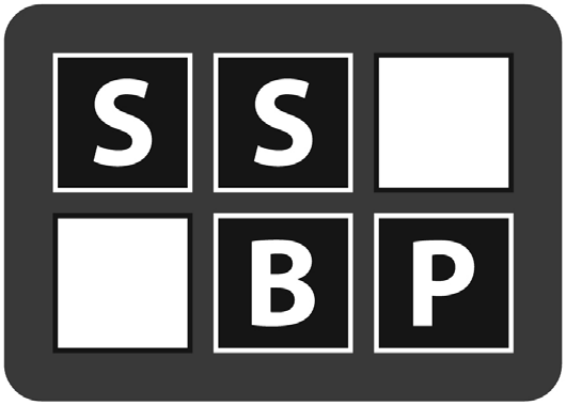
17th SSBP International Research Symposium

Developmental trajectories of behavioural phenotypes

Programme Book

10–13 October 2014 • New York, USA



The Society for the Study

of Behavioural Phenotypes

10th – 13th October 2014

The 17th SSBP International Meeting

Developmental Trajectories of Behavioural Phenotypes

New York, USA

Contents

Welcome

Dear Colleagues,
We are delighted to welcome you to **New York, USA** for the 17th SSBP International Research Symposium and Educational Day.

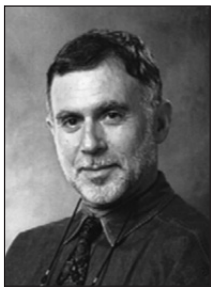
The theme for the 2014 meeting is ***'Developmental Trajectories of Behavioural Phenotypes'***.

We are extremely grateful to our international keynote speakers who agreed to join us in New York. We have no doubt that we will have lively discussions throughout the Conference.

We are pleased to report that all oral abstracts for the Research Symposium and Educational Day have been published in the October 2014 issue of the *Journal of Intellectual Disability Research* (JIDR). The SSBP has had a long-standing collaboration with the JIDR, and we hope to strengthen this relationship over the next few years.

Gene Fisch
Conference Co-ordinator

New York Conference Organiser



Gene Fisch, Ph.D. is currently Research Professor at the NYU Colleges of Dentistry & Nursing, and Interim Director of Statistics Unit in the Department of Epidemiology and Public Health. He began his career 30 years ago at the New York State Institute for Developmental Disabilities where he was appointed research scientist on the first funded grant to examine the association between autism and the fragile X syndrome.

His subsequent research went on to evaluate longitudinal development of the cognitive-behavioral features of the fragile X syndrome, in males and females with the FMR1 full mutation, in females with the FMR1 premutation, and in children with the FRAXE mutation. Given the unusual nature of cognitive-behavioral development among male children with the FMR1 full mutation, i.e., declining IQ and adaptive behavior scores as they aged, he wondered how widespread the phenomenon was among children with other genetic abnormalities which produced developmental or other learning disabilities, or intellectual disabilities. His curiosity led him to examine children with Williams-Beuren Syndrome (WBS) or Neurofibromatosis Type I (NF1). Although there were initial cross-sectional similarities in cognitive-behavioral features between males with the FMR1 full mutation and children with WBS, it became clear that their respective longitudinal developments followed different paths. He found these differences while a faculty member at Yale University, and discussed them with one of Yale's most notable geneticists, Dr. Margaret Seashore. She had recently come upon an article noting a relationship between the loss of telomeric chromatin in older individuals and the onset of cognitive dementia. In their discussions, he thought it would be of some interest to examine the cognitive-behavioral profiles of children born with subtelomeric deletions and examine the extent to which those profiles changed as the children aged. This led to his most recent research, funded by the Lejeune Fondation – a major sponsor for this SSBP meeting – to examine children with one of four subtelomeric deletions: deletion 4p (Wolf-Hirschhorn Syndrome), deletion 2q37, invdupdel8p21–3, and deletion 11q23–5 (Jacobsen Syndrome).

