: SSBP 20th International Research Symposium 2017, in Leiden, 10:15-10:30 the Netherlands 10:30-11:15 SSBP AGM and Award Ceremony 11:15–11:45 Refreshments 11:45-12:15 Keynote 30: Randi Hagerman – Gene Dosage Effects at the 16p11.2 Genomic Region Conference Conclusions. Antonio Federico, Petrus de Vries 12:15-12:30 12:30 **Close of Research Symposium**

Abstracts for Educational day:

(in order of presentation)

KEYNOTE 1: Rett Syndrome: From Discovery to Treatment.

Naidu S.

Hugo Moser Research Institute, Kennedy Krieger Institute, Johns Hopkins Medical Institutions, Baltimore MD. USA

The discovery by Andreas Rett of Rett syndrome as a distinct clinical entity, more common in females, led to an active pursuit for a genetic basis. The subsequent identification of mutations in the X-linked MECP2 gene distinguished this syndrome, with microcephaly, seizures, respiratory anomalies and autonomic dysfunction, from other conditions with intellectual disabilities, in a definitive manner. The discovery of the genetic defect brought attention to the wide clinical variability. Study of the human disease led to recognition of the basis for the primary brain involvement and the associated systemic abnormalities. These changes were then found to be replicated in the murine models with various mutations in MECP2 that were then observed and experimented on.

Studies at the Kennedy Krieger Institute were initiated by Hugo Moser in 1985. At the Kennedy Krieger Institute, we have studied both humans and animal models with MECP2 mutations. We have performed neuroimaging, gastroenterology evaluations, bone mineral densities, PET scans, olfactory neuron biopsies, and ocular expression of MECP2 to understand the disease. Based on our observation of age related increase in glutamate/NMDA receptor increases in humans and mice with Rett syndrome we initiated a clinical trial in younger children using dextromethorphan, which is an NMDA antagonist. The results of this trial and above studies will be presented to show the advances made at our Institute to understand the biological basis of Rett syndrome.

Keywords: Phenotypic variability; immature neurons; increased CSF glutamate/NMDA receptors; preserved vision; neuroimaging; treatment.

KEYNOTE 2: Dissecting the Genomic Complexity Underlying the Rett Spectrum Disorders.

Renieri A.

Genetica Medica, Azienda ospedaliera Universitaria Senese, Siena, Italy Genetica Medica, Universita' di Siena, Siena, Italy

Rett syndrome is a neurodevelopmental disorder ranging from the classic MECP2-related form to a FOXG1related congenital variant. The FOXG1-related variant shows a shorter perinatal normal period and more severe microcephaly. In order to unveil the complex nature of this monogenic disorder we have previously performed whole exome sequencing on two pairs of phenotypically discordant MECP2-mutated sisters. Such analysis unmasked the role of oxidative stress, muscle impairment and intellectual disability and/or autism genes in the onset of the classic, more severe Rett phenotype and the key function of immune system modulation in driving toward a milder phenotype.

Given the presence of shared signs/symptoms between MECP2 and FOXG1-related phenotypes and the overlapping function of these genes, we also hypothesized a common molecular mechanism behind RTT phenotypic spectrum. Therefore, to better investigate this hypothesis, taking advantage of the breakthrough genetic reprogramming technology, we investigated morphological and RNA-seq transcriptome changes on iPSC-derived neurons from several patients for each disease-related gene. Such analysis led to the identification of a unique neuronal morphological phenotype related to a cumulative effect of axon guidance signal disruption, cell migration, adhesion and GABA-ergic circuit impairment. Transcriptome analysis also revealed a shared up-regulation of enzymes that regulate the acetylation of tubulin and microtubules-related genes, MAP2 and MAPT, and the resulting reduction in acetylated α -tubulin was demonstrated by Western blot. These findings strongly support the role of modifier genes in Rett syndrome phenotypic features and the involvement of shared pathways in the pathomechanism of the whole Rett phenotypic spectrum, providing the opportunity for a combined therapeutic approach.

Keywords: Rett spectrum disorders, modifier genes, iPSC-derived neurons, axon guidance, GABAergic circuits, extracellular matrix

KEYNOTE 3: From Molecules to Large Scale Networks in Brain Protection and Recovery After Stroke

Muresanu D. F.

Chairman Department of Clinical Neurosciences 'Iuliu Hatieganu' University of Medicine and Pharmacy, Cluj-Napoca, Romania

This presentation will focus on the principles of homeostatic mechanism that modulates all three levels of brain's organization: cellular/molecular, local circuitry and network level.

The concept of endogenous neuromodulation refers to the brain's capacity to balance anti-correlated processes, such as pro-survival signaling mechanisms versus pro-death signaling mechanisms at the cellular and molecular level, long-term potentiation versus long-term depression at the local circuit level, synchronization versus desynchronization at the dynamic network level. Every level in turn comprises several sublevels, each of which is characterized by a multitude of anti-correlated processes.

Brain networks strength is determined by the capacity of neuronal groups to fire synchronously, modulated by synaptic communication and by resting membrane potential, which are determined by the expression of genes tightly linked to neurotransmitters and ion channels activity. This crosstalk between genetic and neuronal networks is staring to be increasingly more studied in neurological and psychiatrically pathologies; recent data showed that stroke imbalances the miRNA-genes network leading to alteration of the processes regulated by targetgenes such as MAPK signaling pathway, with important consequences upon inflammation, oxidative stress and neuroprotection .

Recent data support the idea of inter-correlation between molecular/cellular level and network level showed that an ischemic lesion, even of small dimensions, may trigger a progressive molecular disorganization of axons, even at a distance from the infarct core, possibly incriminating mechanisms being widespread inflammation and neuro-vascular unit (NVU) dysfunction.

The presentation will also highlight on the mechanism that underlies the pathobiology of post-stroke cognitive impairment that affects the relationships among the brain's levels: inter-hemispheric functional connectivity, interconnectivity of behavioral processes, integration and segregation of functional networks and network efficiency.

KEYNOTE 4: The "Vegetarian Brain": Behind our Dietary Habits and Ethical Beliefs

Filippi M.

Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

One of the hallmarks of social cognition in humans is the ability to understand conspecifics as beings like oneself, with intentional and mental lives like one's own. Such abilities rely on the activity of several brain regions, which are also critically involved in the processing of emotions. This suggests that the merging between emotions and feelings experienced by oneself and those perceived in other individuals may be a key ingredient of social understanding, and it may play a major role in promoting empathy, prosocial behaviours, and moral norms. Empathic responses can be modulated by the subjective attitude held toward suffering individuals, as well as by personal experience. The majority of studies attempting to characterize empathy-related responses did not separate empathy towards humans from that towards animals. A fMRI investigation hypothesized that vegetarians and vegans, who made their feeding choice for ethical reasons, might show brain responses to conditions of suffering involving humans or animals different from omnivores. Compared to omnivores, vegetarians and vegans recruited different areas of the empathy network during observation of negative affective pictures of human beings and, more critically, animals. Substantial differences between vegetarians and vegans were also found, with a prevailing activity of the anterior cingulum in vegetarians and the inferior frontal gyrus (IFG) in vegans. Another investigation tested the hypothesis that the representation of mouth actions within different brain regions might differ among individuals with different dietary habits and ethical beliefs during processing of actions performed by other humans and other species (monkey and pig). Compared to omnivores, vegetarians and vegans had increased functional connectivity between regions of the frontoparietal and temporal lobes vs the cerebellum during observation of mouth actions performed by humans and animals. During human mouth actions, increased amygdala activity in vegetarians and vegans was found. More critically, vegetarians recruited the right middle frontal gyrus and insula, which are involved in social mirroring, whereas vegans activated the IFG and middle temporal gyrus, which are part of the mirror neuron system. Monkey mouth actions triggered language network activity in both groups, which might be due to the attempt to decode monkey mouth gesture, whereas pig mouth actions activated empathy-related regions, including the anterior cingulum. These results support the role of the action observation-execution matching system in social cognition, which enables us to interact not only with our conspecifics, but also with species in phylogenetic proximity to humans.

Keywords: Action observation-execution matching system, animals, humans, mouth action, empathy, vegetarians, vegans.

KEYNOTE 5: Brain Connectivity During Development

Giorgio A.

Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy

The development of the human brain is mediated by a complex interplay of a series of neurogenetical and histological events (neuronal proliferation and migration, cell aggregation, axonal growth, dendritic arborization, synaptic pruning and myelinization) and the environment. Our brain is a complex neuroarchitecture of structurally and functionally interconnected regions, which are continuously shaped through infancy, childhood and adolescence in order to efficiently perform complex cognitive abilities. Understanding the development of the human brain organization is critical for gaining insight into the function of the adult brain and for characterizing the basis of neurodevelopment disorders.

Nowadays, with the advances in neuroimaging technology, especially non-invasive magnetic resonance imaging (MRI) tools, it is possible to indirectly assess the events occurring in the developing brain. In particular, diffusion tensor imaging (DTI) tractography, new tissue segmentation and registration methods allow us to map the changes in structural connectivity (SC) of the developing brain. Moreover, the newest technologies such as functional connectivity (FC) derived from resting functional MRI (fMRI), which is believed to be a proxy for neuronal communication across brain networks, provides the opportunity to study the developing brain beyond single anatomical regions.

Voxelwise DTI studies have consistently demonstrated increasing connectivity from childhood into adolescence especially along the superior longitudinal fascicle and this showed significant association with better verbal working memory and verbal fluency. Recent studies have shown that various key principles underlie the development of FC across brain: (a) although the global functional architecture of the brain is already in place by the end of the first decade of life, FC continues to undergo relevant reshaping during late childhood and adolescence, leading to a shift from a local to a more distributed pattern, with the formation of a more hierarchical organization and functional hubs on the cortex; (b) increased segregation of functional networks, with a shift from short-range connections in children to stronger and more distinct long-range connections in adults; (c) reconfiguration of basal ganglia-cortical FC; (d) pruning of over-connectivity, which rewires connections at synaptic level, also operates at brain network level; (e) reconfiguration of FC within and between spatially independent brain networks; (f) changes in local circuit properties (i.e., balance between neural excitation and inhibition) may also play a role in altering global brain FC. All these FC changes are probably the foundation for the refinement of information processing occurring in the adolescent brain.

Some findings suggest that SC develop earlier than FC, the former serving as the anatomical backbone, the latter demonstrating a more clear-cut maturational change.

Although emerging findings provide a relevant insight into the development of the human brain, important methodological and scientific issues remain to be addressed, including the contribution of hormonal and genetic influences.

KEYNOTE 6: Brain Connectivity in Neurodegenerative Diseases – from Phenotype to Proteinopathies

Cappa, S.

Institute for Advanced Study (IUSS), Pavia, and IRCCS Centro S. Giovanni di Dio, Fatebenefratelli, Brescia, Italy

The in vivo connectivity approach applied to the analysis of imaging data is providing new insights into the investigation of the phenotypes of neurodegenerative disorders (ND). The clinical manifestations of ND are characterized by disorders of cognition, behavior and motor function, which can be assessed in depth taking advantage of the developments in the fields of cognitive and system neuroscience. The traditional anatomoclinical approach, as extended to imaging investigation, is based on the correlation between quantitative parameters, such as test performance, and structural and functional indices derived from quantitative imaging data collected using magnetic resonance imaging or positron emission tomography. Connectivity approaches, assessing in vivo the functional integration of brain activity, provide a complementary approach to functional segregation data. This array of methodologies, which can be applied to functional data collected both during active tasks or at rest, has already provided important results related several crucial issues on ND research. These include the assessment of early changes in prodromal Alzheimer's disease, the correlates of social cognition dysfunction in the early stages of fronto-temporal lobar degeneration, or the metabolic signature of dementia with Lewy bodies. The results are encouraging, and suggest the possibility that connectivity data may represent an intermediate biomarker between clinical symptoms and the underlying molecular pathology.

Keywords: Functional connectivity; resting state; fronto-temporal dementia; neuroimaging

KEYNOTE 7: Eye Movements in Neurodegenerative Disorders

Zee, D.

Professor of Neurology, Johns Hopkins University, School of Medicine, Baltimore, MD 21287 USA

Eye movements and saccades in particular have become essential clinical tools for bedside diagnosis of neurodegenerative disorders. Furthermore measurement and quantification of the properties of saccades have become important biomarkers of disease progression and response to therapy. We will distinguish among disorders of saccade initiation (latency), saccade speed, saccade accuracy, inappropriate saccades, and higher level disorders related to apraxia. Here we review the behavioural characteristics of saccade, their functional anatomy, and characteristic disorders related to cerebellar, brainstem, basal ganglia and cerebral hemisphere disorders. We will discuss using saccades as indicators of disorders of attention, prediction, and decision making.

Keywords: Saccades, cerebellum, Frontal and Parietal Eye fields, Superior colliculus, Eye movements

Abstracts for Research Symposium Oral Presentations (in order of presentation)

KEYNOTE 8: Autism Spectrum Disorders: Complex Disorders with a Complex Genetic Architecture

Chiocchetti, A.

Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Autism Research and Intervention Center of Excellence Frankfurt, J.W. Goethe-University Frankfurt am Main, Germany

Autism Spectrum Disorders (ASD) encompass a set of pervasive neurodevelopmental conditions defined by impairments in social interaction and communication, and by repetitive/stereotypical behaviours. ASD is often accompanied by atypical or absent language development, and presents with a wide clinical and etiological heterogeneity. Twin studies estimate the heritability of the disorders to be around 64%-91%. However, the complex underlying genetic architecture of ASD remains poorly understood. Overall, 3-10% of the estimated heritability can be explained by rare and/or de-novo variants, while common variants explain up to 49%, thus leaving a large proportion of heritability unaccounted for. Currently, genetic aberrations known to cause syndromes with ASD-like phenotypes (e.g. fragile-X-syndrome) have been identified in less than 10% of cases. For all other cases, ASD is most likely to result from complex interactions between common and rare genetic variants, as well as environmental risk factors. Findings from genome wide association studies investigating common variants converge in suggesting that identified candidate-genes for ASD are implicated in neuronal development and differentiation, synaptic function or chromatin remodelling. A similar observation was made for genes hit by rare or non-transmitted 'de-novo' copy number variations (CNVs), or 'loss of function' variants in ASD individuals. Notably, the most recent sequencing studies estimate the ASD phenotype to be influenced by variants in as many as 400 to 1000 different genes. This increase in the number of identified genes might partially be explained by the increase in sample size within and across studies. Moreover, it has been shown that different ASD subgroups (e.g. ASD comorbid for intellectual disability, ID) have a unique (i.e. distinct) genetic architecture. For example, while ASD with ID was associated with a higher prevalence for loss of function mutations, ASD with normal to high IQ predominately involved common variants. There is also a remarkable overlap between ASD associated genes and genes implicated in ASD-related traits within the general population (e.g. language development or social interaction), i.e. independent of affection status. The current challenge for genetic research is thus to (1) identify and characterize the heritability of ASD-related (endo)phenotypes, (2) identify rare and common genetic variants influencing the complex genetic architecture of these ASD related phenotypes, and (3) to elucidate the underlying pathological mechanisms in ASD. This talk will therefore focus on current genetic insights in the aetiology of ASD, recent findings of genotype-phenotype association studies, and future challenges for elucidating the genetics of ASD phenotypes.

Keywords: Clinical and genetic heterogeneity; heritability; syndromal, rare and common genetic variants; genetic and phenotypic subgroups.

TALK 9: Autism Symptoms and Gender Ratios Across Different Disorders – The Role of Aetiology and Degree of Intellectual Disability

Nærland T.N.^{1,2}, Andersen Bakke K.A.B.¹, Nag H.E.N.³, Solbakken G.S.^{4,5}, Ørstavik K. Ø⁵, Andreassen O.A.A.¹ and Howlin P.H.⁶

¹ University Hospital of Oslo, NevSom, Norwegian Centre of Expertise for Neurodevelopmental Disorders and Hypersomnias.

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⁴Vestre Viken Health trust, Dept of Neurology.

⁵ University Hospital of Oslo, Dept of Neurology.

⁶ Kings College, Institute of Psychiatry.

Background: A substantial amount of research has shown significantly higher rates of autistic type of problems in boys compared to girls. This male bias in the prevalence of autism spectrum disorders (ASD) is not fully understood and gender ratios differ substantially from study to study and with degree of intellectual disability (ID). The different biological aetiologies underlying the autistic problems are probably also relevant, even when degree of intellectual impairment is controlled for.

Methods: At the Norwegian Centre of Expertise for Neurodevelopmental Disorders, we have collected information about severity of autism symptoms (SCQ or AQ) and ID (ICD-10 F7x code or IQ) in Down syndrome (N=170), Angelman syndrome (N=51), Myotonic Dystrophy (N=45), Fragile X (N=23), Smith Magenis syndrome (N=12), Cornelia de Lange syndrome (N=8) and in a group of "œidiopathic ASD" (N=480). In this combined dataset, we will investigate how gender is related to ASD symptoms in different biological subpopulations. Further we will explore how much variation in gender ratios seems to be explained by degree of intellectual impairment.

Results: Data analysis is in progress. Preliminary analyses show considerable syndrome variation in gender ratios; from about 5:1 >ASD cut-off in the idiopathic group to no gender differences in the Angelman sample. The potential effects of aetiology on the differences in gender ratios when level of ID is controlled for will be presented at the meeting.

Conclusion: Cross syndrome comparison of autism-like problems may contribute to the understanding of the male bias in ASD.

Keywords: Gender, Autism symptoms, Angelman, Down, CdLS, Smith Magenins, Myotonic Dystophy, Fragile X.

TALK 10: Executive Functioning and the Hypodopaminergic State in Adults with Phenylketonuria

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Background: Phenylketonuria (PKU) is an inborn error of metabolism characterized by the inability to convert the amino acid phenylalanine (Phe) into tyrosine, a precursor of the neurotransmitter dopamine. Executive functioning (EF-)deficits in PKU are thought to be related to dopamine deficiencies in the brain. Evidence to date is however indirect, linking plasma Phe-levels to EF in PKU. The present study for the first time assessed correlations between EF and central and peripheral dopaminergic markers in adults with PKU.

Methods: Fifty-seven PKU patients (mean age 27.7, SD 6.0 years) and 57 healthy controls (HC, mean age 25.7, SD 5.6 years) performed computerized EF-tasks, measuring inhibitory control, working memory and cognitive flexibility, and completed the Barratt Impulsiveness Scale. Historical pPhe-levels were collected. Current plasma levels of homovanillic acid (pHVA), the main dopamine metabolite, and pPhe were assessed on the study day. *In vivo* striatal D_{2/3} receptor (D_{2/3}R) availability, as an index for synaptic dopamine concentrations, was measured using single photon emission computed tomography and the radioligand [¹²³I]IBZM in a subsample of 15 adults with PKU and 12 HC.

Results: PKU-patients performed worse than HCs on tasks when working memory or inhibitory control were required, and reported higher levels of impulsivity in daily life. EF was related to pPhe- levels during childhood (o-12 years), but not to current pPhe-levels. $D_{2/3}R$ availability was higher in PKU compared to HC (p = 0.032), and pHVA levels were lower in PKU (p < .001). $D_{2/3}R$ availability correlated positively with error rate during the working memory and cognitive flexibility tasks (r = 0.49, p = 0.037 and r = 0.57, p = 0.016, respectively), and with reported impulsivity (r = 0.72, p = 0.003).

Conclusion: The neuropsychological profile of adults with PKU is characterized by EF-deficits. Our study demonstrates a direct link between EF-impairments and a hypodopaminergic state in PKU.

Keywords: phenylketonuria, phenylalanine, dopamine, executive functioning.

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TALK 11: Biological Pathway Analysis of Rett Syndrome Transcriptomics Data from Published Studies.

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Background: Rett syndrome is a rare disease but one of the most abundant neurological disorders in females. Rett females generally suffer from mental retardation and motoric abnormalities, and often develop breathing problems, scoliosis or epilepsy which leads to a reduced life span. The cause for Rett syndrome is one single gene mutated: the methyl-CpG-binding-protein-2 (MECP2). MECP2 is a central signaling gene which influences neuronal function in many ways. The cause and the clinical phenotype of Rett are well known but the biological processes leading from mutation to phenotype are not yet elucidated.

Methods: Pathway and network analysis allows the combination of molecular data from experiments with existing knowledge. WikiPathways is an example of a repository of biological pathways used in such analysis. It allows community curation and development of pathways diagrams such as molecular mechanisms involved in rare disease. Specialized bioinformatics tools are necessary for visualization, analysis and interpretation e.g. PathVisio and Cytoscape. The strength of this approach is that hypothesis-free studies, starting from the full pathway collection, and targeted analysis can be performed to find how the biological network is affected by the experiment (or disease).

Results: We created a pathway describing the functions of MECP₂ that are affected in Rett syndrome. We investigated which biological pathways are altered in a published transcriptomics dataset of individuals with an impaired MECP₂ gene.

Conclusions: From these preliminary results we conclude that application of pathway and network analysis is going to improve the understanding of the different phenotypes in Rett syndrome.

Keywords: Rett syndrome, pathway analysis, omics data, rare diseases, systems biology

PAT HOWLIN PRIZE LECTURE – TALK 12: A Randomised Controlled Trial of Simvastatin in Neurofibromatosis Type 1 Autism

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Background: Neurofibromatosis Type 1 (NF1) is a single gene neurodevelopmental disorder with a known neurobiology. Our studies have shown a high prevalence of autism within NF1, making it therefore a potentially important single-gene model of autism development. Statins specifically target the pathogenic pathway in NF1 and achieve phenotypic rescue in mouse models. Statin trials to date in older children and adolescents have shown mixed phenotypic effects, but evidence of normalisation of functional connectivity on brain imaging. Study of statins earlier in development to target autism as well as NF1 symptoms is therefore indicated. **Methods:** Single site, 2 parallel group, triple (clinician/patient/assessor) blinded early phase randomised trial of simvastatin (n=15) vs placebo (n=15) in a dose escalation design. Outcomes: functional imaging parameters; blinded parent and clinician rated autism and behavioural symptoms; patient acceptability and adverse effects - measured at baseline, 4 weeks and at 12 week primary endpoint. Analysis will test feasibility and acceptability of treatment and imaging; along with signals of intervention effect on imaging parameters and symptom measures. **Results:** The trial has been completed and the results will be presented at the conference. This will be the first experimental trial of statin treatment in young children with combined NF1 and autism. It will include detailed functional brain imagining. It will provide internationally innovative proof of concept, feasibility, and early phase data in this area - providing the platform for design of a later phase 3 trial.

Conclusion: Understanding the effect of statin in this form of symptomatic autism has outstanding potential to give insight into pathogenesis and intervention for the autism phenotype generally.

Keywords: NF1, Autism.

KEYNOTE 13: The Rise of Neurodevelopmental Disorders (NDS): from Genetics to Epigenetics

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The NDS are a set of conditions with onset in the early stages of development and variously associated with cognitive and psychiatric dysfunction. The high heritability of these conditions argues in favor of a genetic component. On the other hand, the impressive increase of NDS calls into question environmental factors and epigenetic mechanisms. From a neurobiological point of view autism involves early brain overgrowth and dysfunction that may be related to abnormal laminar development and cortical disorganization of neurons, in prefrontal and temporal cortical areas, where social, emotional, communication and language functions are located. Interestingly, the same genes that might have facilitated the evolutionary expansion of the human brain are now implicated with autism severity. The genetic variants associated with NDS may explain only a tiny proportion of the estimated heritability and hundreds of loci are involved. New exome sequencing (NGS) technology has identified many rare variants present only in children and, at least in some cases, in the parental gametes (de novo mutations). These variants frequently do not relate to coding sequences, and there is no evident gene in their vicinity. For some of them regulatory functions have been recognized; for many others only hypothesized. It is also relevant that among the sequences more frequently associated, those coding for microRNAs, influencing the regulation of many genes, are emerging. Also the appreciation of a major role in regulation mainly involves epigenetics, which is by definition the science that studies the mechanisms of regulation of gene expression and, above all, of the genome programming in the early stages of life (fetal programming). Many rare genetic variants, overlap among different disorders such as schizophrenia, bipolar disorder, ASD, and ID, which makes necessary a "spectrum approach", connecting previously disjointed conditions. Moreover, the same de novo genetic variants, first of all the CNVs, are implicated in more than one psychiatric disorder and involve the same chromosomal loci often increasing the risk in both states, deletion or duplication.

Keywords: epigenetics; fetal programming; CNVs.

KEYNOTE 14: Lesch Nyhan Syndrome A Quarter Century of Progress

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Lesch-Nyhan Syndrome (LNS) is a rare, X-linked recessive neurogenetic syndrome caused by deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGprt), an essential enzyme in the purine salvage pathway; self injury is the most prominent feature of the behavioural phenotype. Since the 1990's there have been significant advances in understanding pathways from genes to cognition and complex behavior and the extended behavioral phenotype by investigating the spectrum of HPRT deficiency in classic LNS (less than 1%) and it variants (from 2% to to 20% enzyme). The methods involved in these studies include, gene sequencing, measurement of HPRT and GPRT levels in skin fibroblasts, measures of metabolites in CSF, studies of brain structure with MRI, studies of brain chemistry using spectroscopy (MRS), studies of the presynaptic dopamine receptor binding in vivo with PET, measurement of white matter tracks (DTI), neuropsychological testing and IQ testing, standardized neurological examination, systematic assessment of behavior and personality (NEO) and Deep Brain Stimulation. The **results** of these studies document correlations of genetic mutations with symptom severity, correlation of guanine recycling with the LND/LNV behavioural phenotype (dystonic movement disorder, patterns of neurocognitive impairment, and behavioural features), structural differences on MRI versus controls, reductions of NAA in basal ganglia and dorsolateral and orbitofrontal prefrontal cortex using MRS, reductions in presynaptic dopamine transporter binding with PET imaging in both classic and variant cases, correlations of dystonia scores with PET measures, characterization of a neurocognitive phenotype that is consistent across classical and variant cases, a behavioral profile for variant cases that is intermittent between control subjects and classic cases, a characteristic personality profile on the NEo, reduction or elimination of self-injury using Deep Brain Stimulation targeted to the Gpi. To conclude, studies of LNS, the first syndrome with an identified behavioural phenotype, over the past 25 years document that the benefits of applied basic and clinical neuroscience findings in understanding the neurobiological underpinning of the behavioural and neurocognitive phenotype of LNS and its variants. These studies demonstrate the advantages of studying the dose response effects of the HGprt enzyme in both classical LNS and its variants in examining the extended phenotype.

Keywords: Lesch Nyhan Syndrome, self-injurious behavior, behavioural phenotype, HGprt enzyme, Positron emission tomography, Deep Brain Stimulation, neuropsychological testing

TALK 15: Adjunctive Everolimus Therapy for the Treatment of Refractory Seizures in Patients with Tuberous Sclerosis Complex

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Background: Everolimus is approved for the treatment of renal angiomyolipoma and subependymal giant cell astrocytoma in tuberous sclerosis complex (TSC). Here we present results from the first randomised, placebocontrolled, phase 3 adjunctive study of everolimus for the treatment of refractory seizures associated with TSC (EXIST-3, NCT01713946).

Methods: Following an 8-week baseline phase, patients aged 1-65 years with TSC and refractory seizures on 1-3 antiepileptic drugs were randomised to everolimus 3-7 (low trough [LT]) or 9-15 ng/mL (high trough [HT]) targeted trough concentration (Cmin) ranges or placebo, and treated in an 18-week core phase (6-week titration + 12-week maintenance). The primary endpoints were change from baseline in average weekly frequency of TSC seizures during the maintenance period of the core phase expressed as response rate (RR; ≥50% reduction) and percentage reduction.

Results: Overall, 366 patients were randomised to everolimus LT (n=117), HT (n=130), or placebo (n=119). The median percentage reduction in TSC seizures was significantly greater with everolimus LT (29.3%, P=0.003) and HT (39.6%, P<0.001) vs placebo (14.9%). RR was also significantly greater with everolimus LT (28.2%, P=0.008) and HT (40%, P<0.001) vs placebo (15.1%). The most frequent (\geq 10%) all-grade adverse events (AEs) reported with everolimus LT/HT vs placebo included stomatitis (28.2%/30.8% vs 3.4%), diarrhoea (17.1%/21.5% vs 5%), mouth ulceration (23.9%/21.5% vs 4.2%), nasopharyngitis (13.7%/16.2% vs 16%), upper respiratory tract infection (12.8%/15.4% vs 12.6%), aphthous ulcer (4.3%/14.6% vs 1.7%), and pyrexia (19.7%/13.8% vs 5%). Discontinuations due to AEs (5.1%/3.1% vs 1.7%) were low.