In addition to his own research, Dr. Fisch provided research design and statistical analyses for many medical researchers in departments as varied as pediatrics, neurology, rehabilitative medicine, and child and adolescent psychiatry. While at Yale, he was appointed biostatistician to both the Child and Adult General Clinical Research Centers, and Research Scientist to the Yale Child Study Center. He was eventually promoted to Full Professor and Senior Research Scientist. At NYU's College of Dentistry, he provided research design and statistical analyses for both clinical and basic research scientists in matters related to oral health. As both research scientist and biostatistician, he has had published more than 80 peer-reviewed articles examining genetic disorders and cognitive-behavioral development, as well as providing research design and statistical analysis for various other scientists.

Scientific Committee

Pat Howlin
Psychologist, Department of Psychology
Institute of Psychiatry, London

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Maastricht University Medical Centre, The Netherlands

Stewart Einfeld
Psychiatrist, Brain & Mind Research Institute,
University of Sydney, Australia

Gene Fisch
Research Professor and Interim Director, Biostatistics Unit, Dept. of Epidemiology & Public Health,
New York University, USA.

Stephan Huijbregts
Psychologist, Behavioural Sciences,
Leiden University, The Netherlands

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 :

President *Dr Martin Bax* (London) (joy.allsop@imperial.ac.uk)
Chair *Professor Petrus de Vries* (Cape Town) (petrus.devries@uct.ac.za)
Hon. Secretary *Professor Leopold Curfs* (Maastricht) (leopold.curfs@maastrictuniversity.nl)
Hon. Treasurer *Professor Christopher Howe* (Cambridge) (ch26@cam.ac.uk)

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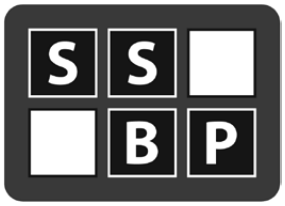
Administrator *Elizabeth Walmsley* (ssbpliz@gmail.com)



Meetings of the SSBP

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

Forthcoming Meetings of the SSBP

2014	New York, USA	17th International
2015	London, United Kingdom	18th 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

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

2014 Tom Oppé Lecturer: Professor Stewart Einfeld

Professor Stewart Einfeld is the Chair of Mental Health, Centre for Disability Research and Policy, ad Senior Scientist at the Brain and Mind Research Institute, University of Sydney, Australia. His research and teaching interests are in child and adolescent psychiatry, developmental disabilities, including intellectual disability and its genetic causes and autism. He is co-developer of the Developmental Behaviour Checklist. This instrument is widely used in clinical and research settings to measure and describe behavioual and emotional problems in people with developmental disabilities. Professor Einfeld is co-Chief Investigator of the Australian Child to Adult Development (ACAD) Study, a 20-year cohort study examining biological, psychological and social factors influencing the development of behavioural and emotional problems in children and adolescents with intellectual handicap.

He has also conducted numerous descriptive and intervention studies in the behaviour phenotypes of Williams, Down, Fragile X, Prader Willi and other syndromes. Professor Einfeld is currently evaluating a public health roll out of a parenting program for parents of children with disabilities. He is also the lead investigator on a parenting program for Australian indigenous families affected by Fetal Alcohol Spectrum Disorder. Through advocacy, presentations and writings, Professor Einfeld has been a leader in promoting a re-emergence of the field of psychiatry of developmental disabilities in Australia.

Patricia Howlin and the Patricia Howlin Prize Lecture

Patricia Howlin

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

Pat Howlin Prize Lecture:

Area of Research:

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

Eligibility of applicants:

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

Award Procedure:

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

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

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

Patricia Howlin Lecturers

2014	Hayley Crawford
2013	Mary Heald
2012	Sheena Grant
2011	Leah Bull
2010	Debbie Allen

2014 Pat Howlin Prize Winner: Hayley Crawford

Hayley graduated from the University of Birmingham in 2010 with a first class honours degree in Psychology. She then worked as a research associate at the Cerebra Centre for Neurodevelopmental Disorders before securing funding from the ESRC to complete a Masters of Research degree and a PhD under the supervision of Professor Chris Oliver, Dr Joanna Moss and Dr Joseph McCleery. During her PhD, Hayley has been investigating the social impairments exhibited by individuals with rare genetic syndromes and neurodevelopmental disorders associated with intellectual disability. Hayley is currently using eye-tracking technology and behavioural observation to investigate social anxiety, social motivation and the processing of social information in children and adults with Fragile X, Cornelia de Lange and Rubinstein-Taybi syndromes, as well as autism spectrum disorder.

Sponsors

The SSBP is extremely grateful to the following organisations for their sponsorship of SSBP 2014 in New York:

Jérôme Lejeune Foundation.

March of Dimes

Williams Syndrome Association

4p Support Group

WHST – Wolf Hirschhorn Syndrome Trust

Behavior Analysis – CUNY Graduate Center

New York University,College of Dentistry

Keynote Speaker Profiles

(in order of presentation)

Prof. Catherine Lord

Catherine Lord, Ph.D. is the Director of the Center for Autism and the Developing Brain a joint project of New York - Presbyterian Hospital, Weill Cornell Medical College, Columbia University College of Physicians and Surgeons in partnership with New York Collaborates for Autism. She completed degrees in psychology at UCLA and Harvard, and a clinical internship at Division TEACCH at the University of North Carolina at Chapel Hill. Dr. Lord is a licensed clinical psychologist with specialties in diagnosis, social and communication development and intervention in autism spectrum disorders (ASD). She is renowned for her work in longitudinal studies of social and communicative development in ASD. She has also been involved in the development of standardized diagnostic instruments for ASD with colleagues from the United Kingdom and the United States (the Autism Diagnostic Observation Schedule (ADOS) an observational scale; and the Autism Diagnostic Interview – Revised (ADI-R) a parent interview), now considered the gold standard for research diagnoses all over the world. Dr. Lord was the Chair of the National Research Council's Committee on the Effectiveness of Early Intervention in Autism and is a member of the DSM5 Neurodevelopmental Disorders Committee. Her work at the Center for Autism and the Developing Brain involves continued research in validity and longitudinal studies, early diagnosis of children with autism, and regression in children with autism and clinical evaluations and diagnoses of children and adults who may have autism.

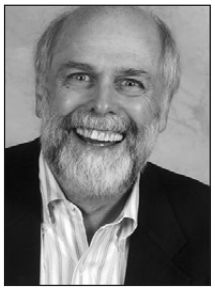
Dr Carolyn B. Mervis

Carolyn B. Mervis, PhD is Distinguished University Scholar and Professor of Psychological and Brain Sciences at the University of Louisville in Louisville, KY. She received her AB in Linguistics and her PhD in Psychology from Cornell University. Her research is transdisciplinary in nature and is focused primarily on the development of children with 7q11.23 deletions (Williams syndrome) or duplications (7q11.23 duplication syndrome) and on genotype/phenotype relations involving the 7q11.2 3 region. She has been conducting research on individuals with Williams syndrome for more than 20 years and on individuals with 7q11.23 duplication syndrome since 2005, when her research team was asked to assess the first individual identified with that syndrome. Dr. Mervis' research on Williams syndrome has been supported by the National Institutes of Health (NIH) continuously since 1993 and currently is supported by an NICHD MERIT award. Her research on 7q11.23 duplication syndrome is supported by the Simons Foundation. Dr. Mervis is a member of the Professional Advisory Board of the Williams Syndrome Association (WSA) and in 2012 received an Award of Appreciation from the WSA for her "commitment to improving the lives of individuals with Williams syndrome and their families." She also advises Duplication Cares, the support group for families of individuals with 7q11.23 duplication syndrome.