Conclusion: Adjunctive everolimus therapy demonstrated a clinically and statistically significant reduction in seizure frequency with a tolerable safety profile compared with placebo in patients with TSC.

Keywords: TSC, EXIST-3, everolimus, seizures.

TALK 16: Comparing Difficult Behaviours in Younger and Older Children with Tuberous Sclerosis Complex

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Background: Tuberous sclerosis complex (TSC) is a genetic disorder associated with benign tumour growth, epilepsy, and intellectual disability. A number of difficult behaviours are also associated with the condition including self-injury, aggression, impulsivity and repetitive behaviours. Although there is evidence that some of these behaviours can manifest in childhood, relatively little is known about the rates of these behaviours in very young children. Therefore the aim of this study was to compare the behavioural profiles of younger (1 to 4 years) and older children (5 to 11 years) with TSC.

Methods: Caregivers of younger (n = 21; M age = 2.81, SD = 1.05) and older children (n = 21; M age = 9.22, SD = 1.06) with TSC completed questionnaire measures of adaptive functioning and behaviours including challenging behaviour, impulsivity, overactivity, and repetitive behaviours.

Results: As anticipated, younger children had lower adaptive behaviour scores and lower verbal ability than older children with TSC. Although younger children had higher rates of self-injury (62%) and aggression (76%) than older children with TSC (self-injury: 33%; aggression: 48%), these differences were not statistically significant. However, younger children did have significantly higher rates of overactivity and stereotyped behaviour than the older children, whereas older children had higher scores on the insistence on sameness repetitive behaviour subscale.

Conclusion: These findings suggest that behaviours such as self-injury and aggression are evident in very early childhood in TSC. While rates of these behaviours did not differ significantly between younger and older children, there may be changes in the profile of repetitive behaviours between younger and older children with TSC. A planned follow-up study of the younger TSC group will help to determine longitudinal change in these behaviours.

Keywords: Tuberous sclerosis complex, difficult behaviours, self-injury, aggression, repetitive behaviours, children.

KEYNOTE 17: Genetic and Metabolic Consequences in Brain Functions and Dysfunctions and Phenotypic Presentations

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Garrod in the Cronian Lecture, in 1908 reports that "... the factors which confer upon us our predispositions to and immunities from the various mishaps which are spoken of as diseases, are inherent in our very chemical structure; and even in the molecular groupings which confer upon us our individualities, and which went to the making of the chromosomes from which we sprang."

The development of neurogenetic and metabolic approaches to neurological disorders lead to the explanation of the pathogenesis of many conditions with primary nervous system perturbancies related to dysfunctions of lysosomes, peroxysomes, mitochondria, etc.

Collecting genetic, biochemical and clinical data, we can consider that several metabolic changes will influence mainly neuronal cells (GM2 and GM1 gangliosidosis, Niemann Pick type C disease, ceroid lipofuscinosis, etc), others glial cells (Metachromatic leucodystrophy, Krabbe disease, adrenoleukodystrophy, etc) or endothelial cells and in early presentations the metabolic change may influence brain development.

The specific vulnerability to the different brain cells and also of the different brain system (cortical, subcortical, basal nuclei, cerebellum, etc.) will be discussed in relationship to the clinical presentation.

The findings that a same enzyme deficiency may result in different age of onset with a very heterogeneous clinical presentation, will be analyzed in relationship to genotype or to other factors able to influence the phenotypic expression.

In consequence of this, we can consider that a genetic regulation of brain functions is present, reflecting on the metabolic equilibrium and that the pathologic conditions that the nature offers may be useful for understanding the role of these substances in brain functions and dysfunctions.

We will here discuss several human genetic metabolic diseases in order to understand the role of different substances during brain development and aging and consequences of their dysregulation.

We will select metabolic disorders involving:

- Storage material for a primary lysosomal dysfunction of glycoconjugate metabolism
- Plasma membrane lipid changes due to peroxisomal impairment
- Cell cholesterol trafficking disturbancies
- Energy metabolism mitochondrial impairment
- Neurotransmitters or membrane permeability changes
- Chromosomal instability and DNA repair functions
- Cell nutrients deficiency
- Small vessel diseases

All conditions may have early (more severe) and late (less severe) presentations in relationship to the amount of residual enzyme activity able to differently influence the metabolic pathways. We will also discuss the possibility that the primary metabolic and genetic disturbance may differently involve neuronal or glial cell functions as well as specific neuroaxonal pathways leading to the different phenotypic presentations.

All these data on brain biochemical and genetic abnormalities in human model of diseases are also important for better understanding the physiologic role of all these molecules during normal brain functions.

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KEYNOTE 18: Approaches to Evaluating the Earliest Manifestations of Alzheimer's Disease in Down Syndrome

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The successful management of medical co-morbidities associated with the Down syndrome phenotype has resulted in a dramatic improvement in longevity. However, with ageing people with DS now face the likelihood of being diagnosed Alzheimer's disease (AD) about 15 to 20 years earlier than the general non-DS population. By the age of forty almost all people with DS will have the neuropathological feature of AD even in the absence of significant signs and symptoms of AD. The central determinant is likely to be due the triplication of the Amyloid Precursor Protein (APP) gene (located on chromosome 21) because of the aneuploidy (trisomy) of chromosome 21. The challenge is how to develop means of detecting the underlying neuropathology even in the absence of clinical features so that those who would eventually develop AD could be targeted for preventative or diseasemodifying treatments. I will present data from a cohort of adults with DS who have undergone positron emission tomography (PET) neuroimaging of fibrillary amyloid-beta (a key defining feature of AD pathology) using [11-C]-Pittsburgh Compound-B as a amyloid-beta tracer and magnetic resonance imaging (MRI) to evaluate brain morphology and function. The data supports the notion that early detection of AD pathology is possible even in the presence of the atypical neurodevelopment characteristic of DS and in the absence of features that would fulfil the clinical criteria for AD. I will also discuss how a range of measures could prove to have clinical utility and lead to a better understanding of the pathogenesis of AD in DS and how using this data we will need to consider formulating new criteria for categorising the pre-clinical state of AD in DS.

Keywords: Down's syndrome, Alzheimer's disease, PET, MRI, Amyloid

TALK 19: The Developmental Trajectory of Glutamate in the Human Brain: From Neonatal Life to Early Infancy

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Background: There is compelling evidence to suggest that abnormalities in excitatory and inhibitory neurotransmission may underpin both typical and atypical development, including a variety of neurodevelopmental disorders. Therefore, we have used proton magnetic resonance spectroscopy ('HMRS) to examine the developmental trajectory of glutamate in the human brain, from neonatal life to early infancy. **Methods:** We recruited a mixed cohort of participants including those considered at higher risk of autism spectrum disorder (ASD), chosen because they have an older sibling with a diagnosis of the condition. We acquired 'HMRS at 3T from the basal ganglia of neonates (N=26) and infants (N=33). Using a single voxel point resolved spectroscopy sequence (PRESS), set at an echo time of 55ms, glutamate measures comprised glutamate plus glutamine (Glx) expressed relative to Choline (Cho) and Creatine (Cr); i.e. Glx/Cho and Glx/Cr respectively. **Results:** A Spearmans rank correlation revealed a significant increase with age, between the neonatal and infancy time-points, for both Glx/Cho (r=0.735, p<0.001) and Glx/Cr (r=0.599, p<0.001) ratios. In a preliminary analysis using the Mann-Whitney test, differences in the glutamate levels of neonates and infants at high- and low-risk of ASD were identified. Specifically, those at high-risk showed greater levels of Glx/Cr compared to those at low-risk, although only at trend level (p=0.093).

Conclusion: HMRS can be used to non-invasively map the developmental trajectory of glutamate in the human brain within the first few months of life. In this study, we found that glutamate increases with age from neonatal life to early infancy. Also, an exploratory analysis suggested that young infants at high-risk of ASD may have higher levels of glutamate, but greater numbers are needed to confirm this. We emphasize that these results are preliminary and that data acquisition is still on-going to better understand if variations in glutamate maturation may impact on development.

Keywords: Proton magnetic resonance spectroscopy, glutamate, metabolic development, basal ganglia, neurodevelopmental disorders, infancy.

TALK 20: Executive Functioning in Adults with Down Syndrome: An Exploration of Frontal Cortical Activity using Functional Near Infrared Spectroscopy

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Background: Executive functioning (EF) describes cognitive processes used to guide and control thoughts and behaviour, often associated with the frontal cortex. Individuals with Down syndrome (DS) show impairments in EF tasks and are suggested to have reduced frontal lobe volume compared to non-DS individuals. Adults with DS are also exceptionally susceptible to Alzheimers disease (AD). In AD in this population, decline in EF may precede memory decline, however there remains a paucity of functional imaging work in DS exploring these processes. Functional near infrared spectroscopy (fNIRS) uses near infrared light to measure changes in the oxygen concentration of the blood in the underlying cortex. This inferred measure of neural activity matches the BOLD signal used in fMRI studies, without needing participants to lie in a scanner, making fNIRS an increasingly widely used technique for cortical imaging research in vulnerable populations.

Methods: Healthy adults with DS (N=7) complete 4 EF tasks: go/no-go (inhibition), picture Stroop (inhibition/ interference), dimensional change card sort (rule-learning, set-shifting) and verbal fluency. Frontal cortical activity is simultaneously recorded using an NTS Optical Imaging System (Gower Labs) with a specifically designed frontal array of 16 light sources and detectors set at 30mm distance for each channel. Two short-separation channels (15mm) are included to allow measurement of systemic responses.

Results: We will present preliminary data comparing responses to each task, allowing us to determine whether fNIRS is a suitable technique for measuring EF-related cortical activity in adults with DS.

Conclusion: This is, to our knowledge, the first fNIRS study in adults with DS. Results will inform the development of a larger study (proposed N=75) using fNIRS with the tasks here that show the most robust responses, to look at differences in EF-related cortical activity in adults with DS both with and without cognitive decline, in a 12-month, longitudinal design.

Keywords: Neuroimaging, Down syndrome, fNIRS, executive functions, cognition.

TALK 21: Long Term Predictors of Quality of Life for Adults with Genetic Syndromes

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Background: A major concern for parents whose child has been diagnosed with a genetic syndrome is for their child's long term development and future lifestyle. However, for the majority of these rare syndromes lifespan research is scarce. This may leave parents with an uncertain outlook for their child's future. Long term outcome measures of Quality of Life (QoL), may help to address some of these parent's concerns. This study aims to describe the QoL of individuals with five genetic syndromes and to utilise longitudinal date to explore early predictors of adult QoL over 12 years.

Methods: 69 parents and carers of individuals with Angelman syndrome, Cri du Chat syndrome, Cornelia de Lange syndrome, fragile X syndrome, and Prader-Willi syndrome, completed questionnaires describing the behaviour of the person they cared for. These included the mood, interest and pleasure questionnaire (MIPQ). After a follow-up period of 12 years parents/carers completed the World Health Organisation Quality of Life scale (WHOQOL-Bref) including an additional module that addresses factors that specifically relate to the quality of life of individuals with an intellectual disability (WHOQOL-Dis).

Results: MIPQ scores significantly predicted scores on all four domains of the WHOQOL-Bref [Physical (β =.52, p<.01), Psychological (β =.68, p<.01), Social (β =.57, p<.01) and Environment (β =.74, p<.01)] and on the WHOQOL-Dis (β =.44, p<.01). When this variable was included in the model, relationships with other predictor variables (e.g. characteristics of autism and daily living skills) were no longer significant.

Conclusion: Low mood, interest and pleasure in childhood and adolescence predicts poorer quality of life outcomes in adulthood for individuals with genetic syndromes. This is an important area to target for interventions aiming to improve the QoL of adults with genetic syndromes.

Keywords: Quality of Life, Genetic Syndromes, Longitudinal, Mood, Adulthood.

TALK 22: The Neurocognitive Profile of 22q11.2 Deletion Syndrome and Implications for Functioning

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Background: 22g11.2 deletion syndrome (22g11.2DS) is one of the most common causes of intellectual disability. The associated 22q11.2 deletion conveys a >20-fold increased risk for schizophrenia and early-onset Parkinson's disease. In this study we aimed to delineate the neurocognitive profile of 22g11.2DS in adults with and without schizophrenia, and to assess this neurodevelopmental phenotype with respect to functional outcome. Methods: We investigated neurocognitive functioning in 100 adults with 22q11.2DS, 57 with no psychotic illness (NP, mean age=25.5, SD=9.7 y) and 43 with schizophrenia (SZ, mean age=28.2, SD=6.6 y). We used Vineland Adaptive Behaviour Scales (VABS) to assess adaptive functioning. Analyses included multivariate regression. Results: As expected, FSIQ was significantly higher in the NP vs the SZ group (74.2, SD=9.3 vs 68.7, SD=6.4; p=0.0008), and there were significant between-group findings across most neurocognitive domains assessed. Remarkably, there were similar patterns to neurocognitive profiles across both groups. Compared to IQ expectations for 22g11.2DS, there were relative strengths in recognition verbal learning, visual memory, and verbal fluency. Indeed, the NP group performed slightly above general population norms on the RAVLT recognition test. Reading and spelling were better than arithmetic performance, and visual memory better than verbal memory. Motor skills and arithmetic were relative weaknesses. Verbal learning, visual-spatial skills and cognitive flexibility were significantly associated with adaptive functioning, even when considering IQ and absence of schizophrenia. Additional neurocognitive domains were also important for functioning in the SZ group.

Conclusion: The results support a characteristic neurocognitive profile for 22q11.2DS. The findings have implications for real-life functioning and potential remediation. Domains showing the highest effect sizes for 22q11.2DS NP-SZ comparisons are consistent with those reported for idiopathic schizophrenia. Prospective studies will be needed to determine whether selected tests could enhance risk prediction in this molecular model of schizophrenia.

Keywords: neurocognitive battery, neurobehavioural phenotype, DiGeorge syndrome, velocardiofacial syndrome, psychosis.

TALK 23: Towards Better Measurement of Cognitive Control in Individuals with Genetic Neurodevelopmental Disorders

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Background: Cognitive control – also known as executive functioning – is the ability to monitor and regulate thoughts and behaviours, particularly in novel and complex situations. Specific cognitive control deficits are associated with several genetic neurodevelopmental disorders such as Prader-Willi, fragile X and Williams syndromes. Relationships have also been suggested between such deficits and clinically important aspects of certain behavioural phenotypes. However, valid measurement of cognitive control – which is challenging at the best of times – is subject to important limitations due to the nature of cognitive phenotypes that can be associated with genetic neurodevelopmental disorders.

Methods: A battery of 25 cognitive control and matched non-control tests was piloted with 125 typically developing children (6-12yrs) and 12 with genetic syndromes. Tests were designed to minimise the influence of cognitive strengths and weaknesses that do not comprise part of an individual's cognitive control skill. A metaanalysis of functional neuroimaging data from 1,177 children engaging in cognitive control tasks; alongside clinical observations and statistical modelling with the pilot data; informed development of an online cognitive control assessment system comprising 11 tests (total duration 1 hour).

Results: The CAN MEASURE assessment battery has now been administered to almost 700 typically developing 6 to 12 year olds, with at least another 160 scheduled by July 2016. Test re-test reliability and concurrent validity with a standardised informant report measure of behavioural indicators of executive function (assessed in sub-samples of children) is strong. Statistical modelling will be applied to examine the internal consistency of the CAN MEASURE battery in children from three age groups, with respect to widely applied models of cognitive control. Further, measurement invariance across children from different socioeconomic status backgrounds will be examined.

Conclusion: The CAN MEASURE battery should facilitate the examination of associations between specific profiles of cognitive control and behavioural phenotypic features in individuals with genetic neurodevelopmental disorders.

Keywords: Executive functioning; Switching; Inhibition; Working memory updating; Children; Neurodevelopmental disorders.

TALK 24: Characterisation of Rare Pathogenic Cnvs At 2q13 And 4p16.3 in Intellectual Disabilities and Co-Morbid Psychiatric Disorders

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Background: Chromosomal copy number variations (CNVs) are highly implicated in the aetiology of neurodevelopmental disorders. Research in paediatric cohorts with developmental delay/intellectual disabilities (DD/ID) has led to the identification of new pathogenic CNVs. Rare pathogenic CNVs have also been identified in cohorts with autism spectrum disorder and schizophrenia. There is a higher prevalence of psychiatric disorders in adults with ID, yet many have not undergone chromosomal microarray analysis to test for the presence of CNVs. Thus many adults with ID harbouring rare CNVs remain unidentified, precluding description of later onset psychiatric phenotypes.

Methods: We undertook genome wide chromosomal microarray analysis on adults with idiopathic ID recruited from ID psychiatry services across England. Analysis was undertaken on the Nimblegen 135k array using a clinical diagnostic pipeline. Comprehensive psychiatric and behavioural phenotyping was also undertaken. **Results:** Of the 202 adults recruited 11% had CNVs classed as pathogenic. These included a 1.7Mb deletion at 2q13 and a 2.4Mb duplication at 4p16.3, both of which are poorly characterised in adulthood. We undertook further targeted recruitment of children and adults with CNVs in these regions from support groups and regional genetics laboratories to expand the phenotypic data on these emerging pathological CNVs. **Conclusion:** Study of adults with idiopathic ID and psychiatric disorders has enabled the phenotypic characterisation of two CNVs associated with co-morbid pathologies. Ongoing characterisation of rare CNVs in adulthood could inform clinical management of children with emerging CNV syndromes.

Keywords: Intellectual disabilities, copy number variation, 2q13, 4p16.3, autism spectrum disorder.

KEYNOTE 25 – TOM OPPÉ DISTINGUISHED LECTURE: Cognitive decline and dementia in Down syndrome

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The life expectancy of individuals with Down syndrome (DS) has improved significantly over the past 50 years. DS is associated with a greatly increased risk of dementia due to the presence of three copies of the gene encoding amyloid precursor protein (APP), which is implicated in Alzheimer's disease (AD), but extra copies of other chromosome 21 genes may also play a part. As 40% of older adults with DS in Europe are now aged 40 and older, there is a growing population at risk of developing dementia due to AD. This population should be considered for clinical trials of potential treatments for AD, particularly those that target the amyloid cascade. However, the presentation of dementia in individuals with DS differs somewhat from typical AD in the general population or familial AD.

I will review the latest data from our longitudinal study of cognitive ability and AD in individuals with DS to highlight aspects of the DS cognitive phenotype across the lifespan, and how that relates to the development of dementia symptoms. I will emphasize differences between AD in DS and familial AD, particularly AD due to duplication of APP, and consider the implications for diagnosis, treatment and issues related to measuring clinical outcomes in this population.

I will conclude that a good understanding of the typical pattern of cognitive decline in this population and its causes are required to enable early diagnosis and to develop clinical outcome measures that can be used in clinical trials to treat or prevent AD in DS. Further study of the mechanisms underlying the development of Alzheimer disease in people with Down syndrome could also provide insights into the mechanisms that cause dementia in the general population, and successful treatment trials in this population would have major implications for treatment of AD in other populations.

Keywords: Down syndrome, dementia, Alzheimer's disease, cognitive phenotype

KEYNOTE 26: Social, Emotional and Behavioral Problems in Individuals with an Extra X Chromosome (47,XXX And 47,XXY): A Focus on Underlying Neurocognitive Mechanisms

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In this presentation I will give an overview of studies from our lab that have focused on brain functioning and neurocognitive functioning in relation to risk for psychopathology in individuals with an extra X chromosome (47,XXX and 47,XXY). Up to now, more than 60 adults and 120 children with an extra X have participated in these studies. Clinical assessments have shown an increased vulnerability for social, emotional and behavioral problems. Using neuropsychological tests, MRI, EEG, eyetracking, and psychophysiological measures (heart rate, skin conductance), we have gained insight in the underlying mechanisms driving this increased risk. Based on this, three key domains of vulnerability were identified: social cognition, language and executive functioning (i.e. cognitive control functions involved in the regulation of thought, emotion and behavior). I will present data illustrating how these domains are compromised, how this is related to social, emotional and behavioral problems, and to what extent these aspects of neurodevelopment are impacted by environmental factors such as socio-economic status, life stressors and cognitive-behavioral intervention.

Keywords: Klinefelter syndrome; trisomy X, sex chromosomes, behavioral phenotype, neurocognition, eyetracking

TALK 27: The Pathogenic Mechanism(s) of Fragile X-Associated Tremor/Ataxia Syndrome

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Background: Clinical phenotypes affecting individuals who carry premutation expansions (55 to 200 CGG repeats) of the FMR1 gene are thought to involve over-expression of the gene, with pathogenesis believed to result from the FMR1 mRNA (RNA toxicity). Although mRNA involvement is generally believed to be through its direct, post-transcriptional interactions with one or more RNA binding proteins, newer evidence suggests that the RNA may be acting co-transcriptionally by increasing the propensity for DNA damage, in part through the formation of transcriptional R-loops.

Methods: A combination of immunocytochemistry, molecular biology, gene-induction models, and premutation mouse models.

Results: We have identified a number of proteins (e.g., phosphoH2AX, phospho ATM) in the intranuclear inclusions of FXTAS cases that point to a novel model for FXTAS pathogenesis in which initial DNA damage events at/near the FMR1 locus lead to a prolonged/unresolved DNA damage repair (DDR) response. This response is likely to lead to downstream effects, including mitochondrial dysfunction and calcium dysregulation, which ultimately result in cell death.

Conclusion: Although FXTAS was initially considered to be a distinct disorder, it is increasingly recognized as only one facet of a much broader clinical pleiotropy among children and adults who carry premutation alleles of the FMR1 gene. Our work on the pathogenic mechanisms underlying FXTAS indicates that the origins of the late-onset neurodegenerative disorder actually lie in early development, raising the likelihood that all forms of clinical involvement among premutation carriers have a common, underlying mechanistic basis.

Keywords: Fragile X syndrome, autism, neurodegeneration, premutation, RNA toxicity, neurodevelopment.

TALK 28: Altered Molecular Phenotypes in 22q Deletion Syndrome

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Objectives: A hemizygous deletion of 1.5-3 Mb on chromosome 22 at locus 11.2 gives rise to 22q11.2 deletion syndrome (22qDS), which is characterized by a complex display of endophenotypes. Despite this apparent relatively clear genetic etiology, little is still known about how genes contribute, singly or in combination, to the range of phenotypic variation.

Methods: ddPCR was used to characterize deletion size and deletion endpoints. qRT-PCR and Western blot analyses were used to determine expression levels of several genes within the deleted region. miRNA profiling was obtained using Firefly® particle technology on both PBMCs and plasma from children with 22q and compared to TD (typical developing controls). Genome-wide CNV data were generated using HumanCytoSNP-12v2.1 beadchip single nucleotide polymorphism array (Illumina).

Results: qRT-PCR and Western blot analyses revealed a decreased expression of the DGCR8 gene, which play a pivotal role in the miRNA biogenesis, in children with 22qDS. Using total RNA isolated from PBMCs and plasma from children with 22qDS, we demonstrate that some miRNAs are down- regulated compared to TD, in both plasma and PBMCs, including miR-185, miR-206, miR-1. Further, genomic analysis found that 10% of individuals with the 22qDS deletions also carry additional rare CNVs and the CNV burden appears to modify the phenotypic expressivity, specifically, for intellectual disability features, observed in some of the 22qDS participants of this study.

Conclusions: Preliminary findings indicate that several molecular phenotypes, including altered miRNAs expression profiling and high CNV burden may be playing a role in the pathogenesis of 22qDS. The identification of cellular pathways controlling and/or controlled by miRNAs in 22qDS is of relevance, as it would allow the identification of targets for development of therapeutic approaches. Importantly, a potential contribution of higher CNV burden in the genetic background to the intellectual disability phenotype may play a role in 22qDS.

Keywords: 22q deletion, CNV, miRNA, mitochondrial dysfunction, intellectual disabilities.

TALK 29: Large Prospective Study of the Neurodevelopmental Outcome in Prenatally Diagnosed Males with 47,XXY

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Background: 47,XXY is the most commonly occurring sex chromosome variation, affecting 1:660 men. When left untreated the phenotype is associated with androgen deficiency, language-based learning disorders, and developmental dyspraxia. Previous research has shown boys with 47, XXY who receive biologic treatment perform better on measures of neurocognition, neuromotor, and neurobehaviour than untreated boys. A large cohort of prenatally identified boys with 47,XXY was prospectively analysed to provide the first detailed characterization of preschool-aged cohort in more than thirty years.

Methods: 158 prenatally identified males with 47,XXY were administered the Bayley Scales of Infant Development (BSID) and a sensory profile as part of a comprehensive neurodevelopmental examination. 39 of the boys had received Early Hormonal Treatment in infancy (EHT) and 119 were untreated. Results were analysed across motor, language, cognition and behaviourally. Parents in both groups were predominantly Caucasian with similar SES and educational levels.

Results: 96.4% were diagnosed by amniocentesis, the remaining by NIPT or CVS. The untreated group had significantly depressed scores on MDI (p=0.0297), PDI (p=0.0089), Language (p=0.0407), and receptive communication (p=0.0062). Treated 47,XXY boys had significantly normalized visual processing (p=0.002) and behavioural outcome (p=0.0002) when compared to the untreated group. Congenital muscular torticollis occurred in 15% of the infants.

Conclusion: This is the first well-described study on a large cohort of prenatally diagnosed boys with 47,XXY, their response to EHT, and the impact on neurodevelopment in more than 30 years. These results further support that EHT may have a positive outcome on neurodevelopmental progression, as well as provide characterization of prenatal and perinatal aspects. With proactive care, academic and behavioural differences associated with 47,XXY can be minimized and possibly ameliorated.

Keywords: Klinefelter syndrome, 47,XXY, preschool age, neurodevelopment, sex chromosome disorder.

KEYNOTE 30: Advances in Research in Fragile X Syndrome

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Advances in fragile X syndrome (FXS) research have included new treatments and new mechanisms of dysfunction that occur when FMRP is missing or deficient. FMRP has been found to control the translation of hundreds of messages important for other disorders including schizophrenia and autism spectrum disorder. One new discovery (Talbot et al PNAS) has found that the absence of FMRP has a very important mRNA target in neurons, diacylglycerol kinase kappa (Dgkk), a master regulator that controls two signaling pathways that activate protein synthesis. The reduction of Dgk κ leads to synaptic plasticity alterations, dendritic spine abnormalities and behavioral problems in the mouse that duplicates what is found in the fmr1 KO mouse. Overexpression of Dgk κ rescues the FXS features of the *fmri* KO mouse. Another important target for FMRP is the mRNA encoding bone morphogenetic protein type II receptor (BMPR2) and depletion of FMRP increased the BMPR2 pathway that binds to LIMK1, important for actin reorganization to promote synapse formation and neurite outgrowth. Inhibition of LIMK1 rescued the FXS phenotype in the mouse and Drosophila models of FXS (Kashima et al 2016 neuroscience). Both of these new findings identify new targets for treatment in FXS. Targeted treatment trials in FXS are improving related to the benefit of new outcome measures including the use of event related potentials (ERPs) particularly habituation paradigms that target brain processing abnormalities with deficient GABA inhibitory input, expressive language sampling measures developed by Dr Len Abbeduto and colleagues and the use of the NIH toolbox adapted by Dr David Hessl for children with FXS to assess improvements in cognitive processes and attention. We have also learned that early intervention with targeted treatments can significantly improve developmental testing in young children with FXS as seen by the controlled trial of low dose sertraline in those ages 2 to 6yo. Early intervention will also be tried with the mGluR5 antagonist, AFQ056, combined with intensive language intervention provided by videoconferencing to the family in their home for young children with FXS ages 3 to 6yo in a multicenter trial funded by NIH.

Abstracts for Poster Presentations

(in alphabetical order of primary author)

POSTER 1: Predictors of Academic Functioning in Children with Sex Chromosome Aneuploidies

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Background: Impairments in cognitive functioning, speech-language development and social-emotional regulation are common across all sex chromosome aneuoploidies (SCAs), but the degree of impairment is variable. There are higher rates of language-based learning disabilities, as well as difficulties with attention and executive functioning in children with SCA. However, there have been few studies that have examined the rates of learning disability (LD) comorbidity in SCAs, or the extent to which attention and executive functioning skills predict academic outcome.

Methods: 105 children and adolescents with SCA were seen in the eXtraordinarY Kids Clinic at Children's Hospital Colorado. Participants completed comprehensive neuropsychological evaluations, which included measures of verbal and non-verbal cognition, reading, math, language, working memory, and executive functions (EF). Means were computed for primarily variables, and composites created for Basic Literacy, Attention/Inhibition and EF. Hierarchical regression analyses were conducted to identify significant predictors of academic functioning. **Results:** There were high rates of LD comorbidity in our SCA sample, with 44% having at least two areas of deficit. Basic literacy was significantly predicted by working memory, phonological awareness, and rapid naming, consistent with non-SCA populations with dyslexia. Perceptual reasoning and working memory predicted math computation. Reading comprehension was predicted by basic literacy and verbal comprehension, consistent with the Gough Simple Model of Reading. Attention and executive functioning did not add unique variance to any academic outcome once more basic processes were taken into account.

Conclusions: Although language and reading disorders are the most commonly identified difficulties in children with SCA, there is a high comorbidity rate with math disorder. Similar predictors of learning disability were found in children with SCA as have been identified in non-SCA learning disability populations. Attention and EF difficulties did not account for unique variance in basic academic skills, but may be more influential in higher-level academic tasks.

Keywords: learning disability, executive function, comorbidity, sex chromosome aneuploidy.

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POSTER 2: Manual Dexterity as a Possible Marker of Neuropsychiatric Disorders in Adults with 22q11.2 Deletion Syndrome

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Background: 22q11.2 deletion syndrome (22q11.2DS) is associated with a one in four risk of developing schizophrenia and a >20-fold increased risk for early-onset Parkinson disease. Preventive intervention strategies are hampered by our inability to predict which patients will develop these disorders. Our aim was to determine whether manual dexterity is related to psychiatric symptomatology and could thus help to identify patients at high risk for psychotic illness.

Methods: We assessed manual dexterity using the Purdue Pegboard Test (dominant hand) in 35 adults with 22q11.2DS (mean age 29.5, SD 10.4 years; 23 female). Ten met DSM-V criteria for schizophrenia (22q11.2DS-SZ) and 25 had no psychotic illness (22q11.2DS-NP). The Positive and Negative Syndrome Scale (PANSS) was administered to all subjects. Results: As expected, the 22q11.2DS-SZ group had significantly higher scores than the 22q11.2DS-NP group on the PANSS (positive symptoms; p=0.028, negative symptoms; p=0.006, general psychopathology; p=0.006, total PANSS score; p=0.003). Manual dexterity was not significantly different between the two groups (p=0.362). However, there were significant correlations between manual dexterity and positive symptoms (r=-0.44, p=0.008), negative symptoms (r=-0.36, p=0.036), general psychopathology (r=-0.46, p=0.006), and total PANSS scores (r=-0.49, p=0.003) across the entire sample. Correlations were at the trend level within the 22q11.2DS-NP group for general psychopathology (r=-0.37, p=0.071) and total PANSS scores (r=-0.37, p=0.067), and significant within the 22q11.2DS-SZ group for general psychopathology (r=-0.67, p=0.039) and total PANSS scores (r=-0.37, p=0.067), and significant within the 22q11.2DS-SZ group for general psychopathology (r=-0.67, p=0.039) and total PANSS scores (r=-0.37, p=0.067), and significant within the 22q11.2DS-SZ group for general psychopathology (r=-0.67, p=0.039) and total PANSS scores (r=-0.37, p=0.067), and significant within the 22q11.2DS-SZ group for general psychopathology (r=-0.67, p=0.039) and total PANSS scores (r=-0.72, p=0.018).

Conclusion: These initial findings suggest that motor disturbances may be associated with schizophreniasymptom severity in adults with 22q11.2DS. Longitudinal studies are needed to determine whether impaired manual dexterity may precede the onset of psychosis and/or could predict the development of Parkinson disease in later life.

Keywords: 22q11 deletion syndrome, manual dexterity, schizophrenia, Parkinson disease.

POSTER 3: Cognitive and Language Profile in Kabuki Syndrome Caused by MML2 and KDM6A Mutation: A Preliminary Study

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Background: Kabuki syndrome (KS) is a disorder characterized by multiple congenital anomalies that affects the development and function of multiple organ systems. Over the years, many works have also contributed to the neurobehavioral characterization in subjects with KS; however, participants were selected based on clinical diagnosis alone. Only a recent study examined the language deficits in a sample of individuals with KS diagnosed based on clinical features and genetic testing. The aim of our study is to investigate both cognitive and language abilities in individuals who had both clinical and genetical diagnosis confirming the presence of KS.

Methods: Cognitive and language abilities were assessed in 15 patients (14 with MLL2 mutation and 1 with KDM6A mutation) by using Leiter-R (brief IQ) and standardized lexical and morphosyntax measures (PPVT for lexical comprehension, BNT for lexical production and TroG-2 for morphosyntax comprehension). Oromotor function was assessed by a speech therapist, evaluating through non-verbal movements like jaw, mouth, lips and tongue movements.

Results: The preliminary results show that both cognitive level and language profile of individuals with KS are very heterogeneous. Considering cognitive level, the 47% of KS obtained an average score, 20% obtained a borderline score while 33% obtained a score below average. Considering language profile, we observed a heterogeneous pattern of language deficits. Abnormal oromotor function was evident in 53% of KS. **Conclusion:** Preliminary results seem to support the multisystem nature of the disorder. Cognitive deficits, neurological, orofacial structural, abnormal oromotor function and hearing may contribute to language impairment. In conclusion, it appears to be great variability in the cognitive and linguistic profile of KS.

Keywords: Kabuki Syndrome, MLL2 mutation, KDM6A mutation, cognitive profile, language profile.

POSTER 4: Neurodevelopmental Profile for Boy with 47,XYY and Prader-Willi Syndrome

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Background: Prader-Willi Syndrome (PWS) may be caused by paternal 15q11-13 deletion or maternal uniparental disomy (UPD) and is characterized by short stature, hyperphagia, behavioral outbursts, and intellectual impairment. 47,XYY is a sex-chromosome variation associated with tall stature, language-based learning disabilities, ADHD, and IQ within normal limits. This case presents a 9-year-old boy with PWS-maternal UPD, and 47,XYY, which has previously only been reported in other one case. The phenotypic and genotypic data will be presented.

Methods: Neurodevelopment evaluation included assessment of neurocognition (verbal and nonverbal), behavior, and reading domains.

Results: Anthropomorphic measurements reveal increased head circumference (70th percentile), height (75th percentile), and weight (95th percentile). This child demonstrated a complex neurodevelopmental profile. VIQ was below average, with a score of 65. He struggled with subtests requiring word knowledge and practical social judgement, but did well in subtests of abstract thinking, long-term memory, and word reasoning. PIQ was 71, and non-verbal IQ was 72, both within low-average limits. Further testing revealed selective preservation in oral comprehension (standard score=90) but difficulty with story recall and passage comprehension (standard scores of 62 and 72, respectively). SRS was within normal limits on all domains. CBCL indicated externalizing and oppositional-defiant behavior within clinical range, as well as borderline-significant anxiety and aggressive behavior.

Conclusion: This case presents a complicated neurodevelopment profile. Increased head circumference and height are consistent with 47,XYY but not PWS. Additionally, externalizing and oppositional-defiant behaviors are described in PWS, but less consistently in XYY. The complex interaction between phenotype and genotype expresses common features of PWS and 47,XYY. Genotypic studies of regulating genes on the Y chromosome may provide further insight into the phenotypic profile.

Keywords: XYY, Jacob's Syndrome, Prader-Willi Syndrome, maternal UPD, SCA, neurodevelopment.

POSTER 5: Diverse Profiles of Anxiety-Related Disorders in Fragile X, Cornelia De Lange and Rubinstein-Taybi Syndromes

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Background: Anxiety disorders are heightened in specific genetic syndromes in comparison to intellectual disability of heterogeneous aetiology. Existing research has not consistently explored the prevalence of types of anxiety disorder using comparable assessments. Identifying the types of anxiety disorder most associated with different genetic syndromes is important for targeted syndrome-specific interventions. The present study delineates the profile of anxiety disorders in individuals with fragile X (FXS), Cornelia de Lange (CdLS) and Rubinstein-Taybi syndromes (RTS).

Methods: Parents of individuals with FXS (n=19), CdLS (n=13), and RTS (n=27) completed the Spence Child Anxiety Scale-Parent Version (SCAS-P). These data were compared to normative data for typically-developing children and children diagnosed with an anxiety disorder. Subscale-level analysis was conducted to identify differences in the profile of anxiety disorder in individuals with FXS, CdLS and RTS, and compared to normative data.

Results: Participants with CdLS scored higher than participants with FXS and RTS on the separation anxiety and generalised anxiety subscales of the SCAS-P. Scores did not differ between children diagnosed with an anxiety disorder and a) participants with FXS on social phobia, panic/agoraphobia, physical injury fears, and obsessive-compulsive subscales b) participants with CdLS on separation anxiety, generalised anxiety, panic/agoraphobia, physical injury fears and obsessive-compulsive subscales, and c) participants with RTS on panic/agoraphobia and obsessive-compulsive subscales.

Conclusion: The results support findings of elevated levels of anxiety in FXS, and obsessive-compulsive disorder in RTS. The results also document the severity and breadth of anxiety in CdLS, and highlight divergent profiles of anxiety between these groups.

Keywords: Anxiety, genetic syndromes, fragile X syndrome, Cornelia de Lange syndrome, Rubinstein-Taybi syndrome.

POSTER 6: Psychiatric Disturbances in Cerebrotendinous Xanthomatosis

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Introduction: Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive lipid storage disease due to mutations of the CYP27A1 gene resulting in deficiency of sterol-27-hydroxylase, which plays a key role in the conversion of cholesterol to bile acids. The clinical picture is characterized by a variable association of systemic signs, such as chronic diarrhea, cataracts, and tendon xanthomas, and neurological symptoms including low intelligence, psychiatric disturbances, spasticity, ataxia, epilepsy, parkinsonism and polyneuropathy. Early diagnosis and replacement therapy with chenodeoxycholic acid (CDCA) can prevent clinical deterioration. Herein we aimed at evaluating the frequency and the characteristics of psychiatric disturbances in CTX. Methods: We performed a retrospective evaluation of the clinical data of 55 CTX patients (28 females, 27 males) belonging to 39 unrelated families. The median age of our subjects was 36 years (range 1-67). All patients were diagnosed in our Unit for Neurometabolic Disorders in the period 1986 to 2015. In 37 out of 55 patients, serum cholestanol levels at diagnosis were assessed and compared with those of normal controls. When present, brain MRI scans were analyzed. We also evaluated the response of psychiatric disturbances to CDCA treatment. **Results:** Psychiatric disturbances, including depression, bipolar disorder, anxiety, panic disorder and psychosis, were reported in about half the patients, typically manifesting in the third decade. In some cases, most often in female patients, psychiatric disorders represented the main clinical manifestation of the disease. No correlation was found with peculiar MRI patterns, serum cholestanol levels, or genotype. CDCA treatment often improved psychiatric symptoms, which poorly responded to "conventional" treatments.

Discussion: CTX patients show variable psychiatric disturbances, including personality, affective and psychotic disorders: they can be the main manifestation of the disease or may complicate the other neurologic disturbances. Psychiatric disorders have a considerable weight in determining disability, however they often respond to CDCA treatment. Therefore, early diagnosis and timely introduction of replacement therapy are crucial in CTX patients.

POSTER 7: Maternal Mental Health and Family Functioning in Five Disorders

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Background: Parents of children with intellectual disabilities (ID) experience higher levels of stress and psychopathy than parents of children without ID. Maternal mental health correlates positively with the severity of emotional and behaviour problems displayed by the child with ID. This correlation was found in a cohort of families with a child with an intellectual disability due to mixed causes. The severity of emotional and behavioural problems varies across disorders. For example, individuals with Prader Willi syndrome tend to exhibit more severe behavioural problems than do people with Down syndrome, William syndrome or Fragile X syndrome. To date, much of the research has examined parental mental health and family well-being within rather than across syndrome groups. Thus, this study reports findings of maternal mental health and family functioning across five disorders, autism spectrum disorder (ASD), Prader Willi syndrome (PWS), Williams syndrome (WS), Down syndrome (DS) and fragile X syndrome (FraX). The authors hypothesise that families with a child with ASD or PWS will have more maternal mental health problems and lower family function than families of children with DS, WS or FraX.

Methods: Maternal mental health and family functioning were assessed using the General Health Questionnaire and a checklist based on the Family Assessment Device respectively. Emotional and behavioural problems were assessed using the Developmental Behaviour Checklist. Results: To be presented at the conference.

Keywords: family functioning, maternal mental health, Prader Willi syndrome, Down syndrome, autism, fragile X syndrome, Williams syndrome.

POSTER 8: The Development of Social Cognitive Abilities in Individuals with Fragile X Syndrome: From Infancy to Adulthood.

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Background: Individuals with Fragile X syndrome (FXS) have a unique socio-behavioural profile relative to those with autism or other genetic syndromes. Previous studies indicate that other disorders with atypical social profiles, such as Rubinstein-Taybi syndrome, evidence divergent developmental trajectories of social cognitive skills, which may underpin their social development. This study investigated the developmental sequence of social cognitive skills emerging from infancy into adolescence in individuals with FXS.

Methods: 43 individuals with FXS aged 2 to 44 years old (Mage=12.6, SD=10.7) participated in one of two batteries of tasks assessing social cognitive skills that emerge in a strict developmental order. The 'Early Social Cognition Scale' (ESCS), assesses early understanding of others intentions (typically developing between 14->24 months), whereas the 'Theory of Mind Scale' (ToMS) assesses later explicit understanding of other's mental states (3->9 years).

Results: Scalogram analyses revealed that children with FXS did not pass the ESCS tasks in the same sequence as that observed in typical development (TD). While many children with FXS passed tasks that required understanding simple intentions in others (86% passed 'Reenactment of intended acts, 82% passed 'helping'), few passed tasks that required understanding simple intentions in others (36% passed 'gased 'tubes-with-handles', 32% passed 'point', 23% passed 'gaze' and 18% passed 'trampoline'). In contrast, children and adults passed the ToMS tasks in a similar order to TD (co-efficient of reproducibility = 0.99, index of consistency = 0.96). However, whereas most passed the first three tasks at the developmental age expected, many showed a delay in passing the final three ToMS tasks.

Conclusions: These results indicate that individuals with FXS show a distinct pattern of spared and impaired abilities across early and later social cognitive development relative to TD. The findings will be discussed relative to how they inform models of social cognitive development, and how social cognition may influence sociobehavioural phenotypes.

Keywords: Fragile X syndrome, Social cognition, Autism spectrum disorders, Socio-behavioural phenotypes, Social development, Theory of Mind

POSTER 9: Social Cognition in Williams Syndrome

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The ability to recognize, manipulate and behave with respect to the socially relevant issues, requires neural systems that are able to process social signals and connect them to the motivations, emotions and adaptive behavior.

In particular, the social cognition explores the processes through which people acquire information from the environment, interpret and store it in memory, to understand themselves and their social context and in a consequential way to organize their behavior.

Williams syndrome (WS) is a neurodevelopmental condition that occurs as a result of a contiguous deletion of ~26-28 genes on chromosome 7q11.23. WS is often associated with a distinctive social phenotype characterized by an increased affinity toward processing faces, reduced sensitivity to fear related social stimuli and a reduced ability to form concrete social relationships.

In this paper we tested 4 Williams Syndrome patients and 8 controls (4 matched for sex and mental age and 4 matched for sex and chronological age). In order to study the attentional components, also with social attention characteristics we administered three versions of Attention network Task: the ANT-Fish, the ANT-Face, and the ANT-Photograph. Williams patient exhibited a percentage of errors significantly higher than both groups of controls in all the three tasks. The percentage of errors made by William patients in experiments with social stimuli (photos and faces) in higher than the percentage of errors made in the experiment with non social stimuli. In this case, the William patients didn't differs in the number of errors from mental age matched controls (ANT. fish). The most important result, emerged from our work, is that Williams patients seems do not have attention deficits; they exhibits deficits only when the task involves social relevant stimuli.

POSTER 10: Congenital Heart Disease and Psychotic Disorder Later in Life in the 22q11.2 Deletion Syndrome

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Background: Individuals with the 22q11.2 deletion syndrome (22q11DS) have a 25% risk for developing psychotic disorders. In addition, 22q11DS is associated with severe medical conditions, in particular congenital heart disease (CHD), which frequently require major surgical interventions. At present it is unclear whether this somatic phenotype early in life is and the neuropsychiatric phenotype later in life share a common causal mechanism, or that they are distinct, unrelated phenotypes. In the general population, an association between CHD and increased risk for psychosis has been reported. The purpose of this study is to determine whether in patients with 22q11DS, CHD is associated with an increased risk for developing psychotic disorders.

Methods: 161 subjects (11.3 to 21.6 years old) with confirmed 22q11DS were included. CHD was determined on the basis of patient record analysis. All subjects underwent psychiatric and cognitive assessment by a multidisciplinary team. A semi-structured DSM-IV interview and the Schedule for Affective Disorders and Schizophrenia for School-age Children - Present and Lifetime version mood and psychosis sections (K-SADS) were used to evaluate the presence of a psychotic disorder and/or psychotic symptoms.

Results: 90 (55.9%) of individuals were diagnosed with a CHD while 20 (12.4%) of individuals were diagnosed with a psychotic disorder. Our results reveal no significant association between CHD and neuropsychiatric outcomes, contrary to our hypothesis. If anything, there is a trend for an association between CHD and a lower risk for psychosis (p=.052).

Conclusion: Our findings reveal that in patients with 22q11DS, CHD is not significantly associated with an increased risk for developing psychotic disorders. Our first analyses indicate that CHD cannot be considered a clinical marker that is predictive of psychosis in 22q11DS. Moreover, these findings suggest that these are two unrelated phenotypes that do not share the same biological etiology.

Keywords: 22q11.2 deletion syndrome, schizophrenia, congenital heart disease, genetics, high risk.

POSTER 11: Behavioural Traits, Psychological Distress and Wellbeing in Mothers of Children with Fragile X Syndrome or Autism Spectrum Disorder

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Background: Characterisation of the behavioural phenotype of FXS premutation carriers, particularly female carriers, has received very limited attention within the literature.

Methods: 46 mothers of children with FXS (M-FXS;Mage=42.5) and 26 mothers of children with ASD (M-ASD;Mage=41.9) completed a series of questionnaires tapping into autistic traits (Autism Spectrum Quotient; AQ), psychological distress (stress, anxiety, depression) and positive psychological functioning.

Results: The groups were comparable for age and IQ (p>.o5). There were no significant group differences on measures of anxiety, depression, stress and positive psychological functioning. On the AQ, the M-FXS group scored significantly higher than the M-ASD group on the imagination subscale (p<.o5), reporting less cooperative pretend play as a child and more difficulty accessing another's perspective. In comparison to a group of typical adult females reported by Baron-Cohen et al. (2001), the M-FXS group reported more autistic traits on the AQ as a whole (p<.05), as well as on the imagination and attention-switching subscales (p<.01). Importantly, these self-reported tendencies were far milder and less common than those seen in adults with an ASD diagnosis. Correlations revealed significant associations between the imagination and attention-switching subscales of the AQ and levels of anxiety, depression and positive psychological functioning (all p<.o1). In contrast, only one significant correlation was identified in the M-ASD group between attention-switching and anxiety (p<.o1). Conclusion: Mothers of children with FXS show increased risk of traits that are indicative of the Broader Autism Phenotype relative to mothers of children with ASD, specifically within the domains of imagination and attention-switching. These traits appear more likely to influence parental stress and well being in this population relative to mothers of children with ASD, highlighting the need for improved and targeted support for mothers of children with FXS. Future studies should investigate further the cognitive profile of this population and how this impacts on family adjustment.

Keywords: FXS premutation, broader autism phenotype, autistic traits, stress, wellbeing, ASD.

POSTER 12: Electrophysiological and Clinical Longitudinal Study of Down Syndrome, Rett Syndrome, Fragile X Syndrome, and Autism Spectrum Disorders

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Background: The pathogenic mechanisms of these syndromes may differ, but they are all associated with morphological and functional abnormalities of dendritic spines. In Down Syndrome (DS) there are fewer of spines and they are larger, in Rett Syndrome (RTT) their number is lower, in autism spectrum disorders (ASD) and Fragile X Syndrome (FXS) they are more numerous but structurally abnormal.

Methods: The subjects included 49 individuals with FXS (2 to 34 years of age), 18 with DS (5 to 16 years), 70 with RTT (1,5 to 18 years), and 120 with ASD (3 to 26 years). The intellect, adaptive behaviour, and autistic symptoms were tested. The EEG spectral data were presented in narrow frequency bands and compared to our extensive normative database.

Results: Nonverbal intellect of FXS showed slower development compared to typically developing individuals (TD). The verbal intellect and adaptive skills showed less affected development. Slow sensorimotor theta-activity dominated in EEG of FXS until the age of 18. Then EEG flattens, and occipital alpha-rhythm may emerge. Alpha-rhythm matures more slowly and slower activity increases in DS of 3 to 12 years. After the age of 12 alpha-rhythm dominates in occipital areas. The cognitive deficits persist, but adaptive skills improve. In RTT the EEG pattern depends on the type, location of the mutation, X chromosome inactivation skewness, and, most importantly, on the stage of illness. 85% of RTT demonstrate theta-activity after regress. Its amount negatively correlates with the severity of cognitive deficit. The ASD have a flat EEG at the age of 2 to 5. Until 10-12 years they have either more advanced or delayed alpha-rhythm features. Compared to TD the power of slower activity is lower and of beta-activity is higher. This pattern does not change with age.

Conclusion: Thus, every syndrome has a peculiar EEG pattern which is age-dependent.

Keywords: EEG, Autism, Fragile X Syndrome, Down Syndrome, Rett Syndrome, Development.

POSTER 13: Can we find Natural Clusters of Tuberous Sclerosis Complex Associated Neuropsychiatric Disorders? A Pilot Feasibility Study

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Background: Tuberous Sclerosis Complex (TSC) is a multisystem genetic disorder with a wide range of neuropsychiatric manifestations, referred to as TSC-Associated Neuropsychiatric Disorders (TAND). TAND affect up to 90% of those with TSC in an apparently unique, individual pattern. This 'uniqueness', however, poses significant challenges for psycho-education and intervention planning. To date, no studies have examined whether there may be natural TAND clusters. The purpose of this pilot study was to investigate a) the practicability of identifying natural TAND clusters, and (b) to identify a suitable multivariate data analysis technique for larger-scale studies. Methods: TAND Checklist data were collected from 56 individuals with a clinical diagnosis of TSC (n= 20 from South Africa; n = 36 from Australia). Exploratory cluster analysis was performed on TAND Checklist data. Using R, the open-source statistical platform, methods examined included hierarchical clustering (single linkage, complete linkage, average linkage, Ward, McQuitty), and PAM and FANNY, two non-hierarchical clustering methods. Results: Of all analysis methods Ward was identified as most suitable to identify potentially clinically-meaningful clusters. Ward generated 8 distinct clusters - two 'impact/impairment' clusters, and six 'behavioural' clusters. The 'behavioural' clusters included an 'ASD-related' cluster, a 'mood & memory' cluster, a 'language & scholastic' cluster, an 'anxiety & inattention' cluster, an 'externalization' cluster, and an 'hyperactivity/impulsivity/inflexibility' cluster. Intellectual ability and impact clusters showed strong correlation, and the behavioural clusters showed distinct patterns of co-occurrence across intellectual ability groups. That is, the level of intellectual ability strongly predicted the presence of specific behavioural clusters. For instance, the normal intellectual cluster did not co-occur with the ASD-related or externalizing clusters, but co-occurred with the language & scholastic cluster in 42% and with anxiety & attention in 22% of cases. Conclusion: These pilot results suggest that natural TAND clusters may be identifiable using Ward hierarchical cluster analysis.

Keywords: Tuberous Sclerosis Complex, TAND, Neuropsychiatric, ASD

POSTER 14: Neurodevelopmental Aspects of 48, XXXY: A Rare Variant of 47, XXY (Klinefelter Syndrome)

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Background: 48,XXXY is a rarely occurring sex chromosome disorder (1:50,000) characterized by a complex neurodevelopmental profile that includes musculoskeletal anomalies, language based learning disorders (LLD), developmental dyspraxia and hypogonadotropic hypogonadism. This study presents an expansion of the phenotypic characterization of this rare XY disorder.

Methods: 19 boys with 48,XXXY between the ages of 3 months and 15 years had comprehensive neurodevelopmental evaluations. These evaluations assessed domains of intelligence, motor, language and vocabulary. Prenatal and perinatal factors were explored and early biomarkers for neurodevelopmental dysfunction were identified.

Results: Ethnicity was predominately Caucasian (94.1%), with 73.6% receiving testosterone replacement. Mean gestational age was 37 weeks (SD:2.3weeks) and mean birth-weight was 2.2 kg(SD:0.5kg). Growth hormone deficiency was detected prior to 18 months in two boys. All but one child was postnatally diagnosed and referred because of global developmental delay. MDI was within normal limits (90.8;SD:17.3). Mean VIQ was 82(SD:13.8; range:66-108) and PIQ was 91.6(SD:7.6; range:78-102). Both expressive (89.3;SD:12.5) and receptive vocabulary (91;SD:16.0) were within normal limits with preponderance of LLD present and evident by 5 years of age. Motor dysfunction was apparent, with delayed independent ambulation at 18 months, and at later ages significant deficits in planning with mean motor coordination of 74.8(SD:10.0).

Conclusion: This is the largest comprehensive study of boys with 48,XXXY, which reveals an evolving phenotypic profile. LLD and gross motor delay are presenting features, with intact verbal and performance intelligence. Motor planning deficits were present in infancy with hypotonia (>70%), delayed walking and later graphomotor dysfunction. The benefits of Androgen replacement were evident but less impactful than in 47, XXY. Further investigation is the underway to evaluate the impact of the additive X chromosomes on neurodevelopmental progression.

Keywords: Klinefelter syndrome, 48, XXXY, Sex Chromosome Variation, Neurodevelopment, Phenotype.

POSTER 15: Common Medical Comorbidities have no Impact on Cognitive and/or Behavioral Outcomes in Children with 22q11.2 Deletion Syndrome

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Background: Congenital heart disease (CHD) is one of the most common features (~75%) associated with 22q11.2 deletion syndrome (22q11.2DS). Neurodevelopmental dysfunction is the most common adverse outcome of CHD with the prevalence of adverse effects varying according to cardiac diagnoses. Hypocalcemia is also common in patients with 22q11.2DS (~50%) and has been suggested to affect long-term developmental outcome. Overall mean Full Scale IQ (FSIQ) scores in children with 22q11.2DS fall in the borderline range (70-79) and several behavioral differences are observed including ADHD, anxiety and ASD. Knowledge of medical associations with potential to alter cognitive outcomes/behavioral phenotypes is useful in providing anticipatory care and counseling for families and caregivers.

Methods: We retrospectively audited our records on 1305 patients with 22q11.2DS for the presence and severity of CHD, hypocalcemia, a behavioral diagnosis of ADHD/anxiety/ASD and FSIQ scores.

Results: 1073 (82%) patients were found to have a CHD of any kind including those that resolved spontaneously. 360/1073 (34%) had an age appropriate Wechsler neuropsychological evaluation yielding a FSIQ score. 265/1073 (25%) patients had both calcium levels measured and a FSIQ. Medical comorbidities, as well as presence or absence of ADHD/anxiety/ASD, were compared with FSIQ scores. Mean FSIQ for patients with CHD was 75.32 v. those sans CHD which was 76.64; MFSIQ for those with a history of hypocalcemia was 77.09 v. no hypocalcemia which was 77.27; a combination of CHD and hypocalcemia yielded a FSIQ of 77.41 v. no CHD or hypocalcemia which was 77.22; neither presence nor absence of CHD/hypocalcemia affected behavioral outcomes; likewise behavioral findings were not correlated with FSIQ.