Dr Barbara Pober

Dr Barbara Pober received a BA and MD degrees from Yale University. She completed pediatric residency at Tufts New England Medical Center, and a genetics fellowship at Massachusetts General Hospital, Boston MA. She has more than 25 years of experience providing care for individuals with Williams syndrome. Dr Pober started one of the first multi-disciplinary clinics for Williams syndrome at Boston Children's Hospital in 1987 and has continuously been involved in providing care at Yale University (1991–2003) and most recently at Massachusetts General Hospital (2003-present). She has has also actively participated in research, often focusing on natural history. In 2013, Dr Pober relocated to the new Frank H Netter School of Medicine, Quinnipiac University, North Haven, CT and is heavily involved in curriculum development. She continues to see her patients with Williams syndrome, and engage in research activities, at MGH in Boston, MA.

Prof. John Carey



John C. Carey, MD, MPH, is Professor and Vice Chair of Academic Affairs, Department of Pediatrics, at the University of Utah. Throughout his career, Dr. Carey has been interested in birth defect syndromes and the care of children with these conditions. Dr. Carey graduated from Villanova University in 1968 with an A.B. and obtained his M.D. from Georgetown University School of Medicine in 1972. He trained in pediatrics, genetics and dysmorphology as a resident and fellow at the University of California San Francisco, 1972–1979. Dr. Carey obtained an M.P.H. from the University of California at Berkeley in 1976 in between his residency and fellowship years. Dr. Carey joined the facult y at University of Utah Health Sciences Center in 1979. He became Chief of the Division of Medical Genetics in 1985 and remained in that leadership position until 1999 when he stepped down to assume the role as Editor-in-Chief of the American Journal of Medical Genetics. He has held that editorial position since 2001. Dr. Carey established the Medical Genetics Fellowship Program at the University of Utah and continues as Program Director.

Dr. Carey's research focus has been in congenital malformations, neurofibromatosis and syndrome delineation. He has authored or co-authored over 280 papers, chapters, invited articles and editorials for scientific journals. He also co-authored the textbook, "Medical Genetics," by Jorde, Carey, & Bamshad, now in its 4th edition. The book is a widely used text in schools of medicine throughout North America and Europe.

Dr. Carey has served as medical adviser and "founding professional" for the Support Organization for Trisomy 18, 13 and Related Disorders (SOFT) since 1980. The medical and ethical aspects of care of infants and children with these conditions are currently some of his major academic interests.

Prof. Agatino Battaglia

JANUARY 1st 2002 to date ADJUNCT PROFESSOR OF PEDIATRICS, Division of Medical Genetics, Department of Pediatrics, The University of Utah School of Medicine & Health Sciences Center - Primary Children's Medical Center, Salt Lake City, UT, USA.
From January.2011 he is Adjunct FULL PROFESSOR of PEDIATRICS at the Department of Pediatrics- University of South Dakota, Sanford School of Medicine, Sioux Falls, SD, USA.
1994–95 to date contract Professor of Child Neuropsychiatry, Post-Graduate Medical School, in Child Neuropsychiatry, University of Pisa. Lecturer in Clinical Neurophysiology, and in Neurogenetics in several University Courses for Postgraduate Medical students, held in Italy and abroad.

- 15–17 may 2000 he organized in Pisa, in collaboration with the University of Utah, The International Workshop on "The role of genetics in child neuropsychiatry" (workshop faculty: 30 international speakers).
- Associate Editor of the American Journal of Medical Genetics and Member of the Editorial Board of Autism Research and of Molecular Autism.
- Reviewer for 50 international scientific journals.
- Invited Guest Editor for the American Journal of Medical Genetics Part C-Seminars in Medical Genetics –for the volumes (vol. 117C, 142C, 148C, 154C) published in 2003, 2006, 2008, and 2010, on the "Genetics of mental retardation", "Genetics of autism", "Wolf-Hirschhorn sindrome and the 4p- related syndromes"; and "Behavioral phenotypes in neurogenetic syndromes".
- Invited speaker for 90 presentations to national and international congresses, and to Universities abroad (Stanford, Loma Linda, Salt Lake City, S. Antonio, Philadelphia, Boston, Sioux Falls).
- He has a strong research interest in clinical dysmorphology, neuropsychiatric genetics (autism and intellectual disability fields, and rare diseases), and clinical neurophysiology.
- He's part of the Autism Genome Project (AGP), an international scientific consortium made of the world leading scientists involved in the molecular genetic study of autism.