Conclusion: We found common medical comorbidities have no impact on cognitive/behavioral outcomes in our cohort of children with 22q11.2DS. This data may reflect the benefits of early diagnosis and optimal surgical/ medical remediation or the intractable effect of haploinsufficiency of genes within the 22q11.2 region.

Keywords: 22q11.2 deletion; chromosome; comorbidities; behavioral phenotype; FSIQ.

POSTER 16: A Structured Assessment of Motor Function and Behavior in Patients with Kleefstra Syndrome

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Background: Kleefstra syndrome has only recently been described and is considered a rare disorder. Data on this syndrome are scarce. Therefore, we conducted a structured assessment of a group of Norwegian patients with Kleefstra syndrome. The aim of this study was to further our understanding of this syndrome. **Methods:** All patients were subjected to a structured observation by a pediatrician and a physiotherapist.

Standardized questionnaires and structured interviews were utilized. Eight patients (age between 2 and 27) and their parents participated.

Results: Overall, the clinical picture we found in Norwegian patients with Kleefstra syndrome is similar to the findings described in the literature. Muscular hypotonia and its manifestations were present in all patients, regardless of their age. The mean values for all Vineland Adaptive Behavior Scale II domains (communication, socialization, daily living skills, and motor skills) were significantly lower than the mean of the reference population (p < 0.001). The results from the Social Communication Questionnaire indicated that all patient values exceeded the cut-off value, suggesting the possibility of autism spectrum disorder. The emotional and behavioral problems assessed by the Child/Adult Behavior Checklist frequently occurred in the borderline clinical range (n=6) but were less frequent in the clinically significant range (n=4). In the present study, almost half of the patients reported significant sleep problems.

Conclusion: Muscular hypotonia and its manifestations were observed in all patients with Kleefstra syndrome in this study, and these features persisted into adulthood. Behavioral issues, such as significantly compromised adaptive behavior or possible autistic behavior, were present in all patients, and sleep problems were also noted in almost half of the patients. In conclusion, patients with Kleefstra syndrome present in all age groups with a broad range of clinical problems. Therefore, these patients require a multidisciplinary follow-up that continues after their transition into adulthood.

Keywords: autism spectrum disorders, behavior, growt, Kleefstra syndrome, motor function, rare disorder, sleep.
POSTER 17: Incontinence in Persons with Genetic Syndromes

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Background: Rates of incontinence are higher in persons with genetic syndromes than in typically developing peers. They are associated with the level of intellectual disability (ID). So far, incontinence was examined only in specific syndromes. The aim of this study was to compare the rates of incontinence over the life span and to identify risk factors in a large cohort of several syndromes using the same methods.

Methods: Parents/carergivers of persons with Down Syndrome (DS), Williams Syndrome (WBS), Noonan Syndrome (NS), Angelman Syndrome (AS) and Mowat-Wilson Syndrome (MWS) filled out two questionnaires on incontinence, as well as the Developmental Behavior Checklist (DBC). Data from 773 individuals aged 4-59 years (n_{DS}=317, n_{WBS}=231, n_{NS}=29, n_{AS}=153, n_{MWS}=43) in 3 age groups (children: 4-12 years; teenagers: 13-17 years; adults: >18 years) were evaluated.

Results: The overall rate of incontinence ranged between 21.7% (WBS) and 97.5% (MWS) (DS=25.5%; NS=29.2%; AS=85.6%). Incontinence rates decreased significantly over the age groups in DS (64.0% - 10.3% - 14.0%), WBS (51.5% - 19.4% - 4.7%) and AS (96.6% - 92.6% - 74.0%), but not in NS (50.0% - 14.3% - 16.7%) and MWS (95.7% - 100% - 100%). Constipation was found in NS only in childhood (30%), while there was a significant increase with age in MWS (13.0% - 55.6% - 50.0%). In DS, WBS and AS, the rates remained constant through the lifetime. Incontinence is associated with psychological symptoms in WBS and DS, with epilepsy in AS and with physical disability in DS.

Conclusion: This is the largest study on incontinence conducted in persons with genetic syndromes, so far. Incontinence is common and remains a problem from child- to adulthood, especially in syndromes with severe ID. Not only ID, but also other medical influences (anomalies/malformations, epilepsy, dementia, psychiatric disorders) are involved as risk factors for incontinence.

Keywords: Intellectual disability, genetic syndromes, incontinence, constipation, psychological symptoms.

POSTER 18: Visual Perception Skills: A Comparison between Patients with Noonan Syndrome and 22q11.2 Deletion Syndrome

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Background: Visuo-perceptual abilities in genetic syndromes has not been yet fully characterized in the cognitive domains. A specific study of this function could give us the possibility to better understanding the relation between behavioral phenotypes and genetic characteristics. At this aim, we compared the functionality of the two visuo-perceptual streams in two populations affected by different genetic disorders: the Noonan Syndrome (NS) and the 22q11.2 deletion syndrome (DS).

Methods: Visuo-spatial abilities were evaluated in 19 participants with NS, in 20 participants with 22q11.2 DS and compared to 55 chronological age matched controls. We have proposed an analogous 'form coherence' measure of global processing in the ventral stream and 'motion coherence' measure of global processing in the dorsal stream.

Results: The results of the analysis on the scores obtained at Form Coherence task documented a main effect for Group (p < 0.01). The correct responses in the group with NS and in the group with 22q11.2 DS did not differ from each other and both were significantly lower than that of Controls. A main effect for Group (p < 0.01) emerged also from the analysis on the Motion Coherences Task scores: 22q11.2 DS group obtained significantly lower correct responses than the group with NS and Controls, which did not differ. Conclusion: The performance of groups of children with these genetic syndromes were equivalent for the Form Coherence task and significantly lower in respect to the performance of the control group. On the other hand, in the Motion Coherence task, the performance achieved by the group of children with NS and the Controls was significantly better in respect to the performance achieved by children with 22q11.2 DS. This dissociation in the syndromic groups seems therefore indicative of a better information processing ascribed to the dorsal occipital-parietal stream in children with NS.

Keywords: dorsal stream, ventral stream, visuo-perceptual abilities, Noonan syndrome, 22q11.2 deletion syndrome.

POSTER 19: Fetal Alcohol Spectrum Disorders (FASD): A Neglected Problem in the Field of Intellectual Disability

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Background: Fetal Alcohol Spectrum Disorders (FASD) refers to a spectrum of disorders caused by prenatal alcohol consumption. FASD is a neglected problem in the field of Intellectual Disability (ID). Remarkable, because it is hundred percent preventable. Our research focusses on a systematic approach for prevention and clinical management of FASD. The current study aims to provide the required evidence to estimate the FASD prevalence and identify which alcohol consumption patterns are most in need of a strategy for health promoting programs. **Methods:** A systematic literature search on global FASD prevalence and related maternal alcohol consumption was conducted in multiple databases up to August 2015, including PubMed, PsychINFO, PsychARTICLES, ERIC, CINAHL, EMBASE and MEDLINE. A query was generated and resulting hits were exported and screened by two independent screeners, after which results were extracted and (meta-) analyzed.

Results: Results showed that FASD is a worldwide problem with prevalence estimates ranging from o to 176.77 per 1,000 live births. Substantial heterogeneity prompted meta-regressions, revealing geography as important moderator, and suggested cautious interpretation. Furthermore, studies lacked information to indicate when drinking during pregnancy becomes harmful for the unborn child. Also, a substantial variation in alcohol consumption measures was found, ranging from any consumption to fine-grained specification of intensity and frequency. While precluded meta-analysis, this variation did enable development of guidelines for measuring alcohol consumption. Our latest research findings will be presented.

Conclusion: The results show that alcohol use during pregnancy is an important health problem. There is a need to gain more understanding in preventive strategies and clinical aspects of FASD.

Keywords: Fetal Alcohol Spectrum Disorder(s); Fetal Alcohol Syndrome; Intellectual Disability; Systematic Literature Review; Prevention; Clinical Management.

POSTER 20: Delineating Anxiety in William Syndrome Utilising Meta Analytical and Interview Methodologies

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Background: The profile of anxiety in rare genetic syndromes such as Williams Syndrome (WS) may be atypical; however, anxiety in WS has often been assessed with psychiatric tools developed for the general population. These tools may overlook important markers for anxiety associated with the behavioural phenotype of WS. In this study, a meta-analysis was conducted to synthesise and evaluate existing literature on anxiety in WS. In addition, a bottom-up interview was conducted to delineate the profile of anxiety in WS.

Method: The PRISMA guidelines were applied for the meta-analysis. The bottom-up interview was developed to capture the profile of anxiety in WS and included questions about the development of anxiety, broad setting events, immediate triggers, behaviours, and management strategies. Interviews were conducted over the telephone with parents of individuals with WS (*n*=13, *M* age=21.92, *SD*=11.12).

Results: The meta-analysis indicated that anxiety disorders were highly prevalent in WS. Specific phobias (39%) and generalised anxiety disorder (10%) were most commonly reported. The risk of anxiety in individuals with WS increased four-fold (risk ratio 4.00 [95% Cl 2.27 - 7.06]; p<0.001) in comparison to individuals with heterogeneous intellectual disability. Triggers and behaviours associated with anxiety were identified during the interviews that were not captured by the psychiatric assessments.

Conclusion: Specific anxiety disorders are elevated in WS and understanding the development and profile of these disorders in WS may further our understanding of anxiety in other groups. However, research studies that utilise a range of methodological approaches are needed to delineate atypical profiles of anxiety.

Keywords: William Syndrome, Phobia, Generalised-Anxiety, Meta-analysis

POSTER 21: Investigating the Role of Treatable Genetic Diseases in Schizophrenia and Bipolar Disorder Populations and its Clinical Diagnostic Impact

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Background: Many rare genetic syndromes are known to phenotypically manifest with psychiatric symptoms that can be indistinguishable from primary psychiatric disorders. While the majority of ongoing psychiatric genetic research has been dedicated to the identification and characterization of genes involved in primary psychiatric disorders, little research has been done to determine the extent to which rare genetic variants contribute to the overall psychiatric disease load. Within schizophrenia and bipolar populations, we are conducting the first study of its kind to determine the prevalence of four treatable genetic syndromes (Niemann Pick disease type C (NPC), Wilson disease, acute intermittent porphyria (AIP), and homocystinuria (HOM)) manifesting as primary psychiatric disorders.

Methods: We are screening 1323 schizophrenia and 1200 bipolar disorder samples, along with 980 sex- and age-matched healthy controls, all with available DNA and extensive phenotype data. We are using a matrix-type pooled targeted deep sequencing of the genes *NPC1*, *NPC2*, *ATP7B*, *HMBS*, and *CBS* to screen for the four genetic diseases. Pathogenic variants within the targeted genes will be identified using an in-house analytic pipeline with quality control, variant discovery designed specifically for identifying variants in the matrix pooled targeted sequencing approach, and functionality prediction programs (i.e. Polyphen, SIFT, Scone) to determine variant pathogenicity. Sanger sequencing will be used to validate identified mutations and decrease false positive calls. **Results:** We hypothesize that a significant sub-population of patients with psychiatric disorders have underlying rare genetic conditions.

Conclusion: Screening for treatable genetic diseases, such as NPC, WD, AIP and HOM, within schizophrenia and bipolar samples could provide a possible explanation for severe treatment resistance and treating the genetic condition can effectively "cure" patients of their otherwise difficult-to-treat psychiatric symptoms. Ultimately, this proof-of-principle study will lead to the development of molecular diagnostic tools for detection of underlying genetic disorders in psychiatric patients and will allow for precision medicine.

Keywords: rare genetic diseases, psychiatric diseases, schizophrenia, bipolar, targeted sequencing, personalized medicine.

POSTER 22: Improving Outcome Measures for Clinical Trials in Fragile X Syndrome: Psychometric Properties of Fragile X Syndrome-Specific Rating Scales in a Treatment Trial of Trofinetide

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Background: Fragile X syndrome (FXS) is a genetically determined neurological disorder characterized by intellectual disability and associated psychiatric symptoms. Recent trials of medications targeting neurobiological abnormalities in FXS have highlighted how critical high quality outcome measures are to well-designed clinical trials. To complement existing validated measures used in studies of FXS, we designed two novel FXS-specific assessments: FXS Rating Scale (FXSRS) and a FXS-specific, clinician-rated visual analog scale (FXSDS-VAS) following a paradigm of elaboration from natural history studies. The FXSRS is a 34-item clinician rating scale providing a total and subscale scores (Core Phenotype, FXS with Autism Spectrum Disorder (ASD), and Associated Phenotypic Features). The FXSDS-VAS captures clinician ratings of Repetitive/Stereotyped Behaviors, Speech/ Language, Anxiety/Phobias/Social Withdrawal, Motor Performance, Sensory Sensitivity and Cognition. Both are designed to assess clinically meaningful changes across the FXS phenotype. We report preliminary data on the use of these scales in a Phase 2 study in FXS of trofinetide, an investigational IGF-1 terminal tripeptide analog. Methods: The FXSRS and FXSDS-VAS were assessed as efficacy outcomes in a randomized, placebo-controlled clinical trial. 70 adolescent and adult males with FXS received double-blinded treatment of trofinetide, 35 mg/kg (n=24) or 70 mg/kg (n=21), or placebo (n=25), twice daily. Psychometric properties of the scales were analyzed. Results: Both the FXSRS and FXSDS-VAS captured positive treatment effects at 70 mg/kg. Internal reliability for the FXSRS was high at both initial and end of treatment administrations (Cronbach's alpha=0.881 and 0.911). Preliminary data on inter-rater reliability and construct validity will be presented.

Conclusion: Preliminary data demonstrate excellent consistency of the items on the FXSRS and both scales were sensitive to change in a placebo-controlled medication trial. Both assessments show potential as useful measures of treatment effects on FXS-related symptoms in intervention studies. They also have potential for applicability to other disorders such as ASD.

Keywords: Fragile X, outcome measures, clinical trials.

POSTER 23: Molecular Biomarkers Predictive of Sertraline Treatment Response in Young Children with Fragile X Syndrome

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Background: Several neurotransmitters involved in brain development are altered in Fragile X syndrome (FXS), the most common monogenic cause of autism spectrum disorder. Serotonin plays a vital role in synaptogenesis and postnatal brain development. Deficits in serotonin synthesis and abnormal neurogenesis have been shown in young children with autism, suggesting the presence of a developmental window within the first years of life when treatment with a selective serotonin reuptake inhibitor may be most effective. In this study we aimed to identify molecular biomarkers predictive of response to sertraline treatment in young children with FXS. **Methods:** We conducted a double-blind, randomized, placebo-controlled 6-month clinical trial of low-dose sertraline in children ages 24-68 months old with FXS. Genotypes were determined for several genes including Serotonin Transporter, Brain Derived Neurotrophic Factor (BDNF), Monoamine Oxidase A (MAOA), CYP4502D6, and CYP4502C19. Plasma levels were measured for BDNF, APP and MMP9. Associations between genotypes and changes from baseline in primary and secondary outcome measures were modeled using linear models.

Results: A significant association was identified between the BDNF polymorphism and improvement on several clinical measures including the Clinical Global Impression score (P= 0.008), and the Cognitive T Score (P= 0.017) in those treated with sertraline compared to the placebo group. Additionally, MAOA, CYP4502C19 and 2D6, and the serotonin transporter gene showed a significant correlation with secondary measures including fine motor age equivalent score, social participation raw score and clinical global impression.

Conclusion: This study shows that polymorphisms of genes involved in the serotonin pathway could play a potential role in predicting response to sertraline treatment in young children with FXS. However, studies with a larger sample size are warranted to confirm these initial findings.

Keywords: Fragile X Syndrome, Serotonin, Selective Serotonin Reuptake Inhibitor, BDNF, biomarkers.

POSTER 24: The Association between Cortical Tubers and Autism Severity in Tuberous Sclerosis Complex

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Background: Tuberous Sclerosis Complex (TSC) is an autosomal dominant disorder characterized by the presence of cortical tubers and high prevalence rates of autism spectrum disorders (ASD). Previous studies have suggested tuber burden to be an important predictor for an ASD diagnosis. To date, no studies have investigated the association between tuber count and continuous measures of ASD severity. Furthermore, the role of cognitive functioning in the association has been insufficiently studied.

Methods: In a sample of 52 TSC patients (24 boys, 0-17 years) ASD severity was assessed using the Autism Diagnostic Observation Scale (ADOS). Continuous standardized calibrated severity scores were calculated. Cognitive functioning was assessed using different intelligence measures according to best practice standards, and IQ or developmental quotients (DQ) were calculated. Tuber count and location were manually recorded, using FLAIR or T2-weighted images from a 1.5T Siemens scanner. Regression and mediation analyses were performed.

Results: Total tuber count was strongly related to total ASD severity (β =0.46, p<0.001), as well as to the severity of restricted and repetitive behaviors (β =0.49, p<0.001) and social affect (β =0.37, p=0.008) specifically. When IQ/ DQ was added to the analyses, only total (β =0.29, p=0.046) and frontal (β =0.30, p=0.042) tuber count remained significantly associated to the severity of restricted and repetitive behaviors. Formal mediation analyses confirmed these findings and showed that all other initial associations were fully mediated by IQ/DQ. **Conclusion:** Children with more cortical tubers displayed more severe ASD symptoms. Cognitive functioning was identified as an important explanatory factor in this association. However, regardless of intelligence, children with more frontal and temporal tubers displayed more severe restricted and repetitive behaviors. Finally, our study underlines the importance of separately studying problems in social communication and interaction, and restricted and repetitive behaviors.

Keywords: TSC, tubers, autism, social affect, restricted/repetitive behaviors, intelligence.

POSTER 25: EU Rare Disease Policy and Rett Syndrome

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Background: Rett syndrome (RTT) is a rare neurodevelopmental disorder arising from a genetic mutation on the X chromosome. In recent years there has been an increasing focus in Europe on developing links, both within and between countries, between researchers, clinicians, therapists, individuals with RTT and their families/ caregivers to maximise approaches towards treatment and long-term-management of the disorder.

Methods: This presentation explores the important role played by the European Rett Parent Associations and the Rett Expertise Centres that exist in many EU member states and places the contribution of both within the context of the European Commission policy on rare diseases.

Results: EU policy on rare diseases provides significant political leverage within the member states in the quest to raise awareness, promote research and develop a stronger knowledge base, and to provide more equitable, higher quality services and support for individuals and families affected by rare disorders like RTT. The inclusion of rare diseases within Articles 12 and 13 of the Cross-Border Directive and the subsequent recommendations of EUCERD are clear signals that minority health groups cannot and should not be ignored. Pan-European collaboration between stakeholders (parents, clinicians, therapists, educators, researchers) is recognised as an integral and fundamental requirement.

Conclusion: Umbrella organisations such as the European Scientific Rett Research Association (ESRRA), a collaborative European platform for research focusing on RTT, and Rett Syndrome Europe (RSE), an umbrella organisation for the European Parent Associations, have important roles to play whilst European (and international) conferences offer valuable opportunities for these groups to come together to engage in discussion and dissemination of latest research, treatment and management techniques. A commitment by all EU countries to the sharing of clinical data through pan-European (and/or international) registries/databases for rare diseases such as RTT is also a vital step in the collaborative endeavour.

Keywords: Rett syndrome, parent associations, centres of expertise, European policy, rare disease networks, rare disease registries.

POSTER 26: Variability of Cognitive Behavioral Phenotype in Klinefelter Syndrome (KS) and other Sex Chromosomal Aneuploidies (SCAs)

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Background: SCAs are the most frequently occurring chromosomal abnormalities with an incidence of 1 in 400 births. Males with SCAs are known to have variability in their developmental profile. Different life ages are associated with cognitive and behavioral characteristics. Aim of this paper is to illustrate clinical variability in the different SCAs.

Methods: The sample was composed by 61 subjects (mean age=21.16 yrs, range:1-54) with karyotype 47,XXY (73%), 49,XXXXY (7%), 48,XXYY (9%), mosaicism 47,XXY/48,XXXY (2%), 47,XYY (5%), 48, XXXY (2%), 49, XXXYY (2%). Only 5 subjects have been diagnosed prenatally (4 KS and 1 XXYY). Primary caregivers completed a comprehensive questionnaire detailing birth, medical, developmental and psychological history. Cognitive and behavioral assessment was performed with clinical interviews and psychometric questionnaires (WISC-R, WAIS-R, CPM, Token Test, VABS, SCL90, SCQ) in adolescent and adult subjects (N=55).

Results: Mean IQ in typical KS was 87.45 ± 2 ds (sd=20.12) range 45-123, VIQ 91.74 (sd=19.55) range 50-130 and PIQ 86.87 (sd=20.87) range 50-126. Mean IQ in other SCAs was 68.71 (sd = 20.81) range 45-106, VIQ 69.36 (sd=21.97) range 47-113 and PIQ 74.72 (sd=21.70) range 45-112. In CPM KS subjects scored 27.75 (range 13-36) and 31.50 in the Token Test (range 21-35) while in CPM the other SCAs subjects scored 22.27 (range 10-35) and 22.50 (range 9-31) in the Token Test (p<0.05). VABS scores documented more marked impairment on adaptive behavior in atypical SCAs subjects than in KS subjects. SCL90 documented an elevation of psychotic traits in the 40% of KS subjects and 30% of other SCAs subjects (all of them with XXYY karyotype). Autistic traits were present in 45% of the SCAs subjects

Conclusion: A precise identification of the cognitive and behavioral phenotype in different SCAs may enhance the clinical treatment, anticipatory guidance, and care throughout the lifespan.

Keywords: Sex chromosomal aneuploidies, Behavioral phenotype.

POSTER 27: Incontinence, Psychological Problems and Parental Stress in Children and Adolescents with Autism Spectrum Disorder

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Background: Autism spectrum disorder (ASD) is defined by persistent deficits in reciprocal social interaction, communication and language, as well as stereotyped and repetitive behavior. Children with ASD have higher rates of incontinence and gastrointestinal tract symptoms. Parents of children with ASD show more parental stress and psychological symptoms. The aim was to examine incontinence in children/adolescents with ASD as well as stress and psychopathological symptoms in their parents.

Methods: Preliminary data of 53 children (45 boys, mean age =9.6 years), consecutively presented in an outpatient clinic for autism, as well as 53 matched continent controls (43 boys, mean age = 10.2 years) are shown. All patients and their parents underwent the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R). All children received sonography (rectum, bladder), uroflowmetry, bladder diary, physical examination, IQ test, parental psychiatric interview and a questionnaire regarding incontinence and psychological symptoms (CBCL). Additionally, parents filled out the Social Communication Questionnaire (SCQ), Adult Self Report (ASR) and a questionnaire on parental stress (ESF).

Results: In the patient group, 20 received a diagnosis of ASD. Children with ASD had significantly higher rates of incontinence than controls (nocturnal enuresis 11.1%, daytime urinary incontinence 16.7%, fecal incontinence 22.2% in children with ASD vs. 0% in controls). Constipation was not significantly higher in ASD. Children with ASD showed significantly more pathological uroflow-patterns than controls. Children with ASD had significantly higher CBCL- and SCQ-scores, as well as a significantly lower IQ. Parental stress, as well as psychological problems, was significantly higher in parents of children with ASD than in parents of controls.

Conclusion: Children with ASD have more incontinence-associated problems of the lower urinary tract, as well as psychological symptoms. Parents of children with ASD experience more stress. Screening, assessment and treatment of incontinence in children with ASD are recommended.

Keywords: Autism spectrum disorder, incontinence, psychological symptoms, parental stress.

POSTER 28: Associations between Executive Functioning and Challenging Behaviour: Evidence from Lowe Syndrome

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Background: Deficits in executive functioning (EF) have been implicated in aggressive behaviour, temper outbursts and more severe and persistent self-injurious behaviour (SIB). This study aimed to examine these associations in Lowe syndrome (LS); a syndrome where challenging behaviour has been noted more frequently than in individuals with intellectual disability of heterogeneous aetiology.

Methods: Twenty individuals with LS, aged 6 to 34 years, completed two computerised delay of gratification tasks, a go/no-go inhibition task and a scaled set-shifting task. The duration, frequency and severity of SIB, aggression and temper outbursts were measured using an adapted version of the Challenging Behaviour Questionnaire. The Vineland Adaptive Behavior Scales-II were included as a proxy measure of ability level. In addition to the direct assessments, executive functioning was measured using the Behavior Rating Inventory of Executive Functioning - Preschooler Version (BRIEF-P).

Results: Individuals with LS engaged in SIB (50%), aggressive behaviour (55%), and temper outbursts (75%). Poorer performance on a delay of gratification task was strongly associated with a higher temper outburst composite score (R = -.74, p < .001). Similarly, poorer emotional control measured by the BRIEF-P was associated with a higher temper outburst score (R = .76, p = .001). A higher SIB score was strongly associated with poorer inhibition, shifting, working memory and emotional control measured by the BRIEF-P (Rs >.6), but was not associated with the direct experimental tasks. The significant associations remained after adaptive behaviour and communication were controlled for.

Conclusion: These results provide further evidence of a link between EF and challenging behaviour. Further investigation of these associations in LS may inform understanding of pathways from cognition to behaviour, which may inform models of the development and maintenance of temper outbursts and SIB in other syndrome groups.

Keywords: Executive Functioning, Challenging Behaviour, Self-Injurious Behaviour, Temper Outbursts, Delay of Gratification, Lowe syndrome.

POSTER 29: MTOR Inhibitor Reverses Autistic-Like Social Deficit Behaviours in Adult Rats with both Tsc2 Haploinsufficiency and Developmental Status Epilepticus

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Background: Epilepsy is a major risk factor for autism spectrum disorder (ASD) and complicates clinical manifestations and management of ASD significantly. Tuberous Sclerosis Complex (TSC), caused by TSC1 or TSC2 mutations, is one of the medical conditions most commonly associated with ASD and has become an important model to examine molecular pathways associated with ASD. Previous research showed reversal of autism-like social deficits in Tsc1+/- and Tsc2+/- mouse models by mammalian Target of Rapamycin (mTOR) inhibitors. However, at least 70% of individuals with TSC also have epilepsy, known to complicate the severity and treatment-responsiveness of the behavioural phenotype. No previous study has examined the impact of seizures on neurocognitive reversal by mTOR inhibitors.

Methods: Adult Tsc2+/- (Eker)-rats express social deficits similar to Tsc2+/- mice, with additive social deficits from developmental status epilepticus (DSE). DSE was induced by intraperitoneal injection with kainic acid at postnatal days (P) 7 and P14 (n=12). The experimental group that modelled TSC pathology carried the Tsc2+/- (Eker)-mutation and was challenged with DSE. The wild-type controls had not received DSE (n=10). Four months old animals were analysed for social behaviour (T1), then treated 3 times during one week with 1 mg/kg Everolimus and finally retested in the post-treatment behavioural analysis (T2).

Results: In the experimental group, both social interaction and social cognition were impaired at T1. After treatment at T2, behaviour in the experimental group was indistinguishable from controls.

Conclusion: The mTOR inhibitor, Everolimus, reversed social deficit behaviours in the Tsc2 haploinsufficiency plus DSE animal model to control levels.

Keywords: Animal model, autism spectrum disorder, Everolimus, experimental therapy, social cognition, Tuberous Sclerosis Complex.

POSTER 30: Impulsivity in Children with Tuberous Sclerosis Complex - Informant Report and Direct Assessment

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Background: Tuberous sclerosis complex (TSC) is associated with a range of TSC-Associated Neuropsychiatric Disorders (TAND), including Attention Deficit Hyperactivity Disorder (ADHD). Impulsivity, a diagnostic feature of ADHD, is frequently reported by caregivers in TSC but has received little focussed examination, despite associations with poorer behavioural and achievement outcomes.

Methods: The current study assessed impulsivity in children with TSC (N = 18, mean age 8.9 years) via caregiver report (using The Activity Questionnaire, Burbidge et al. 2010) and direct assessment (using both a *hot* motivationally salient snack delay task and a *cool* cognitive go/no go task). To examine whether children with TSC are more impulsive than typically developing (TD) peers of comparable age and ability, findings were contrasted to those of a chronological age-matched sample of TD children (N = 16, mean age 8.5 years) and a subset of TD children matched on receptive vocabulary (TD N = 15, TSC N = 13).

Results: Children with TSC had higher scores, indicating greater impulsivity, on the caregiver measure than both TD children matched on age and TD children matched on ability. They also waited a significantly shorter time in the snack delay task than both age and ability-matched TD children, but did not make more commission errors (indicative of impulsive responding) in the go/no go task than either age or ability-matched TD children.

Conclusion: Findings confirmed suggestions that impulsivity is a concern for caregivers of children with TSC, with ratings exceeding those for both age and ability-matched TD peers. Novel findings demonstrate this impulsivity was reflected in direct behavioural assessments in a hot impulsivity task, but not a cool task. This suggests that impulsivity described in children with TSC may be related to difficulties with inhibitory control particularly in highly motivated situations, which has implications for behavioural management and intervention strategies.

Keywords: Tuberous sclerosis complex, impulsivity, ADHD.

POSTER 31: Characterizing the Anxiety Phenotype in Triple X Syndrome

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Background: Triple X syndrome (47,XXX) occurs in approximately 1 in 1000 female births, and can be associated with developmental delays and psychological differences. The behavioral phenotype of Triple X includes anxiety and shyness. In a previous study of 35 girls (age 5-24yo), 40% met DSM-IV criteria for anxiety disorder. In this project we studied profiles of anxiety symptoms in Triple X at different stages of development.

Methods: Females with nonmosaic Trisomy X were selected from a large study on health and development in sex chromosome disorders. Participants were divided into 3 age groups (2-6y, 7-11y, and 12-24y). Data were analyzed from a parent checklist of behavioral symptoms and a standardized behavioral questionnaire (BASC-2). To minimize ascertainment effects in a cross-sectional sample that included bias toward affected participants in the older age group, we analyzed profiles of anxiety symptoms into subsets of endorsing anxiety or individuals with an anxiety disorder diagnosis.

Results: Of 65 females, 51 (78.4%) endorsed anxiety symptoms (2-6y: 18/26 (69.2%), 7-11y: 13/15 (86.6%), 12-24y: 20/24 (83.3%)). The most common behavioral symptoms in the youngest age group included shyness (50%) and tantrums/outbursts in (50%). The rates of most behaviors increased in the older age groups, most significant differences between age groups were social difficulties, excessive worry, reclusive behavior, mood lability, and depressive symptoms in the oldest group. Further, 3/26 (11.5%) in the youngest age group met clinical criteria for selective mutism, previously unreported in Trisomy X. Mild to moderate elevations were found in the older age groups on the BASC-2 in anxiety, depression, somatization and atypicality (T score means 61.75-66).

Conclusion: Anxiety symptoms are common in Triple X syndrome across age groups. Further research is needed to better characterize anxiety in Triple X and to understand the interplay between anxiety and other features including cognitive and language deficits.

Keywords: sex chromosome aneuploidy, 47,XXX, Triple X Syndrome, Anxiety.

POSTER 32: The Behavioural Phenotype of XXYY in Childhood: A Comparison with Intellectual Disability

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Background: 48, XXYY Syndrome (XXYY) is a genetic condition associated with intellectual disability (ID) and a higher risk of mental health disorders, most notably autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). People with XXYY typically score in the borderline to intellectually disabled IQ score range. Previously, the XXYY behavioural phenotype has been compared to population samples across all ages. This study aims to compare the phenotype of children with XXYY to matched controls with an intellectual disability, in order to investigate whether the XXYY phenotype is distinct from that of ID.

Methods: The study used online structured psychiatric assessments called the Strengths and Difficulties Questionnaire (SDQ) and the Development and Wellbeing Assessment (DAWBA). The assessments were conducted with the parents of 15 XXYY children and 30 matched controls aged 4-14. Both groups were recruited through the IMAGINE ID study, which is comprised of children with ID due to a genetic cause. The control group is made up of two controls per case; matched for sex, chronological age and mental age.

Results: Analysis of the SDQ showed significant differences between groups on the total difficulties score, and emotional and conduct subscales. DAWBA analysis showed significantly higher rates of oppositional defiant disorder in the XXYY group compared to controls. Overall the rates of social communication difficulty did not significantly differ between groups.

Conclusion: The XXYY behavioural phenotype appears to be associated with increased levels of conduct problems when compared to matched controls with ID. This suggests that these domains of difficulty may relate to the XXYY phenotype rather than ID alone.

Keywords: XXYY, sex chromosome aneuploidies, intellectual disability, conduct disorder.

POSTER 33: Limited Exposure to Flexible Routines as Task Switching Develops may be Associated with More Subsequent Resistance to Change in Individuals with Prader-Willi Syndrome

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Background: Many individuals with Prader-Willi syndrome (PWS) demonstrate a strong resistance to change and unexpected changes are a common trigger for temper outbursts. Our previous experimental work has provided some evidence that increased exposure to certain routines without change may accentuate the difficulties experienced following changes to those routines. Here, we examined the relationships between resistance to change and varying levels of exposure to routines over the life course.

Methods: The caregivers of 10 individuals with PWS (5-23 years) participated in a structured/semi-structured interview in which they used a five-point Likert-type scale to rate the level of rigidity in routines and environments individuals had been exposed to at different stages of their lives. Caregivers also rated individuals' current resistance to change. Open ended questions on routines and resistance to change were included. **Results:** Interviews demonstrated acceptable inter-rater and inter-informant reliability. Descriptive, correlational and comparative analyses converged to suggest that increased exposure to rigid routines during the primary school life phase may be associated with increased resistance to change later in life. However, in individuals with already established resistance to change, structured routines may be particularly important during primary school years, when children's cognitive control processes - including task switching, which has been linked to individuals' abilities to cope with change - develop rapidly. Strategies that increase flexibility in routines during the primary school years may reduce the development of subsequent resistance to change. However, careful research is needed to understand how to increase flexibility in routines during early life without negatively impacting on children's current behaviour and wellbeing.

Keywords: Prader-Willi syndrome; routine; autism spectrum disorder; task switching; temper outbursts; early intervention.

POSTER 34: Improving Task Switching in Children with Prader-Willi Syndrome: Fun, Games and Being in the Moment

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Background: Deficits in task switching - responding flexibly depending on external demands - have been associated with temper outbursts in children with Prader-Willi syndrome (PWS) following changes to routines or plans. Switching can be improved via practise but this does not necessarily extend to daily life gains. However, engagement with certain commercial video games, which are motivating, exciting and embody principles of efficient learning, can mediate improvements in task switching outside the game environment.

Methods: Seven children with PWS collaborated in the design of TASTER, a prototype switching training game. Self and informant report ratings, behaviour observations and measurements of heart rate were applied to make the game usable and motivating. Six children with PWS are engaging with a placebo controlled cross-over evaluation of the effect of 1-3 hours of engagement with TASTER on switching skill. Switching is indexed using four neurocognitive tests and a standardised informant report questionnaire.

Results: TASTER involves controlling a character to collect objects, which participants preferred. Certain game features limited usability, as indicated by repeated questioning by children, so were dropped. Other game features were enjoyed by participants as indicated by positive vocalisations. Heart rate data were useful for triangulating how individuals responded to the game. Participants experienced moderate to high "flow" whilst playing, a state closely linked to motivation. Results from the first phase of the evaluation indicate that gains in the direct measures of switching were limited to children who have engaged with the "active" game. Informant report data indicate non-specific gains. The results of the cross-over phase and those from further participants will be discussed.

Conclusion: Human-centred design with children with PWS allowed a prototype switching training game to be developed in line with children's preferences. Initial results suggest that even short term engagement with the training can have a positive effect on task switching ability.

Keywords: Cognitive training; Prader-Willi syndrome; Video games; Task switching; Executive Functioning; Intellectual Disability.

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SSBP Syndrome Sheets 2016

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 (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 (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). 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-phenotype correlations have been reported (Gentile et al., 2010), with a de novo deletion associated with a greater deficit across all areas of cognition compared to ICD, UPD and UBE3A mutation. 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.

Key references

- Boyd, S., Harden, A., & Patton, M. (1988). The EEG in early diagnosis of the Angelman (happy puppet) syndrome. European journal of pediatrics, 147(5), 508-513.
- Brown, W. M., & Consedine, N. S. (2004). Just how happy is the happy puppet? An emotion signaling and kinship theory perspective on the behavioral phenotype of children with Angelman syndrome. Medical Hypotheses, 63(3), 377-385.
- 3. Horsler, K., & Oliver, C. (2006a). The behavioural phenotype of Angelman syndrome. Journal of Intellectual Disability Research, 50(1), 33-53.
- Horsler, K., & Oliver, C. (2006b). Environmental influences on the behavioral phenotype of Angelman syndrome. American journal of mental retardation: AJMR, 111(5), 311.
- 5. Williams, C. A., Driscoll, D. J., & Dagli, A. I. (2010). Clinical and genetic aspects of Angelman syndrome. Genetics in Medicine, 12(7), 385-395.

Mary Heald and Chris Oliver (updated August 2014)

Autism Spectrum Disorder

Classification

Autism Spectrum Disorder (ASD; DSM-5, APA 2013) is a developmental disorder formerly characterized in ICD-10 and DSM-IV as a "triad of impairments" i.e. deficits in reciprocal social interaction and communication, and the presence of restricted, repetitive patterns of behaviour, interests or activities. In 2013 the latest revision of DSM (DSM-5) collapsed these into two core domains to reflect the fact that delays and abnormalities in language are not specific to autism and that almost all individuals with difficulties in reciprocal social interaction also manifest deficits in communication.

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 included in DSM-IV such as Asperger syndrome or Pervasive Developmental Disorder no longer appear, although DSM-5 criteria specify that "Individuals with a wellestablished diagnosis of autistic disorder, Asperger's disorder or Pervasive Developmental Disorder should be give a diagnosis of Autism Spectrum Disorder"

Associated conditions

There is a significant association between ASD and a number of other conditions including ADHD, Tuberous Sclerosis and FragileX. Links with other conditions are also well documented (e.g. rubella, cytomegalovirus, phenylketonuria) although the phenotype in these cases tends to be atypical (Rutter, 2013). Epilepsy, often with onset in early teens, occurs in around 20-30% of individuals with comorbid intellectual disability, but rates are lower in those with normal IQ (Bolton, *et al.*, 2011).

Regression in development, usually around the age of 12 to 24 months, has been reported in many studies although estimates vary from around 15% to as high as 50%. Pickles *et al.*, (2009) suggest that language regression, in particular, is highly specific to ASD and may index an underlying neurodevelopmental anomaly.

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 firstdegree family members. Although ASD is clearly highly heritable, attempts to identify the specific genes involved have met with limited success (Rutter, 2013). Currently, up to 15% of cases of ASD appear to be associated with some form of genetic mutation and it is suggested that the identification of rare mutations (e.g. SHANK 3) and Copy Number Variations (CNV's; i.e. submicroscopic chromosomal deletions or substitutions) may provide evidence of the neural systems that underlie autism (Geschwind, 2011). However, Rutter (2013) notes that these may be related to intellectual disability as much as to autism. It is evident, too, that both common polymorphic variations and rare mutations play a role; there are also genes that are intermediate between rare and common. "The relative importance of rare, common and intermediate frequency genes has yet to be established" (Rutter, 2013).

There is no evidence that single environmental factors (e.g. MMR or other vaccines) cause ASD although more complex environmental risk factors (e.g. immune system abnormalities; pre or perinatal perturbations etc.) cannot be ruled out and the influence of factors such as high maternal (Sandin *et al.*, 2012) or paternal age (Hultman *et al.*, 2011) remains unclear. Moreover, since autism is clearly a multifactorial disorder, the impact of geneenvironment interactions must also be considered, although current understanding of the complex mechanisms involved in gene x environment interactions in autism is very limited.

Prevalence

Although estimates vary, recent epidemiological research suggests that prevalence rates for both children (Baird *et al.*, 2006) and adults (Brugha *et al.*, 2011) are around 1%.

Physical Phenotype

This is usually normal although minor physical anomalies are not uncommon. Enlarged head circumference and atypical patterns of cerebellar developmental have been reported (e.g. Courchesne *et al.*, 2011) although the findings are not entirely consistent and Chawarska *et al.* (2011) suggest that the increase in brain size may be associated with increased body size, rather than being a distinctive brain feature.

Life expectancy/natural history

Life expectancy appears normal. Many individuals, especially those who are more able show improvements in core autism symptoms and behavioural difficulties with age. Outcome is significantly associated with factors such as IQ and severity of social impairment, but prognosis is also affected by the adequacy of educational, occupational and other support systems (Howlin *et al.*, 2013).

Behavioural and cognitive characteristics

As noted above, 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, recent studies suggest that up to 50% of individuals with ASD may be of average intellectual ability (Baird *et al.*, 2006). In children, nonverbal IQ is frequently higher than Verbal IQ, although this pattern may be reversed in older, more able individuals.

Outcome

Functioning in adulthood is determined both by innate cognitive abilities and the levels of educational and post-school support provided. Mental health problems, especially related to anxiety and depression, often emerge in late adolescence/ early adulthood although estimates of rates of mental health disorders vary widely. Some studies suggest that up to 70% of individuals with ASD have one or more comorbid mental health disorders but in non-clinical adult samples, in which detailed psychiatric assessments have been conducted, rates are much lower, at around 22% (Hutton *et al.*, 2008)

Websites

www.nas.org.uk www.researchautism.net

References

- Baird G., Simonoff E., Pickles A. et al. (2006) Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: The Special Needs and Autism Project (SNAP). Lancet 368, 210-21
- 2. Bolton P.F., Carcani-Rathwell I., Hutton J., Goode S., Howlin P. & Rutter M. (2011) Features and correlates of epilepsy in autism. British Journal of Psychiatry 198, 289-294
- 3. Brugha, T.S., McManus, S., Bankart, J., et al. (2011). Epidemiology of autism spectrum disorders in adults in the community in England. Archives of General Psychiatry 68(5):459-466.
- 4. Chawarska, K., Campbell, D., Chen, L. et al. (2011) Early generalized growth in boys with autism. Archives of General Psychiatry, 68, 1021-1031
- Courchesne, E., Webb, S. & Schumann, C. (2011) From toddlers to adults: the changing landscape of the brain in autism. In D. Amaral, G. Dawson, & D Geschwind (Eds) Autism Spectrum Disorders (pp. 875-892) New York: Oxford University Press.
- American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) Washington DC
- Geschwind, D (2011). Autism genetics and genomics: a brief overview and synthesis. In D. Amaral, G. Dawson, & D Geschwind (Eds) Autism Spectrum Disorders (pp. 812-826) New York: Oxford University Press
- 8. Howlin, P., Moss, P., Savage, S., & Rutter, M. (2013) Social outcomes in mid to later adulthood among individuals diagnosed with autism and average non-verbal IQ as children. Journal of the American Academy of Child and Adolescent Psychiatry, 52, 572-581
- 9. Hultman C., Sandin, S., Levine, S. et al. (2011). Advancing paternal age and risk of autism: new evidence from a population based study and a meta-analysis of epidemiological studies. Molecular Psychiatry, 1203-1212, 1
- Hutton J., Goode S., Murphy M., Le Couteur A. & Rutter M. (2008) New onset disorders in individuals with autism. Autism 12, 373-90
- 11. Pickles, a., Simonoff, E., Conti-Ramsden, G. et al., (2009) Loss of language in early development of autism and specific language impairment. Journal of Child Psychology and Psychiatry. 50, 843-852.
- Rutter, M (2013). Changing concepts and findings on autism. Journal of Autism and Developmental Disorders (43, 1749-1757
- 13. Sandin, S., Hultman, C.M., Kolevzon, A. et al. (2012) Advancing maternal age is associated with increasing risk for autism: a review and meta-analysis. Journal of the American Academy of Child and Adolescent Psychiatry, 51, 477-486

Patricia Howlin, 2013

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

References

- Blake K.D., Davenport S.L., Hall B.D., Hefner M.A., Pagon R.A., Williams M.S., et al. (1998) CHARGE association: an update and review for the primary pediatrician. *Clin Pediatr* 37(3), 159-73.
- 2. Hall B. (1979) Choanal atresia and associated multiple anomalies. *J Pediatrics* 95, 395-98.
- 3. Hartshorne T.S., Hefner M.S., Davenport S.L.H., Thelin J.W. (Eds.). *CHARGE Syndrome*. In press. San Diego: Plural Publishing.
- 4. Hittner H.M., Hirsch N.J., Kreh G.M., Rudolph A.J. (1979) Colobomatous microphthalmia, heart disease, hearing loss and mental retardation: a syndrome. *J Pediatr Ophthalmol Strabismus* 16,122-128.
- Janssen, N.; Bergman, J. E. H.; Swertz, M. A.; Tranebjaerg, L.; Lodahl, M.; Schoots, J.; Hofstra, R. M. W.; van Ravenswaaij-Arts, C. M. A.; Hoefsloot, L. H. (2012). Mutation update on the CHD7 gene involved in CHARGE syndrome. *Human Mutation*, 33(8), 1149-1160.
- 6. Pagon R.A., Zonana J., Graham J.M. (1982). CHARGE association. *Pediatrics* 70(5), 827-8.
- 7. Verloes A. (2005) Updated diagnostic criteria for CHARGE syndrome: A proposal. *Am J Med Genet* 133A, 306-308.
- 8. Vissers L.E., van Ravenswaaij C.M., Admiraal R., Hurst J.A., de Vries B.B., Janssen I.M., et al. (2004) Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. *Nat Genet* 36(9), 955-7.
- Wachtel L.E., Hartshorne T.S., & Dailor A.N. (2007) Psychiatric diagnoses and psychotropic medications in CHARGE syndrome: A pediatric survey. J Dev Phys Disabil 19, 471-483.

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).

References

- Coffin G.S., Siris E. & Wegenkia L.C. (1966) Mental retardation with osteocartilaginous anomalies. *Am J Dis Child* 112, 205–213.
- Delaunoy JP, Dubos A., Marques Pereira P. & Hanauer A. (2006) Identification of novel mutations in the RSK2 gene (RPS6KA3) in patients with Coffin-Lowry syndrome. *Clin Genet* 70, 161-6.
- 3. Field M., Tarpey P., Boyle J., Edkins S., Goodship J., Luo Y. *et al.* (2006) Mutations in the
- 4. RSK2(RPS6KA3) gene cause Coffin-Lowry syndrome and non syndromic X-linked mental retardation. *Clin Genet* 70, 509–515.
- 5. Hanauer A. & Young ID. (2002) Coffin-Lowry syndrome: clinical and molecular features. *J MedGenet* 39, 705–713.
- 6. Hunter AG. (2002) Coffin-Lowry syndrome: a 20-year followup and review of long-term outcomes.
- 7. Am J Med Genet 111, 345–355.
- 8. Hunter AG. Coffin-Lowry syndrome; in Cassidy S, Allanson J (eds): *Management of Genetic Syndromes*, 2nd edn. Hoboken, NJ: Wiley-Liss, 2005; 127–138.
- 9. Lowry B., Miller J.R. & Fraser F.C. (1971) A new dominant gene mental retardation syndrome.
- 10. AmJ Dis Child 121, 496–500
- Nakamura M., Magata T., Mori M. & Momoi M.Y. (2005) RSK2 gene mutations in Coffin-Lowry syndrome with drop episodes. Brain Dev 27, 114–117.
- Rojnueangnit K, Jones JR, Basehore MJ, Robin NH. 2013. Classic phenotype of Coffin–Lowry syndrome in a female with stimulus-induced drop episodes and a genotype with preserved N-terminal kinase domain. Am J Med Genet Part A 164A:516–521.
- 13. Temtamy S.A., Miller J.D. & Hussels-Maumenee I. (1975) The Coffin-Lowry syndrome: an inherited faciodigital mental retardation syndrome. J Pediatr 86, 724–731.
- Trivier E., De Cesare D., Jacquot S., Pannetier S., Zackai
 E., Young I., et al. (1996) Mutations in the kinase Rsk-2 associated with Coffin-Lowry syndrome. Nature 384, 567-70.

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/

References

- 1. Brautbar A., Ragsdale J. & Shinawi M. (2008) Is this Coffin-Siris Syndrome or the BOD Syndrome? Am J Med Genet 149, 559-62.
- 2. Coffin G.S. & Siris E. (1970) Mental Retardation With Absent Fifth Fingernail and Terminal Phalanx. Amer J Dis Child 119, 433-9.
- Fleck B.J., Pandya A., Vanner L., Kerkering K. & Bodurtha J. (2001) Coffin Siris Syndrome: Review and Presentation of New Cases From a Questionnaire Study. Am J Med Genet 99, 1-7.
- 4. McGhee E.M., Klump C.J., Bitts S.M., Cotter P.D. & Lammer E.J. (2000) Am J Med Genet 93, 241- 3.
- McPherson E.W., Laneri G., Clemens M.M., Kochmar S.J. & Surti U. (1997) Apparently balanced t(1;7)(q21.3;q34) in an Infant With Coffin-Siris syndrome. Am J Med Genet 71, 430-3.
- 6. Temtamy S.A., Kamel A.K., Ismail S., Helmy N.A., Aglan M.S., El Gammal M., El Ruby M. & Mohamed A.M. (2007) Phenotypic and cytogenetic spectrum of 9p trisomy. Genet Couns 18(1), 29-48.
- Tsurusaki Y; Okamoto N; Ohashi H; Mizuno S; Matsumoto N; Makita Y; Fukuda M; Isidor B; Perrier J; Aggarwal S; Dalal AB; Al-Kindy A; Liebelt J; Mowat D; Nakashima M; Saitsu H; Miyake N; Matsumoto N. Coffin-Siris syndrome is a SWI/SNF complex disorder. Clinical Genetics. 85(6):548-54, 2014 Jun.

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

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

- Kline AD, Krantz ID, Sommer A, Kliewer M, Jackson LG, FitzPatrick DR, Levin AV, Selicorni A. (2007) Cornelia de Lange syndrome: Clinical review, diagnostic and scoring systems, and anticipatory guidance. *Am J Med Gen, Part A 143A*:1287–1296.
- Moss, J. and Oliver, C. (2012). Autism in genetic syndromes: implications for assessment and intervention. *Cerebra E-briefing*. Cerebra
- Welham, A., Moss, J. and Oliver, C. (2012). Special Report: Growing up with CdLS: Changes in adolescence and young adulthood. *Special Issue Report for the Cornelia de Lange Syndrome Foundation*. March, S1-S16.
- Oliver C., Moss J., Petty J., Arron K., Sloneem J. & Hall S. (2003). Self-injurious Behaviour in Cornelia de Lange Syndrome: A Guide for Parents and Carers. Trident Communications Ltd.: Coventry. – Available from the CdLS Foundation UK and Ireland.
- CdLS Foundation UK and Ireland (2007). *Facing the Challenges: A Guide for Caregivers to*
- People with the Cornelia de Lange Syndrome Book and DVD available from the CdLS Foundation UK and Ireland.
- Oliver, C., Moss, J., Petty, J., Tunnicliffe, P., Hastings, R., Howlin, P., Griffith, G., Bull, L.,
- Villa, D. and Yip, M. (2009). Understanding and Changing Challenging Behaviour in Cornelia de Lange Syndrome. Aerocomm Ltd: Essex – Available from the CdLS Foundation UK and Ireland.

References

- Arron K., Oliver C., Hall S., Sloneem J., Forman D. & McClintock K. (2006) Effects of social interaction on pragmatic communication and self-injurious behavior in Cornelia de Lange Syndrome. *Am J Mental Retard* 111, 184–92.
- 2. Basile E., Villa L., Selicorni A., & Molteni M. (2007). The behavioural phenotype of Cornelia de Lange syndrome: A study of 56 individuals. *J Intell Disabil Res* 51, 671–681.
- 3. Beck B. & Fenger K. (1985) Mortality, pathological findings and causes of death in the de Lange Syndrome. *Acta Paed Scand* 74, 765–9.
- 4. Berney T. P., Ireland M. & Burn J. (1999) Behavioural phenotype of Cornelia de Lange Syndrome. Arch Dis Child 81, 333–6.
- Bhuiyan Z. A., Klein M., Hammond P., van Haeringen A., Mannens M.A.M., Van Berckelaer- Onnes I., & Hennekam R.C.M. (2006) Genotype-phenotype correlations of 39 patients with Cornelia de Lange syndrome: The Dutch experience. J Med Genet 46, 568–575.
- Cochran, L., Moss, J., Nelson, L. and Oliver, C. (2015). Contrasting age related changes in autism spectrum disorder phenomenology in Cornelia de Lange, Fragile X and Cri du Chat syndromes: Results from a 2.5 year follow up. American Journal of Medical Genetics, Part C. 169, 188-197
- Collis L., Oliver C., & Moss J. (2006) Low mood and social anxiety in Cornelia de Lange syndrome. J Intell Disabil Res 50, 791-800.
- 8. Deardorff M. A., Kaur M., Yaeger D., Rampuria A., Korolev S., Pie J. *et al.* (2007) Mutations in cohesion complex members SMC3 and SMC1A cause a mild variant of Cornelia de Lange Syndrome with predominant mental retardation. *Am J Hum Gen* 80, 485–94.
- 9. Deardorff, M.A., Bando, M., Nakato, R., Watrin, E., Itoh, T., Minamino, M. et al. (2012). HDAC8 mutations in Cornelia de Lange syndrome affect the cohesin acetylation cycle. *Nature, 489*, 313-317.
- Deardorff, MA, Wilde, JJ, Albrecht, M, Dickinson, E, Tennstedt, S, Braunholz, et al. (2012): RAD21 Mutations Cause a Human Cohesinopathy. *American Journal of Human Genetics*, 90, 1014-1027.
- Gillis L.A., McCallum J., Kaur M., DeScipio C., Yaeger D., Mariani A., Kline A.D., Li H., Devoto M., Jackson L.G., Krantz I.D. (2004) NIPBL mutational analysis in 120 individuals with Cornelia de Lange syndrome and evaluation of genotypephenotype correlations. *Am J Hum Gen* 75, 610-623.
- 12. Gimigliano, A., Mannini, L., Bianchi, L., Puglia, M., Deardorff, M.A., Menga, S. et al. (2012). Proteomic profile identifies dysregulated pathways in Cornelia de Lange syndrome cells with distinct mutations in SMCA1 and SMC3 genes. *Journal* of *Proteomic Research*, *11*, 6111-6123.
- 13. Goodban M.T. (1993) Survey of speech and language skills with prognostic indicators in 116 patients with Cornelia de Lange syndrome. *Am J Med Gen* 47, 1059–1063.
- 14. Hyman P., Oliver C. & Hall S. (2002) Self-injurious behavior, self-restraint, and compulsive behaviors in Cornelia de Lange Syndrome. *Am J Mental Retard* 107, 146–54.

- Kline A. D., Krantz I. D., Sommer A., Kliewer M., Jackson L. G., FitzPatrick D. R. *et al.* (2007) Cornelia de Lange syndrome: clinical review, diagnostic and scoring systems, and anticipatory guidance. *Am J Med Gen* 143A, 1287–96.
- Krantz I. D., McCallum J., DeScipio C., Kaur M., Gillis L. A., Yaeger D. *et al.* (2004) Cornelia de Lange Syndrome is caused by mutations in NIPBL, the human homolog of Drosophila melanogaster Nipped-B. *Nat Gen* 36, 631–5.
- 17. Liu, J & Krantz, ID (2009): Cornelia de Lange syndrome, cohesion, and beyond. *Clinical Genetics*, 76: 303-314.
- Luzzani S., Macchini F., Valade A., Milani D. & Selicorni A. (2003) Gastroesophageal reflux and Cornelia de Lange Syndrome: typical and atypical symptoms. *Am J Med Gen Part A* 119(Suppl.3), 283–7.
- 19. Miyake N., Visser R., Kinoshita A., Yoshiura K.I., Niikawa N., Kondoh T., Matsumoto N., Harada
- N., Okamoto N., Sonoda T., Naritomi K., Kaname T., Chinen Y., Tonoki H., & Kurosawa K. (2005) Four novel NIPBL mutations in Japanese patients with Cornelia de Lange syndrome. *Am J Med Gen* 135, 103–105.
- 21. Moss J., Oliver C., Wilkie L., Berg K., Kaur G., and Cornish K. Prevalence of autism spectrum phenomenology in Cornelia de Lange and Cri du Chat syndromes.(2008). *Am J Mental Retard* 113, 278-291.
- 22. Moss J., Oliver C., Arron K., Burbidge C. and Berg K. (2009). The prevalence and phenomenology of repetitive behaviour in genetic syndromes. *J Aut Dev Disord* 39, 572-588.
- 23. Musio A., Selicorni A., Focarelli M. L., Gervasini C., Milani D., Russo S. *et al.* (2006) X-linked Cornelia de Lange Syndrome owing to SMC1L1 mutations. *Nat Gen* 38, 528–30.
- 24. Nelson, L., Moss, J<u></u> and Oliver, C. (2014). A longitudinal study of affect in children and adults with Cornelia de Lange syndrome. *American Journal on Intellectual and Developmental Disabilities*, 119, 235-252.
- Oliver, C., Berg, K., Moss, J., Arron K. and Burbidge, C. (2011). Delineation of behavioural phenotypes in genetic syndromes. Comparison of autism spectrum disorder, affect and hyperactivity. *Journal of Autism and Developmental Disorders, 41*, 1019-1032
- 26. Reid, D., J. (2010). Execuitve function in Cornelia de Lange syndrome. *Unpublished Thesis, University of Birmingham*.
- 27. Sarimski K. (1997) Communication, social-emotional development and parenting stress in Cornelia-de-Lange syndrome. *J Intell Disabil Res* 41, 70–5.
- 28. Sloneem J., Oliver C., Hall S. & Arron K. (2009). Self-injurious behaviour in Cornelia de Lange syndrome: 2. association with environmental events. *J Intell Disabil Res* 53, 590-603.
- 29. Tonkin E., Wang T. J., Lisgo S., Bamshad M. J. & Strachan T. (2004) NIPBL, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteisn and fly Nipped-B, is mutated in Cornelia de Lange Syndrome. *Nat Gen* 36, 636–41.
- 30. J Moss & C Oliver, July 2010.

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 5p15.1-5p15.3, using cytogenetic analysis (Niebuhr, 1978). More recent work has mapped specific critical areas within this region as being responsible for the expression of the core clinical features of the syndrome. For example, the characteristic high pitched 'cat-like' cry from which the syndrome derives its name has been mapped to the proximal part of 5p15.3, the speech delay to the distal part of 5p15.3 and severe intellectual impairment to 5p15.2 (Overhauser et al., 1994). This distinctive cry is considered the most prominent clinical diagnostic feature of the syndrome (Mainardi et al. 2006). Though relatively rare, CdCS represents the most common deletion syndrome in humans (Cornish et al, 2001).

Physical features and natural history

The distinctive cat-cry is a core feature of the syndrome and is still regarded as an important early clinical diagnostic feature in most but not all

individuals (Mainardi et al. 2006). The cry is thought to be caused by anomalies of the larynx (small, narrow and diamond shaped) and of the epiglottis that is usually small and hypotonic (Neibuhr, 1978). Many infants tend to be of low birth weight and low weight usually persists in the first two years of life for both sexes (Marinescu et al., 2000). Feeding difficulties are common and the associated failure to thrive may be the initial clinical presentation. Some infants may require tube feeding, a process which may have to continue for several years. Gastroesophageal reflux is common in CdCS during the first years of life. Other health problems include respiratory tract infections, otitis media and dental problems. Many individuals with CdCS are prone to developing a curvature of the spine (congenital scoliosis) and this can become more apparent with advancing age. Some of the most frequently cited physically defining features of CdCS are facial characteristics including microcephaly, rounded face, widely spaced eyes, downward slanting of palpebral fissures, low set ears, broad nasal ridge and short neck (Dykens et al., 2000; Marinescu et al., 1999). Studies indicate that facial features change over time, specifically, lengthening of the face and coarsening of features (Mainardi et al. 2006).

Behavioural characteristics

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

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time. Additionally, the behaviour tends to become less marked with age.

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

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

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

Neuropsychological characteristics

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

Useful websites/associations/resources for more information

- www.criduchat.org.uk/
- Oliver, C., Moss, J., Petty, J., Tunnicliffe, P., Hastings, R., Howlin, P., Griffith, G., Bull, L., Villa, D. and Yip, M. (2009). *Understanding and Changing Challenging Behaviour in Cri du Chat Syndrome*. Aerocomm Ltd: Essex -Available from the CdLS Foundation UK and Ireland.
- Cornish K., Oliver C., Standen P., Bramble D. and Collins M. (2003) *Cri-Du-Chat Syndrome: Handbook for Parents and Professionals*, 2nd ed. CdCS Support Group, Earl Shilton.

References

- Arron, K., Oliver, C., Berg, K., Moss, J. and Burbidge, C. (2011). Delineation of behavioural phenotypes in genetic syndromes. Prevalence, phenomenology and correlates of self-injurious and aggressive behaviour. *J Intell Disabil Res, 55*, 109-120.
- 2. Baird S.M., Campbell D., Ingram R. & Gomez C. (2001) Young children with Cri du Chat: genetic, developmental and behavioral profiles. *Infant-Toddler Intervention: The Transdisciplinary Journal* 11, 1-14.
- 3. Claro, A., Cornish, K. & Gruber, R. (2011). Association between fatigue and autistic symptoms in children with cri du chat syndrome. *Am J Intel Dev Disabil, 116,* 278-289.
- 4. Collins M.S. & Cornish K. (2002) A survey of the prevalence of stereotypy, self-injury and aggression in children and young adults with Cri du Chat syndrome. *J Intell Disabil Res* 46, 133-140.
- 5. Cornish K.M. (1996) The neuropsychological profile of Cridu-Chat syndrome without significant learning disability. *Dev Med Child Neurol* 38, 941-944.
- 6. Cornish K., Bramble D. & Standen P. (2001) Cri du Chat syndrome: toward a behavioral phenotype. *Ment Health Aspects Dev Disabil* 4, 156-160.
- 7. Cornish K. & Munir F. (1998) Receptive and expressive language skills in children with Cri-du Chat syndrome. *J Commun Disord* 31, 73-81.
- 8. Cornish K. & Pilgram J. (1996) Developmental and behavioural characteristics of Cri du Chat syndrome. *Arch Dis Child* 75, 448-450.
- 9. Dykens E.M. & Clarke D.J. (1997) Correlates of maladaptive behavior in individuals with 5p- (Cri du Chat) syndrome. *Dev Med Child Neurol* 39, 752-756.
- Dykens E.M., Hodapp, R.M., & Finucane, B.M. (2000) *Genetics* and Mental Retardation Syndromes. Baltimore, MD: Paul H Brookes Publishing Co.
- Lejeune J., Lafourcade J., Berger R., Vialatte J., Boeswillwald M., Seringe P. & Turpin R. (1963) Trois cas de deletion partielle du bras court d'un chromosome 5. *Acad Sci* 257, 3098–3102.
- Maas A.P.H.M., Didden R. Korzilius H., Braam W., Smits M.G. & Curfs L.M.G. (2009) Sleep in individuals with CdCS: a comparative study. *J Intell Disabil Res* 53, 704-715.
- Mainardi P.C., Pastore G., Castronovo C., Godi M., Guala A., Tamiazzo S., Provera S., Pierluigi M. & Bricarelli F.D. (2006) The natural history of CdCS: a report from the Italian register. *Eur J Med Genet* 49, 363-383.
- 14. Manning K.P. (1977) Larynx in Cri du Chat syndrome. *J* Laryngol Otol 91, 887-892.
- Marinescu C., Johnson E., Dykens E., Hodapp R. & Overhauser J. (1999) No relationship between the size of the deletion and the level of developmental delay in Cri-du-Chat syndrome. *Am J Med Gen* 86, 66-70.
- Moss, J., Howlin, P., Hastings, R., Beaumont, S., Griffith, G., Petty, J., Tunnicliffe, P., Yates, R., Villa, D. and Oliver, C. (2013). Social behavior and characteristics of Autism Spectrum Disorder in Angelman, Cornelia de Lange and Cri du Chat syndromes. *Am J of Intell and Dev Disabil.* 118, 262-283

- 17. Moss, J., Oliver, C., Berg, K., Kaur, G., Jephcott, L. and Cornish, K. (2008). Prevalence of autism spectrum phenomenology in Cornelia de Lange and Cri du Chat syndromes. *Am J Men Ret*, *113*, 278-291.
- 18. Moss J., Oliver C., Arron K., Burbidge C. & Berg K. (2009) The prevalence and phenomenology of repetitive behaviour in genetic syndromes. *J Aut Dev Dis* 39, 572-588.
- 19. Neibuhr E. (1978) The Cri-du-Chat syndrome. *Hum Genet* 42, 143-156.
- Overhauser J., Huang X., Gersch M., Wilson W., McMahon J., Bengtsson U., Rojas K., Meyer M., & Wasmuth J.J. (1994) Molecular and phenotypic mapping of the short arm of chromosome 5: Sublocalisation of the critical region of the Cri du Chat syndrome. *Hum Mol Genet* 3, 247-252.
- 21. Van Buggenhout G.J.C.M., Pijkels E., Holyoet M., Schaap C., Hamel B.C.J. and Fryns J.P. (2000) Cri du Chat syndrome: changing phenotype in older patients. *Am J Med Gen* 90A, 203- 215.
- 22. Wilkins L. E., Brown J. A., and Wolf B. (1980) Psychomotor development in 65 home-reared children with Cri du Chat syndrome. J Pediatr 97, 401-405.

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).

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.

References and suggested reading

- Antonarakis SE, Lyle R, Dermitzakis ET, Reymond A, Deutsch S. (2004) Chromosome 21 and Down syndrome: from genomics to pathophysiology. Nat Rev Genet. 5(10):725-38.
- 2. Arque G, Casanovas A, Dierssen M (2013)Dyrk1A Is Dynamically Expressed on Subsets of Motor Neurons and in the Neuromuscular Junction: Possible Role in Down Syndrome PLoS One. 8(1):e54285
- 3. Block A, Dhanasekaran AR, Ahmed MM, Gardiner KJ. (2014) Abnormal Protein Profiles in Hippocampus of Mouse Models of Down Syndrome: Similarities with Alzheimer's Disease. J Alzheimers Dis Parkinsonism 4: 138.
- Chapman RS, Hesketh LJ. (2000) Behavioral phenotype of individuals with Down syndrome. Ment Retard Dev Disabil Res Rev.;6(2):84-95.
- 5. Dierssen M. (2012) Down syndrome: the brain in trisomic mode. Nat Rev Neurosci.:844-58.
- 6. Dykens EM (2007) Psychiatric and behavioral disorders in persons with Down syndrome Ment. Retard. Dev. Disabil. Res. Rev., 13: 272–278
- 7. Einfeld SL, Brown R (2010) Down Syndrome—New Prospects for an Ancient Disorder JAMA 303(24):2525-2526
- Epstein C. Down Syndrome1(1995) In: Scriver CR, Beaudet AL Sly WS, Valle D, eds. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill 749-94.
- 9. Farriols Danés C (2012). Specific aspects of ageing in Down's syndrome. Rev Med Int Sindr Down. 16(1):3-10
- Fillat C, Bofill-De Ros X., Santos M., Martín ED, Andreu N, Villanueva E, d'Amico D, Dierssen M, Altafaj X (2014) Identification of key genes involved in Down's syndrome pathogenesis by gene therapy. Rev Med Int Sindr Down 18(2):21-8
- Gardiner K, Davisson MT, Pritchard M, Patterson D, Groner Y, Crnic LS, Antonarakis S, Mobley W (2005) Report on the 'Expert Workshop on the Biology of Chromosome 21: towards gene-phenotype correlations in Down syndrome', held June 11-14, 2004, Washington D.C. Cytogenet Genome Res.108(4):269-77.
- 12. Letourneau A,Santoni FA,Bonilla X, Sailani MR, Gonzalez D, Kind J, Chevalier C, Thurman R, Sandstrom RS, Hibaoui Y, Garieri M, Popadin K, Falconnet E, Gagnebin M, Gehrig C, Vannier A, Guipponi M, Farinelli L, Robyr D, Migliavacca E, Borel C, Deutsch S, Feki A, Stamatoyannopoulos J A, Herault Y, van Steensel B, Guigo R & Antonarakis SE. (2014) Domains of genome-wide gene expression dysregulation in Down's syndrome. Nature 508 (7496):345-50
- 13. Lott IT (2012) Neurological phenotypes for Down syndrome across the life span. Prog Brain Res. 97: 101–121.
- 14. Makary A, Testa R, Einfeld SL, Tonge BJ, Mohr C, Gray KM (2014) The association between behavioural and emotional problems and age in adults with Down syndrome without dementia: Examining a wide spectrum of behavioural and emotional problems. Res Dev Disabil. 35(8):1868-77
- Neri G, Opitz JM. (2009) Down syndrome: Comments and reflections on the 50th anniversary of Lejeune's discovery. Am J Med Genet Part A 149A:2647–2654

- Nespoli L, Burgio GR, Ugazio AG, Maccario R (1993) Immunological features of Down's syndrome: a review. J Intellect Disabil Res. 37,543-51.
- Oliver C, Crayton L, Holland AJ, Hall S. (2000). Acquired cognitive impairments in adults with Down syndrome: Effects on the individual, carers and services. AJMR, 105, 455-465.
- 18. Patterson D, Costa AC (2005) Down syndrome and genetics- a case of linked histories. Nat Rev Genet 6(2):137-47.
- 19. Rachidi M, Lopes C. (2007) Mental retardation in Down syndrome: from gene dosage imbalance to molecular and cellular mechanisms.Neurosci Res. 2007 Dec;59(4):349-69
- 20. Roizen NJ, Patterson D. (2003) Down's syndrome. Lancet 361(9365):1281-9
- 21. Ronan A,Fagan K, Christie L, Conroy J, Nowak NJ, Turner G.(2007) Familial 4.3 Mb duplication of 21q22 sheds new light on the Down syndrome critical region. J Med Genet.44(7):448-51
- 22. Shapiro BL (1994) The environmental basis of the Down Syndrome Phenotype. Developmental Medicine and Child Neurology, 36, 84-90.

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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

References

- I. Lemoine P., Harousseau H., & Borteyru J.P. (1968) Les enfants de parents alcoholiques: Anomalies observees a propos de 127 cas. *Quest Med* 21, 476-482.
- 2. 2. Jones K.L., & Smith D.W. (1973) Recognition of the fetal alcohol syndrome in early infancy. *Lancet* **2**, 999-1101.
- 3. 3. Stratton K.R., Rowe C.J., & Battaglia F.C. (1996) *Fetal Alcohol Syndrome: Diagnosis, epidemiology, prevention and treatment in medicine.* Washington DC: National Academy Press.
- 4. 4. O'Malley K.D., & Hagerman R.J. (1998) Developing Clinical Practice Guidelines for Pharmacological Interventions with Alcohol-affected Children. In: *Proceedings of a special focus session of the Interagency Co-ordinating Committee on Fetal Alcohol Syndrome*. Chevy Chase Ma, Sept 10th & 11th, (eds CDC & NIAAA), 145-177.
- 5. 5. Streissguth A.P. & O'Malley K.D. (2000) Neuropsychiatric implications and long-term consequences of fetal alcohol spectrum disorders. *Semin Clin Neuropsychiat* **5**, 177190.
- 6. May P.A., Gossage J.P., Kalberg W.O., Robinson L.K., Buckley D., Manning M., & Hoyme H.E. (2009) Prevalence and epidemiological characteristics of FASD from various research methods with an emphasis on in school studies. *Dev Disabil Res Rev* 15, 176-192.
- 7. McCarver D.G., Thomasson H.R., Martier S.S., Sokol R.J., & Li T.K. (1997) Alcohol dehydrogenase2* 3 allele protects against alcohol-related birth defects among African Americans. J Pharmacol Exp Ther 283(3), 1095-1101.
- 8. 8. Streissguth A.P. (1997) *Fetal alcohol syndrome. A guide for families and communities.* Baltimore:Brookes Publishing.
- 9. 9. Hagerman R.J. (1999) Fetal Alcohol Syndrome. In: *Neurodevelopmental Disorders. Diagnosis and Treatment.* pp.3-59, New York, Oxford: Oxford University Press.
- 10. Chudley A.E., Conroy J., Cook J.L., Loock C., Rosales T., & LeBlanc N. (2005) Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. *Can Med Assoc J* 172(5 suppl)), S1-21.
- 11. Famy C., Streissguth A.P., & Unis A.S. (1998) Mental illness in adults with fetal alcohol syndrome or fetal alcohol effects. *Am J Psychiat* 155(4), 552-554.
- 12. O'Malley K.D. & Storoz L. (2003) Fetal alcohol spectrum disorder and ADHD: diagnostic implications and therapeutic consequences. *Expert Rev Neurotherapeutics*, July, **3 (4)**, 477-489.
- 13. Streissguth A.P., Bookstein F.L., Barr H.M., Sampson P.D., O'Malley K.D., & Young K.(2004) Risk factors for adverse risk outcomes in fetal alcohol syndrome and fetal alcohol effects. *Dev Behav Pediat* 25 (4), 228-238.
- 14. Bookstein F.L., Sampson P.D., Streissguth A.P., & Connor P.L. (2001) Geometric morphometrics of corpus callosum and subcortical structures in fetal alcohol affected brain. *Teratology* 64, 4-32.
- 15. Sobrain S.K., Jones B.L., James H., Kamara F.N., & Holson R.R. (2005) Prenatal alcohol preferentially enhances reactivity of the dopamine D1 but not D2 or D3 receptors in offspring. *Neuorotoxicol Teratol* 27, 73-93.

- 16. Chandrasena A.N., Mukherjee R.A.S., & Turk J.T. (2009) Fetal Alcohol Spectrum Disorders: An Overview of Interventions for Affected Individuals. *Child Adol Ment Health* 14(4), pp 162-167.
- 17. HAYCOCK, P.C. (2009)Fetal alcohol spectrum disorders: The epigenetic perspective. *Biology of Reproduction* 81:607–617,
- 18 BMA Board of Science. Fetal Alcohol Spectrum Disorders, a guide for healthcare practitioners. London: BMA Publishing; 2007

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

References

 Berry-Kravis E. 2014. Mechanism-based treatments in neurodevelopmental disorders: fragile X syndrome. *Pediatr. Neurol.* 50(4):297-302.

- Busquets-Garcia A., Gomis-Gonzalez M., Guegan T., Agustin-Pavon C., Pastor A., Mato S., Perez-Samartin A., Matute C., de la Torre R., Dierssen M., Maldonado R., Ozaita A. 2013. Targeting the endocannabinoid system in the treatment of fragile X syndrome. *Nat. Med.* 19(5):603-607.
- Grigsby J., Cornish K., Hocking D., Kraan C., Olichney J. M., Rivera S. M., Schneider A., Sherman S., Wang J. Y., Yang J-C. 2014. The cognitive neuropsychological phenotype of carriers of the FMR1 premutation. J. Neurodev. Disord. 6(1):28.
- 4. Hagerman R. J., Des-Portes V., Gasparini F., Jacquemont S., Gomez-Mancilla B. 2014. Translating molecular advances in fragile X syndrome into therapy: a review. J. *Clin. Psychiatry* 75(4):e294-307.
- Hagerman R., Hagerman P. 2013. Advances in clinical and molecular understanding of the FMR1 premutation and fragile X-associated tremor/ataxia syndrome (FXTAS). *Lancet Neurol.* 12(8):786-98.
- 6. Hunter J., Rivero-Arias O., Angelov A., Kim E., Fotheringham I, Leal J. 2013. Epidemiology of fragile X syndrome: A systematic review and meta-analysis. *Am J. Med. Genet.* A 164A(7):1648-1658.
- Leigh M. J., Nguyen D. V., Mu Y., Winarni T. I., Schneider A., Chechi T., Polussa J., Doucet P., Tassone F., Rivera S. M., Hessl D., Hagerman R. J. 2013. A randomized double-blind, placebo-controlled trial of minocycline in children and adolescents with fragile X syndrome. J. Dev. Behav. Pediatr. 34(3):147-155.
- Lozano R, Hare E, Hagerman RJ. (2014) Treatment of Fragile X Syndrome and Fragile X-associated Disorders. In Hagerman RJ and Hendren RL (eds). *Treatment of Neurodevelopmental Disorders and Targeting Neurobiological Mechanisms*. Oxford University Press, New York, NY. pp 215-238.
- 9. Lubs H. A. 1969. A marker X chromosome. *Am. J. Hum. Genet.* 21:231-244.
- 10. Martin J. P., and Bell J. 1943. A pedigree of mental defect showing sex linkage. *J. Neurol. Psychiatry* 6:154-157.
- McDuffie A., Thurman A. J., Hagerman R. J., Abbeduto, L. 2015. Symptoms of autism in males with fragile X syndrome: A comparison to nonsyndromic ASD using current ADI-R scores. J. Autism Dev. Disord. 45:1925-1937
- O'Keefe J. A., Espinoza Orias A. A., Hassan K., Hall D. A., Berry-Kravis E., Wimmer M. A. 2014. Implementation of a markerless motion analysis method to quantify hyperkinesis in males with fragile X syndrome. *Gait & Posture* 39(2):827-830.
- 13. Polussa J., Schneider A., Hagerman R. 2014. Molecular advances leading to treatment implications for fragile X premutation carriers. *Brain Disord. Ther.* 3:2.
- Verkerk A. J., Pieretti M., Sutcliffe J. S., Fu Y-H, Kuhl D. P., Pizzuti A., Reiner O., Richards S., Victoria M. F., Zhang F., Eussen B. E., van Ommen G. J., Blonden A. J., Riggins G. J., Chastain J. L., Kunst C. B., Galjaard H., Caskey C. T., Nelson D. L., Oostra B. A., and Warren S. T. 1991. Identification of a gene (FMR1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell* 65:905-914.

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

References

- Abramsky L., & Chapple J. (1997) 47, XXY (Klinefelter syndrome) and 47, XYY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. *Prenat Diagn* 17(4), 363-8.
- 2. Boada R., Janusz J., Hutaff-Lee C., & Tartaglia N. (2009) The cognitive phenotype in Klinefelter Syndrome: A review of the literature including genetic and hormonal factors. *Dev Disabil Res Rev* 15, 284-294.
- Boisen K.A., Chellakooty M., Schmidt I.M., Kai C.M., Damgaard I.N., Suomi A.M., Toppari J., Skakkebaek N.E., & Main K.M. (2005) Hypospadias in a cohort of 1072 Danish newborn boys: prevalence and relationship to placental weight, anthropometrical measurements at birth, and reproductive hormone levels at three months of age. J Clin Endocrinol Metab Jul 90(7), 4041-6.
- 4. Lanfranco F., Karnischke A., Zitzmann M., & Nieschlag E. (2004) Klinefelter's syndrome. *Lancet* 364, 273-283
- 5. Savic I. (2012) Advances in research on the neurological and neuropsychiatric phenotype of Klinefelter syndrome. Current Opinion in Neurology. 25(2):138-43
- Skakkebaek A; Gravholt CH; Rasmussen PM; Bojesen A; Jensen JS; Fedder J; Laurberg P; Hertz JM; Ostergaard JR; Pedersen AD; Wallentin M. 2014 Neuroanatomical correlates of Klinefelter syndrome studied in relation to the neuropsychological profile. NeuroImage Clinical. 4:1-9, 2014.

Rhoshel K Lenroot, 2010 Revised: Stewart Einfeld, 2015

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.

Key references

- 1. www.Lesch-Nyhan.org
- 2. Jinnah H., Friedman, T. Lesch-Nyhan Disease, Chapter 107, In the Metabolic and Molecular Basis of Inherited Disease, 8th Edition, Scriver, CR, Beaudet, AL, Sly, WS, Valle, D., Eds. (2001).
- 3. Catel, W, Schmidt, J, On familial gouty diathesis associated with cerebral and renal symptoms in a small child. Dtsch Med Wochenschr. 1959 Nov 27;84:2145-7.
- 4. Wilson, JM and Kelley, WN, Molecular basis of hypoxanthineguanine phosphoribosyltransferase deficiency in a patient with the Lesch-Nyhan syndrome,
- 5. J Clin Invest. 1983 May; 71(5): 1331–1335.
- 6. Riley, ID. Gout and Cerebral Palsy in a three year old boy. Archives of Disease in Childhood, 1960, 293-294.
- 7. Visser, JE, Bar, PR, and Jinnah, HA. Lesch-Nyhan Disease and the basal ganglia. Brain Research Review 32 (2000) 449-475
- Hoefnagel, D, Andrew, E. D., Mireault, N. G., Berndt, WO, Hereditary choreoathetosis, self-mutilation and hyperuricemia in young males. New Eng. J. Med. 273: 130-135, 1965.
- 9. Nyhan W. Clinical features of the Lesch-Nyhan syndrome, Arch Int Med 130 (1972) 186-192.
- Harris, J. Lee, Jinnah, H et al. Craniocerebral Magnetic Resonance imaging measurement and findings in Lesch-Nyhan Syndrome. Arch Neurol, (1998) April vol 55, 547 – 553.
- 11. Jinnah HA, De Gregorio LJ, Harris JC, Nyhan WL, O'Neill JP. The spectrum of inherited mutations causing HPRT deficiency: 75 new cases and a review of 196 previously reported cases. Mutat Res 463: 309 – 326, 2000
- Robey, K, Reck, J, Giacomini, K, Barabas, G and Eddey, G: Modes of self – mutilation and their patterns of association in persons with Lesch – Nyhan disease, Dev Med Child Neur (2003) 45, 167 – 171.
- Puig JG, Torres RJ, Mateos FA, Ramos TH, Arcas JM, Buno AS, O'Neill P. The spectrum of hypoxathine-guanine phosphoribosyltransferase (HPRT) deficiency: clinical experience based on 22 patients from 18 spanish families. Medicine (Baltimore); 80: 102 – 112, 2001.

- Visser J., Harris J., Barabas G, Eddey G., and Jinnah, H. The Motor Disorder of Classic Lesch–Nyhan Disease. Nucleosides, Nucleotides & Nucleic Acids. Vol 23, pp 1161 – 1164, 2004.
- 15. O'Neill, P. Mutation Carrier Testing in Lesch-Nyhan Syndrome Families: HPRT Mutant Frequency and Mutation Analysis with Peripheral Blood T Lymphocytes. Genetic Testing. April 2004, Vol. 8, No. 1, Pages 51-64.
- 16. CMS standard: 482.13. (e) (6).) Exception: "Repetitive selfmutilating behavior. If a patient is diagnosed with a chronic medical or psychiatric condition, such as Lesch-Nyhan Syndrome, and the patient engages in repetitive selfmutilating behavior, a standing or PRN order for restraint to be applied in accordance with specific parameters established in the treatment plan would be permitted. Since the use of restraints to prevent self-injury is needed for these types of rare, severe, medical and psychiatric conditions, the specific requirements (1-hour face-to-face evaluation, time-limited orders, and evaluation every 24 hours before renewal of the order) for the management of violent or self- destructive behavior do not apply."
- 17. Disappearance of self-mutilating behavior in a patient with Lesch–Nyhan syndrome after bilateral chronic stimulation of the globus pallidus internus. T Akaomi, et al. J Neurosurg 98:414–416, 2003.
- Purine metabolism during neuronal differentiation: the relevance of purine synthesis and recycling. Göttle M, Burhenne H, Sutcliffe D, Jinnah HA. J Neurochem. 2013 Dec;127(6):805-18. doi: 10.1111/jnc.12366. Epub 2013 Aug 18.
- Nucleosides Nucleotides Nucleic Acids. 2014;33(4-6):208-17. doi: 10.1080/15257770.2014.880477. Transcriptomic approach to Lesch-Nyhan disease. Dauphinot L1, Mockel L, Cahu J, Jinnah HA, Ledroit M, Potier MC, Ceballos-Picot I.
- 20. Consequences of Delayed Dental Extraction in Lesch-Nyhan Disease. Goodman,
- 21. Torres, Puig and Jinnah. Movement Disorder; Published online: 6 JUN 2014.

Gary E. Eddey, 2014

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/
- UK Support group: http://www.mowatwilsonsyndrome.org.uk/
- Italian support group:
 http://www.mowatwilson.it/

References

- Abdalla, E. M., & Zayed, L. H. (2013). Mowat-Wilson Syndrome Deafness in the First Egyptian Case Who Was Conceived by Intracytoplasmic Sperm Injection. *Journal of Child Neurology*, 0883073813509120.
- 2. Adam, M. P., Schelley, S., Gallagher, R., Brady, A. N., Barr, K., Blumberg, B., . . . Hudgins, L. (2006). Clinical features and management issues in Mowat-Wilson syndrome. *American Journal of Medical Genetics Part A*, 140(24), 2730-2741.
- Cacheux, V., Dastot-Le Moal, F., Kaariainen, H., Bondurand, N., Rintala, R., Boissier, B., ... Goossens, M. (2001). Loss-offunction mutations in SIP1 Smad interacting protein 1 result in a syndromic Hirschsprung disease. *Human Molecular Genetics*, 10(14), 1503-1510.
- Cecconi, M., Forzano, F., Garavelli, L., Pantaleoni, C., Grasso, M., Dagna Bricarelli, F., . . . Faravelli, F. (2008). Recurrence of Mowat-Wilson syndrome in siblings with a novel mutation in the ZEB2 gene. *American Journal of Medical Genetics Part A*, 146A(23), 3095-3099.
- Dastot-Le Moal, F., Wilson, M., Mowat, D., Collot, N., Niel, F., & Goossens, M. (2007). ZFHX1B mutations in patients with Mowat-Wilson syndrome. *Human Mutation*, 28(4), 313-321.
- Engenheiro, E., Moller, R. S., Pinto, M., Soares, G., Nikanorova, M., Carreira, I. M., . . . Tumer, Z. (2008). Mowat-Wilson syndrome: an underdiagnosed syndrome? *Clinical Genetics*, 73(6), 579-584.
- 7. Evans, E. (2009). *An Investigation of the Behavioural Phenotype of Mowat-Wilson syndrome*. (PhD), The University of Sydney, Sydney.
- Evans, E., Einfeld, S., Mowat, D., Taffe, J., Tonge, B., & Wilson, M. (2012). The behavioral phenotype of Mowat–Wilson syndrome. *American Journal of Medical Genetics Part A*, 158A(2), 358-366. doi: 10.1002/ajmg.a.34405
- 9. Garavelli, L., & Cerruti-Mainardi, P. (2007). Mowat-Wilson syndrome. *Orphanet Journal Of Rare Diseases*, 2, 42.
- Garavelli, L., Zollino, M., Cerruti-Mainardi, P., Gurrieri, F., Rivieri, F., Soli, F., . . . Neri, G. (2009). Mowat-Wilson syndrome: facial phenotype changing with age: study of 19 Italian patients and review of the literature. *American Journal of Medical Genetics Part A*, 149A(3), 417-426.
- 11. Ghoumid, J., Drevillon, L., Alavi-Naini, S. M., Bondurand, N., Rio, M., Briand-Suleau, A., . . . Giurgea, I. (2013). ZEB2 zincfinger missense mutations lead to hypomorphic alleles and a mild Mowat–Wilson syndrome. *Human Molecular Genetics*, 22(13), 2652-2661. doi: 10.1093/hmg/ddt114
- Mowat, D. R., Croaker, G., Cass, D., Kerr, B., Chaitow, J., Ades, L., ... Wilson, M. J. (1998). Hirschsprung disease, microcephaly, mental retardation, and characteristic facial features: delineation of a new syndrome and identification of a locus at chromosome 2q22-q23. *Journal of Medical Genetics*, 35(8), 617-623.
- Mowat, D. R., & Wilson, M. J. (2010). Mowat-Wilson Syndrome. In S. Cassidy & J. Allanson (Eds.), *Management of Genetic Syndromes - Third Edition* (pp. 517-529): John Wiley & Sons.
- Mowat, D. R., Wilson, M. J., & Goossens, M. (2003). Mowat-Wilson syndrome. *Journal of Medical Genetics*, 40(5), 305-310.

- Wakamatsu, N., Yamada, Y., Yamada, K., Ono, T., Nomura, N., Taniguchi, H., . . . Nagaya, M. (2001). Mutations in SIP1, encoding Smad interacting protein-1, cause a form of Hirschsprung disease. *Nature Genetics*, 27(4), 369-370.
- Yoneda, M., Fujita, T., Yamada, Y., Yamada, K., Fujii, A., Inagaki, T., ... Wakamatsu, N. (2002). Late infantile Hirschsprung disease-mental retardation syndrome with a 3-bp deletion in ZFHX1B. *Neurology*, *59*(10), 1637-1640.
- 17. Zweier, C., Albrecht, B., Mitulla, B., Behrens, R., Beese, M., Gillessen-Kaesbach, G., . . . Weschke, B. (2002). "Mowat-Wilson" syndrome with and without Hirschsprung disease is a distinct, recognizable multiple congenital anomaliesmental retardation syndrome caused by mutations in the zinc finger homeo box 1B gene. *American Journal of Medical Genetics*, 108(3), 177-181.
- Zweier, C., Horn, D., Kraus, C., & Rauch, A. (2006). Atypical ZFHX1B mutation associated with a mild Mowat-Wilson syndrome phenotype. *American Journal of Medical Genetics Part A*, 140A(8), 869-872.
- Zweier, C., Thiel, C., Dufke, A., Crow, Y., Meinecke, P., Suri, M., . . . Rauch, A. (2005). Clinical and mutational spectrum of Mowat-Wilson syndrome. *European Journal of Medical Genetics*, 48, 98-111.

Updated by Liz Evans, Meredith Wilson and David Mowat, March 2014.

Neurofibromatosis Type 1 (NF1)

Genetics

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

Incidence/prevalence

About 1 in 2,500 births.

Physical features

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

Life expectancy

Depends on nature and severity of clinical features.

Brain abnormalities

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

Behavioural characteristics

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

Cognitive characteristics

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

Treatment

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

References

- 1. Ardern-Holmes SL, & North KN (2011). Therapeutics for childhood Neurofibromatosis Type 1 and Type 2. *Current Treatment Options in Neurology (Pediatric Neurology)* 13, 529-543.
- 2. Barton B, & North K (2004). Social skills of children with Neurofibromatosis Type 1. *Developmental Medicine & Child Neurology 46*, 553-563.
- 3. Ferner RE, Huson SM, Thomas N, Moss C, Willshaw H, Evans DG, Upadhyaya M, Towers R, Gleeson M, Steiger C, & Kirby A (2007). Guidelines for the Diagnosis and Management of Individuals with Neurofibromatosis 1. *Journal of Medical Genetics* 44, 81-88.
- Garg S, Green J, Leadbitter K, Emsley R, Lehtonen A, Evans G, & Huson SM (2013). Neurofibromatosis Type 1 and Autism Spectrum Disorder. *Pediatrics* 132, e1642-e1648.
- Heervä E, Huilaja L, Leinonen P, Peltonen S, & Peltonen J (2014). Follow-Up of Six Patients with Neurofibromatosis 1-Related Osteoporosis Treated with Alendronate for 23 Months. *Calcified Tissue International 94*,608–612.
- 6. Huijbregts SCJ, & De Sonneville, LMJ (2011). Does cognitive impairment explain behavioural and social problems of children with Neurofibromatosis Type 1? *Behavior Genetics 41*, 430-436.
- Hyman S, Shores EA, & North K (2006). Learning disabilities in children with neurofibromatosis type 1: subtypes, cognitive profile, and attention-deficit-hyperactivity disorder. *Developmental Medicine & Child Neurology 48*, 973-977.
- 8. Loitfelder M, Huijbregts SCJ, Veer IM, Swaab HS, Van Buchem MA, Schmidt R, & Rombouts SA (2015). Functional connectivity changes and executive and social problems in Neurofibromatosis Type 1. *Brain Connectivity 5*, 312-320.
- 9. Payne JM, Moharir MD, Webster R, & North KN (2010). Brain structure and function in neurofibromatosis type 1: current concepts and future directions. *Journal of Neurology Neurosurgery & Psychiatry 81*,304–309.
- Rowbotham I, Pit-ten Cate IM, Sonuga-Barke EJS, & Huijbregts SCJ (2009) Cognitive control in adolescents with Neurofibromatosis Type 1. *Neuropsychology* 23, 50-60.
- Van der Vaart T, Plasschaert E, Rietman AB, Renard M, Oostenbrink R, Vogels M-C, De Wit Y, Descheemaeker M-J, Vergouwe Y, Catsman-Berrevoets CE, Legius E, Elgersma Y, & Moll HA (2013). Simvastatin for cognitive deficits and behavioural problems in patients with neurofibromatosis type 1 (NF1-SIMCODA):a randomised, placebo-controlled trial. *Lancet Neurology* 12, 1076-1083.
- Williams VC, Lucas J, Babcock MA, Gutmann DH, Korf B, & Maria BL (2009). Neurofibromatosis type 1 revisited. *Pediatrics* 123, 124–133.

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.

References

- Adviento, B., Corbin, I.L., Widjaja, F., Desachy, G., Enrique, N., Rosser, T., Risi, S., Marco, E.J., Hendren, R.L., Bearden, C.E., Rauen, K.A. & Weiss, L.A. (2013). Autism traits in the RASopathies. *Journal of Medical Genetics*, *51*, 10–20.
- 2. Alfieri, P., Cesarini, L., De Rose, P., Ricci, D., Selicorni, A., Guzzetta, A., Baranello, G., Tinelli, F., Mallardi, M., Zampino, G., Vicari, S., Atkinson, J. & Mercuri, E. (2011a). Visual processing in Noonan syndrome: Dorsal and ventral stream sensitivity. *American Journal of Medical Genetics Part A*, *155*, 2459-2464.
- Alfieri, P., Cesarini, L., Mallardi, M., Piccini, G., Caciolo, C., Leoni, C., Mirante, N., Pantaleoni, F., Digilio, M.C., Gambardella, M.L., Tartaglia, M., Vicari, S., Mercuri, E. & Zampino, G. (2011b). Long term memory profile of disorders associated with dysregulation of the RAS-MAPK signaling cascade. Behavior Genetics, 41, 423-429.
- Allanson, J.E. (2010). Noonan syndrome. In S.B. Cassidy & J.E. Allanson (Eds.), *Management of genetic syndromes* (3rd ed., pp.569-586). New York: Wiley-Blackwell.
- Aoki, Y., Niihori, T., Banjo. T., Okamoto, N., Mizuno, S., Kurosawa, K., Ogata, T., Takada, F., Yano, M., Ando. T., Hoshika, T., Barnett, C., Ohashi, H., Kawame, H., Hasegawa, T., Okutani, T., Nagashima, T., Hasegawa, S., Funayama, R., Nagashima, T., Nakayama, K Inoue, S., Watanabe, Y., Ogura, T. & Matsubara, Y. (2013). Gain-of-function mutations inRIT1 cause Noonan syndrome, a RAS/MAPK pathway syndrome. *American Journal of Human Genetics, 93*, 173-180.
- 6. Noonan, J. A. (1968). Hypertelorism with Turner phenotype. A new syndrome with associated congenital heart disease. *American Journal of Diseases of Children*, *116*, 373-380.
- 7. Noonan, J.A. & Ehmke, D.A. (1963). Associated non-cardiac malformations in children with congenital heart disease. *Journal of Pediatrics,* 63, 468-470.
- 8. Noonan Syndrome Guideline Development Group, The (2010). *Noonan Syndrome Clinical Management Guidelines*. Dyscerne, University of Manchester.

- Pasmant, E.,Sabbagh, A., Hanna, N., Masliah-Planchon, J., Jolly, E., Goussard, P., Ballerini, P., Cartault, F., Barbarot, S., Landman-Parker, J., Soufir, N., Parfait, B., Vidaud, M.,Wolkenstein, P., Vidaud, D. & France, R.N.F. (2009). SPRED1 germline mutations caused a neurofibromatosis type 1 overlapping phenotype. *Journal of Medical Genetics*, 46, 425-430.
- Pierpont, E.I., Weismer, S.E., Roberts, A.E., Tworog-Dube, E., Pierpont, M.E., Mendelsohn, N.J.& Seidenberg, M.S. (2010). The language phenotype of children and adolescents with Noonan syndrome. Journal of Speech Language and Hearing Research, 53, 917-932.
- 11. Pierpont E.I., Tworog-Dube E. & Roberts A.E. (2013). Learning and memory in children with Noonan syndrome. *American Journal of Medical Genetics Part A*, *161*, 2250–2257.
- 12. Pierpont, E., Tworog-Dube, E. & Roberts, A.E. (2015). Attention skills and executive functioning in children with Noonan syndrome and their unaffected siblings. *Devlopmental Medicine & Child Neurology*, *57*, 385-392.
- 13. Roelofs, R.L., Wingbermühle, E., Freriks, K., Verhaak, C.M., Kessels, R.P.C. & Egger, J.I.M. (2015). Alexithymia, emotion perception, and social assertiveness in adult women with Noonan and Turner syndromes. *American Journal of Medical Genetics Part A, 167A,* 768–776.
- 14. Tartaglia, M., Gelb, B.D., & Zenker, M. (2011). Noonan syndrome and clinically related disorders. *Best Practice and Research: Clinical Endocrinology and Metabolism*, 25, 161-179.
- Van der Burgt, I., Berends, E., Lommen, E., van Beersum, S., Hamel, B., & Mariman, E. (1994). Clinical and molecular studies in a large Dutch family with Noonan syndrome. *American Journal of Medical Genetics*, 53, 187-191.
- 16. Van der Burgt, I. (2007). Noonan syndrome. Orphanet Journal of Rare Diseases, 2(4).
- Verhoeven, W., Wingbermühle, E., Egger, J., Van der Burgt, I., & Tuinier, S. (2008). Noonan syndrome: Psychological and psychiatric aspects. *American Journal of Medical Genetics*, 146, 191-196.
- Vissers, L.E.L.M., Bonetti, M., Paardekooper Overman, J., Nillesen, W.M., Frints, S.G.M., de Ligt, J., Zampino, G., Justino, A., Machado, J.C., Schepens, M., Brunner, H.G., Veltman, J.A., Scheffer, H., Gros, P., Costa, J.L., Tartaglia, M., van der Burgt, I., Ynteman, H.G. & den Hertog, J. (2015). Heterozygous germline mutations in A2ML1 are associated with a disorder clinically related to Noonan syndrome. *European Journal of Human Genetics*, 23, 317-324.
- Wingbermühle, E., Egger, J. Van der Burgt, I. & Verhoeven, W. (2009). Neuropsychological and behavioral aspects of Noonan syndrome. *Hormone Research*, *72* (suppl 2), 15-23.
- 20. Wingbermühle, E., Egger, J.I.M., Verhoeven, W.M.A., Van der Burgt, I., & Kessels, R.P.C. (2012a). Affective functioning and social cognition in Noonan syndrome. *Psychological Medicine*, *42*, 419-426.
- Wingbermühle, E., Roelofs, R. L., Van der Burgt, I., Souren, P.M., Verhoeven, W.M.A., Kessels, R.P.C., & Egger, J.I.M. (2012b). Cognitive functioning of adults with Noonan syndrome: A case-control study. *Genes, Brain & Behavior*, *11*, 785-793.

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

References

- Boer H., Holland A., Whittington J., Butler J., Webb T. & Clarke D. (2002) Psychotic illness in people with Prader Willi syndrome due to chromosome 15 maternal uniparental disomy. *Lancet* 359, 135-136.
- Böhm, B., Ritzén, E.M., Lindgren, A.C. (2014) Growth hormone treatment improves vitality and behavioural issues in children with Prader-Willi Syndrome. *Acta Paediatr* 104 (1), 59-67
- 3. Bull, L., Oliver, C., Callaghan, E., Woodcock, K.A. (2014) Increased Exposure to Rigid Routines can Lead to Increased Challenging Behavior Following Changes to Those Routines. *Journal of Autism and Developmental Disorders* **Nov 25**
- 4. Clarke D.J., Boer H., Whittington J., Holland A., Butler J. & Webb T. (2002) Prader-Willi syndrome, compulsive and ritualistic behaviours: the first population-based survey. *Br J Psychiat* **180**, 358-362.
- 5. Cohen M, Hamilton J, Narang I (2014). Clinically Important Age-Related Differences in Sleep Related Disordered Breathing in Infants and Children with Prader-Willi Syndrome. *PLoS ONE* **June 30**, 9(6)
- De Waele K, Ishkanian S.L., Bogarin R., Miranda C.A., Ghatei M.A., Bloom S.T., Pacaud D., Chanoine J.P. (2008) Long acting octreotide treatment causes a sustained decrease in ghrelin concentrations but does not affect weight, behaviour and appetite in subjects with Prader-Willi syndrome. *Eur J Endocrinol* 159, 381-8.
- Dykens E.M. & Kasari C. (1997) Maladaptive behavior in children with Prader-Willi syndrome, Down syndrome and nonspecific mental retardation. *Am J Ment Retard* 102, 228-37.
- 8. Goldstone A.P. (2004) Prader-Willi syndrome: advances in genetics, pathophysiology and treatment. *Trends Endocrinol Metab* **15**; 12-20.
- 9. Hinton E.C., Holland A.J., Gellatly M.S., Soni S., Patterson M., Ghatei M.A, & Owen A.M. (2005) Neural representations of hunger and satiety in Prader-Willi syndrome. *Int J Obes (Lond)* **30**(2), 313-321.
- Holland A.J., Treasure J., Coskeran P., Dallow J., Milton N. & Hillhouse E. (1993) Measurement of excessive appetite and metabolic changes in Prader-WIlli syndrome. *Int J Obes* 17, 527-532.
- Holm V.A., Cassidy S.B., Butler M.G., Hanchett J.M., Greenswag L.R., Whitman B.Y. & Greenberg (1993) Prader-Willi syndrome: consensus diagnostic criteria. *Pediatrics* 91, 398-402.
- 12. Larson FV, Whittington J, Webb T, Holland AJ (2013) A longitudinal follow-up study of people with Prader-Willi syndrome with psychosis and those at increased risk of developing psychosis due to genetic subtype. *Psychological Medicine* **Dec 13**, 1-5
- Laurier, V., Lapeyrade, A., Copet, P., Demeer, G., Silvie, M., Bieth, E., Coupaye, M., Poitou, C., Lorenzini, F., Labrousse, F., Molinas, C., Tauber, M., Thuilleaux, D. and Jauregi, J. (2014), Medical, psychological and social features in a large cohort of adults with Prader–Willi syndrome: experience from a dedicated centre in France. *Journal of Intellectual Disability Research* 59(5), 411-421

- Longhi, S., Grugni, G., Gatti, D., Spinozzi, E., Sartorio, A., Adami, S., Fanolla, A., Radetti, G. (2015) Adults with Prader-Willi Syndrome have Weaker Bones: Effect of Treatment with GH and Sex Steroids. *Calcif Tissue Int.* **96**(2),160-6.
- Lukoshe, A., White, T., Schmidt, N., Van Der Lugt, A., and Hokken-Koelega A. C. (2013) Divergent structural brain abnormalities between different genetic subtypes of children with Prader–Willi syndrome *Journal of Neurodevelopmental Disorders*, 5(1), 31
- Miller JL & Angulo M. (2013) An open-label pilot study of N-acetylcysteine for skin-picking in Prader–Willi syndrome. Am J Med Genet Part A 164,421–424.
- 17. Ogata H, Ihara H, Murakami N, Gito M, Kido Y, Nagai T. (2014). Autism spectrum disorders and hyperactive/impulsive behaviors in Japanese patients with Prader–Willi syndrome: A comparison between maternal uniparental disomy and deletion cases. *American Journal of Medical Genetics Part A*
- Oto, Y., Tanaka, Y. Abe, Y., Obata, K., Tsuchiya, T., Yoshino, A., Murakami, N. and Nagai, T. (2014). Exacerbation of BMI after cessation of growth hormone therapy in patients with Prader–Willi syndrome. *Am J Med Genet* Part A 9999:1–5.
- 19. Sinnema M., Schrander-Stumpel C.T., Verheij H.E., Meeuwsen M., Maaskant M.S., Curfs L.M. (2010) Dementia in a woman with Prader-Willi syndrome. *Eur J Med Genet* **53**(3), 145-8
- Soni S., Whittington J., Holland A.J., Webb T., Maina E.N., Boer H., Clarke D. (2007) The course and outcome of psychiatric illness in people with Prader-Willi syndrome: implications for management and treatment. *J Intellect Disabil Res* 51(1), Jan.,32-42.
- 21. Soni S., Whittington J., Holland A.J., Webb T., Maina E.N., Boer H., Clarke D. (2008) The phenomenology and diagnosis of psychiatric illness in people with Prader-Willi syndrome. *Psychol Med* **38**, 1505-1514.
- 22. Veltman M.W., Thompson R.J., Roberts S.E., Thomas N.S., Whittington J. & Bolton P.F. (2004) Prader-Willi syndrome--a study comparing deletion and uniparental disomy cases with reference to autism spectrum disorders. *Eur Child Adoles Psy* **13**, 42-50.
- 23. Whittington J.E., Holland A.J., Webb T., Butler J., Clarke D. & Boer H. (2001) Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK Health Region. *J Med Genet* **38**, 792-798.
- 24. Whittington J., Holland A., Webb T., Butler J., Clarke D. & Boer H. (2004) Cognitive abilities and genotype in a populationbased sample of people with Prader-Willi syndrome. *J Intellect Disabil Res.* **48**, 172-187.

Updated by Sarita Soni, May 2015

Rubinstein-Taybi Syndrome (RTS)

Prevalence

Although prevalence estimates have varied it is thought that the most accurate estimate is approximately 1 in 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.

References

- Bartsch, D., Ghirardi, M., Skehel, P.A., Karl, K.A., Herder, S.P., Chen, M.,...Kandel, E.R. (1995). Aplysia CREB2 represses long term facilitation: relief of repression converts transient facilitation into long-term functional and structural change. *Cellular and Molecular Life Sciences*, 83, 979-992.
- 2. Baxter, G. & Beer, J. (1992). 'Rubinstein Taybi syndrome'. *Psychological Reports*, 70, 451-456.
- Bourtchuladze, R., Frenguelli, B., Blendy, J., Cioffi, D., Schutz, G, & Silva, A.J. (1994). Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive elementbinding protein. *Cellular and Molecular Life Sciences*, 79, 59-68.
- 4. D'Archangelo, G., & Curran, T. (1995). Smart transcription factors. *Nature*, 376, 292-293.
- Galéra, C., Taupiac, E., Fraisse, S., Naudion, S., Toussaint, E., Rooryck-Thambo, C., ... & Bouvard, M. P. (2009). Sociobehavioral characteristics of children with Rubinstein-Taybi syndrome. *Journal of autism and developmental disorders*, 39(9), 1252-1260.
- 6. Goots, E.E., & Liemohn, W.P. (1977). Behavioral characteristics of three children with the broad thrumb-hallux (Rubinstein-Taybi) syndrome. *Biological Psychiatry*, 12, 413-423.
- 7. Hennekam, R.M. (2006) Rubinstein-Taybi syndrome. European Journal of Human Genetics, 14, 981-985.
- 8. Hennekam, R.M., Baselier, A.C., Beyaert, E., Bos, A., Blok, J.B., Jansma, H.B.,...& Veerman, H. (1992). Psychological and speech studies in Rubinstein-Taybi syndrome. *American Journal of Mental Retardation*, 66, 645-660.
- 9. Hennekam, R.M., Stevens, C. A., & Van de Kamp, J. J. P. (1990). Etiology and recurrence risk in Rubinstein-Taybi syndrome. *American Journal of Medical Genetics*, *37*(S6), 56-64.
- Hennekam, R.M., Van Den Boogaard, M., Sibbles, B.J., & Van Spijker, H.G. (1990). Rubinstein-Taybi Syndrome in The Netherlands. *American Journal of Medical Genetics*. *Supplement*, 6, 17-29.
- 11. Hennekam, R.M., & Van Doorne, J.M. (1990). Oral aspects of Rubinstein Taybi syndrome. *American Journal of Medical Genetics. Supplement*, 6, 42-47.
- 12. Lacombe, D., Saura, R., Taine, L., & Battin, J (1992). Confirmation of assignment of a locus for Rubinstein-Taybi syndrome gene to 16p13.3. *American Journal of Medical Genetics*, 44, 126-128.

- Oliver, C., Arron, K., Powis, L., and Tunnicliffe, P. (2011).
 Cornelia de Lange, Cri du Chat and Rubinstein Taybi Syndromes. In: P. Howlin, T.Charman, M. and Ghaziuddin, (Eds.) *The SAGE Handbook of Developmental Disorders*. (pp. 239-260). Sage: London.
- Padfield, C.J., Partington, M.W., Simpson, N.E. (1968). The Rubinstein-Taybi Syndrome. *Archives of Disease in Childhood*. 43, 94-101.
- 15. Partington, M.W. (1990). Rubinstein Taybi Syndrome: A Follow-Up Study. *American Journal of Medical Genetics*. *Supplement*, 6, 65-68.
- Petrij, F., Giles, R.H., Dauwerse, H.G., Saris, J.J., Hennekam, R.C., Masuno, M.,...Breuning, M.H. (2002). Rubinstein Taybi syndrome caused by mutations in the transcriptional coactivator CBP. *Nature*, 376, 348-351.
- 17. Powis, L. (2014). *Rubinstein-Taybi syndrome: From Behaviour to Cognition*. Unpublished doctoral thesis, University of Birmingham, UK.
- Roelfsema, J.H., White, S.J., Ariyurek, Y., Bartholdi, D., Niedrist, D., Papadia, F.,...Peters, D.J., (2005). Genetic heterogeneity in Rubinstein Taybi syndrome: mutations in both the CBP and EP300 genes cause disease. *American Journal of Human Genetics*, 76, 572-580.
- 19. Rubinstein, J.H. (1990). Broad Thumb- Hallux (Rubinstein-Taybi) Syndrome 1957- 1988. American Journal of Medical Genetics. Supplement, 6, 3-16.
- Rubinstein, J.H., & Taybi, H. (1963). Broad thumbs and toes and facial abnormalities: A possible mental retardation syndrome. *American Journal of Diseases of Children*, 105, 588-608.
- 21. Stevens, C.A. (2007). *GeneReviews: Rubinstein Taybi syndrome*. Seattle: University of Washington. www.genetests.org.
- 22. Stevens, C.A., Carey, J.C., & Blackburn, B.L. (1990a) Rubinstein-Taybi Syndrome: A Natural History Study. *American Journal* of *Medical Genetics. Supplement*, 6, 30-37.
- 23. Stevens, C.A., Hennekam, R.M, & Blackburn, B.L. (1990b). Growth in the Rubinstein-Taybi Syndrome. *American Journal* of *Medical Genetics. Supplement*, 6, 51-55.
- 24. Stevens, C. A., Pouncey, J., & Knowles, D. (2011). Adults with Rubinstein–Taybi syndrome. *American Journal of Medical Genetics Part A*, 155(7), 1680-1684.
- 25. Waite, J. (2012). *The cognitive and behavioural phenotype of Rubinstein-Taybi syndrome*. Unpublished doctoral thesis, University of Birmingham, UK.
- Yin, J.C., Wallach, J.S., Del Vecchio, M., Wilder, E.L., Zhou, H., Quinn, W.G., & Tully, T. (1994). Induction of a dominant negative CREB transgene specifically blocks long term memory in Drosphilia. *Cellular and Molecular Life Sciences*, 79, 49-58.

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

Rett Syndrome/ Rett Disorder / RTT

First description

Rett Syndrome (RTT) was first described (in German) by an Austrian neurologist, Dr. Andreas Rett, in 1966, following his observation of the characteristic "hand washing" movements of his patients ^[1]. It was not until the 1980s, however, that the syndrome began to be recognised more widely, as a result of English-language publications written by a Swedish neurologist, Dr. Bengt Hagberg ^[2, 3]. It was he who proposed the name "Rett syndrome" in recognition of the role played by Andreas Rett in first identifying the disorder.

Genetics

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

present) and the primary diagnosis remains clinical rather than genetic.

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

Incidence/prevalence

As RTT is an X-linked disorder it is seen predominantly in females, with an estimated prevalence of 1 in 9,000-15,000 live female births ^[12, 13], making this one of the most frequent causes of developmental disorder in girls. It is more rarely found in males, in whom early deaths have been reported.

Life expectancy/ mortality

Individuals with RTT commonly have a reduced life span compared with the general population ^[14], with the most physically challenged being at increased risk of early death and the most able surviving into adulthood in good health. There is a high incidence of sudden death, which may be related to central autonomic dysregulation ^[15]. Some deaths are related to epilepsy, to aspiration pneumonia or nutritional difficulties but less severely affected individuals are likely to die from causes unrelated to RTT.

Physical features and natural history

Typically, RTT has been characterised by 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/

References

- Rett, A., [On a unusual brain atrophy syndrome in hyperammonemia in childhood]. Wien Med Wochenschr, 1966. 116(37): p. 723-6.
- 2. Hagberg, B., *Rett's syndrome: prevalence and impact on progressive severe mental retardation in girls*. Acta Paediatr Scand, 1985. **74**(3): p. 405-8.
- 3. Hagberg, B., et al., A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. Ann Neurol, 1983. **14**(4): p. 471-9.
- 4. Lyst, M.J. and A. Bird, *Rett syndrome: a complex disorder with simple roots*. Nat Rev Genet, 2015. **16**(5): p. 261-75.
- Amir, R.E., et al., *Rett syndrome is caused by mutations in* X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet, 1999. 23(2): p. 185-8.
- Neul, J.L., et al., Developmental delay in Rett syndrome: data from the natural history study. J Neurodev Disord, 2014. 6(1): p. 20.
- Leonard, H., et al., Genotype and early development in Rett syndrome: the value of international data. Brain Dev, 2005. 27 Suppl 1: p. S59-S68.
- 8. Fehr, S., et al., *Atypical presentations and specific genotypes are associated with a delay in diagnosis in females with Rett syndrome*. Am J Med Genet A, 2010. **152A**(10): p. 2535-42.
- 9. Fabio, R.A., et al., *Recent insights into genotype-phenotype relationships in patients with Rett syndrome using a fine grain scale*. Res Dev Disabil, 2014. **35**(11): p. 2976-86.
- Neul, J.L., et al., Specific mutations in methyl-CpG-binding protein 2 confer different severity in Rett syndrome. Neurology, 2008. 70(16): p. 1313-21.

- Cuddapah, V.A., et al., Methyl-CpG-binding protein 2 (MECP2) mutation type is associated with disease severity in Rett syndrome. J Med Genet, 2014. 51(3): p. 152-8.
- 12. Fehr, S., et al., *Trends in the diagnosis of Rett syndrome in Australia*. Pediatr Res, 2011. **70**(3): p. 313-9.
- 13. Bienvenu, T., et al., *The incidence of Rett syndrome in France*. Pediatr Neurol, 2006. **34**(5): p. 372-5.
- Halbach, N.S., et al., Aging in Rett syndrome: a longitudinal study. Clin Genet, 2013. 84(3): p. 223-9.
- Kerr, A.M., et al., *Rett Syndrome: analysis of deaths in the British Survey*. European Child & Adolescent Psychiatry 1997. 6 (Suppl1): p. 71-74.
- 16. Lee, J., et al., Early development and regression in Rett syndrome. Clin Genet, 2013.
- 17. Smeets, E.E., K. Pelc, and B. Dan, *Rett Syndrome*. Mol Syndromol, 2012. **2**(3-5): p. 113-127.
- Einspieler, C., A.M. Kerr, and H.F. Prechtl, *Is the early development of girls with Rett disorder really normal?* Pediatric Research, 2005. 57(5 Pt 1): p. 696-700.
- 19. Marschik, P.B., et al., *Three different profiles: early sociocommunicative capacities in typical Rett syndrome, the preserved speech variant and normal development*. Dev Neurorehabil, 2014. **17**(1): p. 34-8.
- Marschik, P.B., et al., Changing the perspective on early development of Rett syndrome. Res Dev Disabil, 2013. 34(4): p. 1236-9.
- 21. Cass, H., et al., *Findings from a multidisciplinary clinical case* series of females with Rett syndrome. Dev Med Child Neurol, 2003. **45**: p. 325-337.
- 22. Berger-Sweeney, J., *Cognitive deficits in Rett syndrome: what we know and what we need to know to treat them.* Neurobiol Learn Mem, 2011. **96**(4): p. 637-46.
- 23. Urbanowicz, A., et al., *Parental perspectives on the communication abilities of their daughters with Rett syndrome*. Dev Neurorehabil, 2014.
- 24. Bartolotta, T.E., et al., *Communication skills in girls with Rett Syndrome. Focus on Autism and Other Developmental Disabilities*, 2011. **26**(1): p. 15-24.
- 25. Neul, J.L., et al., *Rett syndrome: revised diagnostic criteria and nomenclature*. Ann Neurol, 2010. **68**(6): p. 944-50.
- Townend, G., et al., Eye Gaze Technology as a Form of Augmentative and Alternative Communication for Individuals with Rett Syndrome: Experiences of Families in The Netherlands. Journal of Developmental and Physical Disabilities, 2015: p. 1-12.
- 27. Byiers, B. and F. Symons, *The need for unbiased cognitive assessment in Rett syndrome: is eye tracking the answer?* Dev Med Child Neurol, 2013. **55**(4): p. 301-2.
- Renieri, A., et al., *Diagnostic criteria for die Zappella variant of Rett syndrome (the preserved speech variant)*. Brain Dev, 2009.
 31: p. 208-16.
- 29. Young, D.J., et al., *The diagnosis of autism in a female: could it be Rett syndrome?* Eur J Pediatr, 2008. **167**(6): p. 661-9.
- 30. Kaufmann, W.E., et al., *Social impairments in Rett syndrome: Characteristics and relationship with clinical severity.* Journal of Intellectual Disability Research, 2012. **56**(3): p. 233-247.

- 31. Guy, J., et al., *Reversal of neurological defects in a mouse model of Rett syndrome*. Science, 2007. **315**(5815): p. 1143-7.
- 32. Nissanholtz-Gannot, R., A. Zigdon, and M. Lotan, *The Time is Now: The Need for an Intensive Appropriate Individual Intervention for Individuals with Rett Syndrome*. Journal of Syndromes, 2015. **2**(1): p. 1-7.
- 33. Townend, G.S., et al., *Rett syndrome and the role of national parent associations within a European context*. Rare Diseases and Orphan Drugs 2015. **2**(2): p. 17-26.
- 34. Simacek, J., J. Reichle, and J.J. McComas, *Communication intervention to teach requesting through aided aac for two learners with rett syndrome.* Journal of Developmental and Physical Disabilities, 2015.
- Stasolla, F., et al., *Technological aids to support choice* strategies by three girls with Rett syndrome. Res Dev Disabil, 2015. 36: p. 36-44.
- 36. Stasolla, F., et al., *Comparing PECS and VOCA to promote communication opportunities and to reduce stereotyped behaviors by three girls with Rett syndrome*. Research in Autism Spectrum Disorders, 2014. **8**(10): p. 1269-1278.
- 37. Downs, J., et al., *Guidelines for management of scoliosis in Rett syndrome patients based on expert consensus and clinical evidence*. Spine (Phila Pa 1976), 2009. **34**(17): p. E607-17.
- Leonard, H., et al., Assessment and management of nutrition and growth in Rett syndrome. J Pediatr Gastroenterol Nutr, 2013. 57(4): p. 451-60.
- 39. Jefferson, A., et al., *Clinical Guidelines for Management of Bone Health in Rett Syndrome Based on Expert Consensus and Available Evidence*. PLoS One, 2016. **11**(2): p. e0146824.

Gillian Townend & Friederike Ehrhart : 2016

Triple-X Syndrome (47,XXX)

First description and alternative names

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

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

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.

References

- Barlow, P. W. (1973) X-chromosomes and human development. *Developmental Medicine & Child Neurology*, 15, 205-8.
- Bishop, D. V., Jacobs, P. A., Lachlan, K., Wellesley, D., Barnicoat, A., Boyd, P. A., Fryer, A., Middlemiss, P., Smithson, S., Metcalfe, K., Shears, D., Leggett, V., Nation, K. & Scerif, G. (2011) Autism, language and communication in children with sex chromosome trisomies. *Archives of disease in childhood*, 96, 954-9.
- Jacobs, P. A., Baikie, A. G., Court Brown, W. M., MacGregor, T. N., Maclean, N. & Harnden, D. G. (1959) Evidence for the existence of the human "super female". *Lancet*, 274, 423-5.
- 4. Kelkar, A. & Deobagkar, D. (2010) Methylation profile of genes on the human X chromosome. *Epigenetics*, **5**.
- Leggett, V., Jacobs, P., Nation, K., Scerif, G. & Bishop, D. V. (2010) Neurocognitive outcomes of individuals with a sex chromosome trisomy: XXX, XYY, or XXY: a systematic review. *Developmental medicine and child neurology*, **52**, 119-29.
- 6. Lenroot, R. K., Blumenthal, J. D., Wallace, G. L., Clasen, L. S., Lee, N. R. & Giedd, J. N. (2014) A case-control study of brain structure and behavioral characteristics in 47,XXX syndrome. *Genes Brain Behav*, **13**, 841-9.
- Migeon, B. R. (2007) Females are MOSAICS; X inactivation and sex differences in disease, (Trans. Oxford University Press, New York.
- Netley, C. T. (1986) Summary overview of behavioural development in individuals with neonatally identified X and Y aneuploidy. *Birth defects original article series*, 22, 293-306.
- Olanders, S. (1975) Females with supernumerary X chromosomes; a study of 39 psychiatric cases. In: *St. Jörgen's hospital* (ed H. Forssman). pp. 223. University of Göteborg, Göteborg, Sweden.
- Otter, M., Schrander-Stumpel, C. T. & Curfs, L. M. (2010) Triple X syndrome: a review of the literature. *Eur J Hum Genet*, 18, 265-71.
- Otter, M., Schrander-Stumpel, C. T., Didden, R. & Curfs, L. M. (2012) The psychiatric phenotype in triple X syndrome: new hypotheses illustrated in two cases. *Developmental neurorehabilitation*, **15**, 233-8.
- 12. Patwardhan, A. J., Brown, W. E., Bender, B. G., Linden, M. G., Eliez, S. & Reiss, A. L. (2002) Reduced size of the amygdala in individuals with 47,XXY and 47,XXX karyotypes. *American Journal of Medical Genetics*, **114**, 93-8.
- Ratcliffe, S. G., Masera, N., Pan, H. & McKie, M. (1994) Head circumference and IQ of children with sex chromosome abnormalities. *Developmental Medicine & Child Neurology*, 36, 533-44.
- Robinson, A., Bender, B. G. & Linden, M. G. (1990) Summary of clinical findings in children and young adults with sex chromosome anomalies. *Birth defects original article series*, 26, 225-8.
- 15. Stochholm, K., Juul, S. & Gravholt, C. H. (2010) Mortality and incidence in women with 47,XXX and variants. *American Journal of Medical Genetics. Part A*, **152A**, 367-372.

- Stochholm, K., Juul, S. & Gravholt, C. H. (2013) Poor socioeconomic status in 47,XXX --an unexpected effect of an extra X chromosome. *Eur J Med Genet*, 56, 286-91.
- 17. Tartaglia, N. R., Howell, S., Sutherland, A., Wilson, R. & Wilson, L. (2010) A review of trisomy X (47,XXX). *Orphanet journal of rare diseases*, **5**, 8.
- van Rijn, S., Stockmann, L., Borghgraef, M., Bruining, H., van Ravenswaaij-Arts, C., Govaerts, L., Hansson, K. & Swaab, H. (2013) The Social Behavioral Phenotype in Boys and Girls with an Extra X Chromosome (Klinefelter Syndrome and Trisomy X): A Comparison with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, 44, 310-320.
- 19. van Rijn, S., Stockmann, L., van Buggenhout, G., van Ravenswaaij-Arts, C. & Swaab, H. (2014) Social cognition and underlying cognitive mechanisms in children with an extra X chromosome: a comparison with autism spectrum disorder. *Genes Brain Behav*, **13**, 459-467.
- 20. van Rijn, S. & Swaab, H. (2015) Executive dysfunction and the relation with behavioral problems in children with 47,XXY and 47,XXX. *Genes Brain Behav*, **14**, 200-8.

Maarten Otter, 2015

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Tuberous Sclerosis Complex (TSC)

First description and alternative names

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

References

- Curatolo P., Moavero R., de Vries P.J. (2015) Neurological and neuropsychiatric aspects of tuberous sclerosis complex. Lancet Neurol 14, 733-745.
- 2. de Vries P. et al. (2005) Consensus clinical guidelines for the assessment of cognitive and behavioural problems in Tuberous Sclerosis. *Eur Child Adoles Psy* 14, 183-190.
- de Vries P.J. et al., (2015) TSC-Associated Neuropsychiatric Disorders (TAND) and the TAND Checklist. Pediatr Neurol 52, 25-35.
- Krueger D., Northrup H., et al. (2013) Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 49, 255-265.
- 5. Kwiatkowski D.J., Whittemore V.H. & Thiele E.A. (2010) *Tuberous Sclerosis Complex: Genes, Clinical Features, and Therapeutics*. Weinheim: Wiley-Blackwell.
- 6. Leclezio L., et al. (2015) Pilot validation of the tuberous sclerosis-associated neuropsychiatric disorders (TAND) checklist. Pediatr Neurol 52, 16-24.
- 7. Northrup H., Krueger D., et al. (2013) Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 49, 243-254.
- 8. Osborne J.P., Fryer A. & Webb D. (1991) Epidemiology of tuberous sclerosis. *Ann NY Acad Sci* 615, 125-127.

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

- Bondy C.A. (2007) Turner Syndrome Study Group.
 Care of girls and women with Turner syndrome:
 A guideline of the Turner Syndrome Study Group.
 J Clin Endocrinol Metab 92(1), 10-25.
- Gravholt C.H.(2009) "Turner know your body!" Editor –Published by Novo-Nordisk. Available as a free web-publication http://np.netpublicator.com/netpublication/ n75088268

Useful websites/Associations for more information

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

References

- Cardoso G., Daly R., Haq N.A., Hanton L., Rubinow D.R., Bondy C.A., Schmidt P. (2004) Current and lifetime psychiatric illness in women with Turner syndrome. *Gynecol Endocrinol* 19(6), 313-9.
- 2. Jacobs P., Dalton P., James R., Mosse K., Power M., Robinson D., Skuse D. (1997) Turner syndrome: a cytogenetic and molecular study. *Ann Hum Genet* 61(Pt 6), Nov; 471-83.
- 3. Kuntsi J., Skuse D., Elgar K., Morris E., Turner C. (2000) Ring-X chromosomes: their cognitive and behavioural phenotype. *Ann Hum Genet* 64(Pt 4), Jul, 295-305.
- 4. Skuse, D. (2009) Psychological and Psychiatric Aspects of Turner Syndrome (in) Turner-Know Your Body! Novo-Nordisk, pp 200-217.

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/

References

- 1. Sedlackova, E., Insuficience patrohltanoveho zaveru jako vyvojova porucha. Cas Lek Cesk, 1955. **94**: p. 1304-1307.
- Turnpenny, P. and R. Pigott, *Deletion 22q11 syndrome:* acknowledging a lost eponym as we say farewell to an acronym. Journal of Medical Genetics, 2001. 38(4): p. 271-273.
- 3. Vrticka, K., Present-day importance of the velocardiofacial syndrome. To commemorate the late prof. Eva sedlackova, MD, on the 50th anniversary of her original publication. Folia Phoniatr Logop, 2007. **59**(3): p. 141-6.
- Sedláčková, E., The syndrome of the congenitally shortened velum the dual innervation of the soft palate. Folia Phoniatrica et Logopaedica, 1967. 19(6): p. 441-450.
- 5. DiGeorge, A., Discussion on a new concept of the cellular immunology. J. Pediatr, 1965. **67**: p. 907-908.
- 6. Kinouchi, A., et al., *Facial appearance of patients with conotruncal anomalies*. Pediatr Jpn, 1976(4): p. 17:8.
- 7. Shprintzen, R.J., et al., *A new syndrome involving cleft palate, cardiac anomalies, typical facies, and learning disabilities: velo-cardio-facial syndrome*. Cleft Palate J, 1978. **15**(1): p. 56-62.
- 8. Scambler, P.J., et al., *Microdeletions within 22q11 associated with sporadic and familial DiGeorge syndrome*. Genomics, 1991. **10**(1): p. 201-206.
- 9. McDonald-McGinn, D.M., et al., 22q11.2 deletion syndrome. Nat Rev Dis Primers, 2015. 1: p. 15071.
- Oskarsdottir, S., M. Vujic, and A. Fasth, *Incidence and* prevalence of the 22q11 deletion syndrome: a population-based study in Western Sweden. Arch Dis Child, 2004. 89(2): p. 148-51.
- 11. Tezenas Du Montcel, S., et al., *Prevalence of 22q11 microdeletion*. J Med Genet, 1996. **33**(8): p. 719.

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- 12. Bassett, A.S., et al., *Practical guidelines for managing patients* with 22q11.2 deletion syndrome. J Pediatr, 2011. **159**(2): p. 332-9 e1.
- Costain, G., et al., Sex differences in reproductive fitness contribute to preferential maternal transmission of 22q11.2 deletions. J Med Genet, 2011. 48(12): p. 819-24.
- 14. Repetto, G.M., et al., *Case fatality rate and associated factors in patients with 22q11 microdeletion syndrome: a retrospective cohort study*. BMJ Open, 2014. **4**(11): p. e005041.
- McDonald-McGinn, D.M., et al., *The Philadelphia story: the* 22q11.2 deletion: report on 250 patients. Genet Couns, 1999.
 10(1): p. 11-24.
- Green, T., et al., Psychiatric Disorders and Intellectual Functioning Throughout Development in Velocardiofacial (22q11.2 Deletion) Syndrome. Journal of the American Academy of Child & Adolescent Psychiatry, 2009. 48(11): p. 1060-1068.
- 17. Kates, W.R., et al., A gender-moderated effect of a functional COMT polymorphism on prefrontal brain morphology and function in velo-cardio-facial syndrome (22q11.2 deletion syndrome). American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 2006. **141B**(3): p. 274-280.
- Cirillo, E., et al., Intergenerational and intrafamilial phenotypic variability in 22q11.2 Deletion syndrome subjects. BMC Medical Genetics, 2014. 15(1): p. 1-8.
- Tang, K.L., et al., Behavioral and Psychiatric Phenotypes in 22q11.2 Deletion Syndrome. J Dev Behav Pediatr, 2015. 36(8): p. 639-50.
- Schneider, M., et al., Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. Am J Psychiatry, 2014. 171(6): p. 627-39.
- 21. Swillen, A. and D. McDonald-McGinn, *Developmental trajectories in 22q11.2 deletion*. Am J Med Genet C Semin Med Genet, 2015. **169**(2): p. 172-81.
- 22. Vorstman, J.A., et al., *Cognitive decline preceding the onset of psychosis in patients with 22q11.2 deletion syndrome*. JAMA Psychiatry, 2015. **72**(4): p. 377-85.
- 23. Campbell, L.E., et al., *Executive functions and memory abilities in children with 22q11.2 deletion syndrome*. Aust N Z J Psychiatry, 2010. **44**(4): p. 364-71.
- Simon, T.J., et al., Visuospatial and numerical cognitive deficits in children with chromosome 22q11.2 deletion syndrome. Cortex, 2005. 41(2): p. 145-55.
- 25. Gur, R.E., et al., *Neurocognitive development in 22q11.2 deletion* syndrome: comparison with youth having developmental delay and medical comorbidities. Mol Psychiatry, 2014. **19**(11): p. 1205-11.
- 26. Franchini, M., et al., Visual processing of emotional dynamic faces in 22q11.2 deletion syndrome. J Intellect Disabil Res, 2016.
- 27. Campbell, L., et al., *Visual scanning of faces in 22q11.2 deletion syndrome: Attention to the mouth or the eyes?* Psychiatry Res, 2010. **177**(1-2): p. 211-5.

- Fung, W.L.A., et al., *Practical guidelines for managing adults* with 22q11.2 deletion syndrome. Genetics in medicine : official journal of the American College of Medical Genetics, 2015. 17(8): p. 599-609.
- 29. Habel, A., et al., *Towards a safety net for management of* 22q11.2 deletion syndrome: guidelines for our times. European Journal of Pediatrics, 2014. **173**(6): p. 757-765.

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

References

- 1. Beuren, A.J., Apitz, J. & Harmanz, D. (1962) Supravalvular aortic stenosis in association with mental retardation and a certain facial appearance. Circulation, 26, 1235-40.
- 2. Black, J.A., Carter, RE (1963) Association between aortic stenosis and facies of severe infantile hypercalcaemia. Lancet, 91, 745-9.
- 3. Donnai, D. & Karmiloff-Smith, A. (2000) Williams syndrome: From genotype through to the cognitive phenotype. American Journal of Medical Genetics: Seminars in Medical Genetics, 97 (2), I 64-171.
- 4. Doyle, T. F., Bellugi, U., Korenberg, J. R., & Graham, J. (2004). "Everybody in the world is my friend" hypersociability in young children with Williams syndrome. American Journal of Medical Genetics Part A, 124A, 263-273.
- Einfeld, S. L., Tonge, B. J., & Rees, V. W. (2001). Longitudinal course of behavioral and emotional problems in Williams syndrome. American Journal on Mental Retardation, 106, 73-81.
- Fidler, D.J., Hepburn, S.L., Most, D. E., Philosfsky, A. & Rogers, S.J. (2007) Emotional responsivity in young children with Williams syndrome. American Journal on Mental Retardation, 112, 194-206
- Howlin, P., Elison, S., Udwin, U. & Stinton, C. (2010). Cognitive, linguistic and adaptive functioning in Williams syndrome: trajectories from early to middle adulthood. Journal of Applied Research in Intellectual Disabilities. , 23(4), 322-336.
- 8. Klein-Tasman, B.P. & Mervis, C.P. (2003). Distinctive personality characteristics of 8-, 9-, and 10-yearolds with Williams syndrome. Developmental Neuropsychology, 23, 269-290.

- Leyfer, O. T., Woodruff-Borden, J., Klein-Tasman, B. P., Fricke, J. S., & Mervis, C. B. (2006). Prevalence of psychiatric disorders in 4 to 16-year-olds with Williams syndrome. American Journal of Medical Genetics Part B - Neuropsychiatric Genetics, 141B, 615-622.112
- Martens, M. A., Wilson, S. J. & Reutens, D. C. (2008). Research Review: Williams syndrome: a critical review of the cognitive, behavioral, and neuroanatomical phenotype. Journal of Child Psychology and Psychiatry and Allied Disciplines, 49 (6), 576-608.
- Porter, M. & Coltheart, M. (2005). Cognitive heterogeneity in Williams syndrome. Developmental Neuropsychology, 27 (2), 275-306.
- Skwerer, D.P and Tager-Flusberg, H. (2011)Williams Syndrome,: Overview and Research Advances. In. Howlin, P., Charman, T. and Ghaziuddin, M. (Eds). Sage Handbook of Developmental Disorders. London: Sage.
- Stinton, C., Elison, S. & Howlin, P. (2010). Mental health in Williams syndrome. American Journal on Mental Retardation,115 (1), 3-18
- 14. Stinton, C., Tomlinson, K. & Estes, Z. (2012). Examining reports of mental health in adults with Williams syndrome Research in Developmental Disabilities 33, 144–152.
- 15. Williams, J., Barrett-Boyes, B., & Lowe, J. (1961). Supravalvular aortic stenosis. Circulation, 1311-1318.

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).

References

- Battaglia A, Carey JC, South ST, Wright TJ. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. Gene Reviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2002.
- 2. Bergemann AD, Cole F, Hirschhorn K (2005) The etiology of Wolf-Hirschhorn syndrome. Trends Genet 21:188–195
- Fisch GS, Grossfeld P, Falk R, Battaglia A, Youngblom J, Simensen R. Cognitive-behavioral features of Wolf-Hirschhorn syndrome and other subtelomeric microdeletions. Am J Med Genet C Semin Med Genet. 2010 Nov 15;154C(4):417-26.
- 4. Hirschhorn K, Cooper HL, Firschein IL. 1965. Deletion of short arms of chromosome 4–5 in a child with defects of midline fusion. Humangenetik 1:479–482.
- 5. Wolf U, Reinwein H, Porsch R, Schroter R, Baitsch H. 1965. Defizien an den kurzen Armen eines Chromosoms Nr 4. Humangenetik 1:397–413.
- Zollino M, Di Stefano C, Zampino G, Mastroiacovo P, Wright TJ, Sorge G, Selicorni A, Tenconi R, Zappalà A, Battaglia A, Di Rocco M, Palka G, Pallotta R, Altherr MR, Neri G. Genotypephenotype correlations and clinical diagnostic criteria in Wolf-Hirschhorn syndrome. Am J Med Genet. 2000 Sep 18;94(3):254-61.

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

- Bardsley MZ, Kowal K, Levy C, Gosek A, Ayari N, Tartaglia N, Lahlou N, Winder B, Grimes S & Ross J, 47,XYY Syndrome: Clinical Phenotype and Timing of Ascertainment. J Pediatr. 2013 October ; 163(4): 1085–1094
- Stockholm K, Bojesen A, Skakkebæk J, Jull S, and Gravenholt G. Criminality in men with Klinefelter's syndrome and XYY syndrome: a cohort study. BMJ Open 2012;2: e000650. doi:10.1136/ bmjopen-2011-000650
- 3. Bryant DM, Hoeft F, Lai S, Lackey J, Roeltgen D, Ross J, and Reiss AL. *Sex chromosomes and the brain: a study of neuroanatomy in XYY syndrome*. Dev Med Child Neurol. 2012 December ; 54(12): 1149–1156.
- Lepage JF, Hong DS, Raman M, Marzelli M, Roeltgen DP, Lai S, Ross J, Reiss AL. Brain morphology in children with 47, XYY syndrome: a voxel- and surface-based morphometric study. Genes Brain Behav. 2014 Feb;13(2):127-34.
- Torniero C, Dalla Bernardina B, Fontana E, Darra F, Danesino C, Elia M. *Electroclinical findings in four patients with karyotype 47,XYY*. Brain Dev ,May 2011 Volume 33, Issue 5, p361-448
- 6. Geerts M1, Steyaert J, Fryns JP. *The XYY syndrome: a follow-up study on 38 boys*. Genet Couns. 2003;14 (3):267-79.
- Ross JL1, Tartaglia N, Merry DE, Dalva M, Zinn AR. Behavioral phenotypes in males with XYY and possible role of increased NLGN4Y expression in autism features. Genes Brain Behav. 2015 Feb;14(2):137-44.
- 8. Lalatta F, Folliero E, Cavallari U, Di Segni M, GentilinB , Fogliani R, QuagliariniD, Vizziello P, MontiF and Gargantini L. *Early manifestations in a cohort of children prenatally diagnosed with 47,XYY. Role of multidisciplinary counseling for parental guidance and prevention of aggressive behavior*. Ital J Pediatr. 2012; 38: 52.
- Verri AP, Galimberti CA, Perucca P, Cremante A, Vernice M, Uggetti A. Psychotic disorder and focal epilepsy in a lefthanded patient with chromosome XYY abnormality. Genet Couns. 2008;19(4):373-9.
- Robinson DO, Jacobs PA. The origin of the extra Y chromosome in males with a 47,XYY karyotype. Hum Mol Genet. 1999 Nov;8(12):2205-9.
- Ratcliffe S. Long-term outcome in children of sex chromosome abnormalities. Arch Dis Child. 1999; 80:192–5. [PubMed: 10325742]
- Abramsky L, Chapple J. 47,XXY (Klinefelter syndrome) and 47,XYY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. Prenat Diagn. 1997; 17:363–8. [PubMed: 9160389]

Annapia Verri, April 2016

Maps and Directions

Conference Venue – The Rectorate of the University of Siena.

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