Amongst the research projects lead by dr. Battaglia, the following deserve particular attention:

1. "Neurobiological bases of autism, new methods for diagnostic evaluation and insights into pharmacological treatment" (P.I.; 2-year Strategic Research Project, funded by the Italian Ministry of Health).
2. On-site P.I. for the European Specific Targeted Research Project "Using European and International Populations to Identify Autism Susceptibility Loci" (3-year Research Project funded by the European Union, 2005–2008).

Prof. Ann Swillen

Ann Swillen is professor at the Department of Human Genetics, KU Leuven and at the Department of Rehabilitation Sciences, KU Leuven (University of Leuven, Belgium). Trained as an educational psychologist, she is also affiliated to CME-UZ (the clinical unit of the Department of Human genetics), an international centre of excellence in the field of clinical and molecular genetics. A particular focus is on individuals with genetic, neuropsychiatric, and neurodevelopmental conditions that affect learning and behavior.

Through a multifaceted collaborative approach with many disciplines, we aim for four goals:

1. Better define the studied neuro-genetic syndromes (e.g. del22q11.2, dupl22q11, del22q13.3, Turner syndrome;
2. Identify mechanisms of cognitive impairment;
3. Identify mechanisms for increased psychiatric risk;
4. Using specific neuro-genetic conditions as homogeneous genetic models to better understand the interaction among genetic, behavioural and environmental factors in developmental disorders. Ultimately, a better knowledge of neuropsychiatric and neurodevelopmental conditions will help us to refine our treatment strategies and improve the life of affected children and their families.

Besides her research, Prof. Ann Swillen is (since 1994) the coordinator of the multidisciplinary 22q11 DS clinic, and is actively involved in sharing knowledge on the implications of genetic syndromes on cognition and behavior and the practical implications for education/teaching etc… by giving multiple lectures to professionals on national and international meetings, and to national and international parent-patient associations .
Prof. Ann Swillen is an international recognized authority in the field of development, cognition and behaviour in 22q11 DS, and she is author of more than 60 peer-reviewed scientific publications in the field of medical genetics and behavioural phenotypes. She is member of different international expert panels (e.g. international 22q11 DS Foundation, European VCFS-EF,), and co-founder of the International Brain-Behaviour 22q11 DS Consortium (2011) and the 22q11 DS Society (2014). Finally, Prof. Ann Swillen is PI (Europe A) of the NIH Grant U01 1U01MH101722–01 on" Genomic Risk and Resilience in 22q11 Deletion Syndrome: A Window into the Genetic Architecture of Mental Disorders", the IBBC 22q11 consortium, a collaboration between caregivers and scientists from 22 institutions and five genotyping sites throughout the world.

Prof. Donna M. McDonald-McGinn

As Director of the 22q and You Center and Associate Director of Clinical Genetics within the Division of Human Genetics at The Children's Hospital of Philadelphia (CHOP) and Clinical Professor of Pediatrics at the Perelman School of Medicine of the University of Pennsylvania, Professor McDonald-McGin n has spent much of her professional career, since the introduction of FISH s tudies in 1992, striving to understand the etiology and outcomes associated with the 22q11.2 deletion syndrome (22q11.2DS), and related conditions such as the 22q11.2 duplication syndrome, as well as the relationship between these copy number variants and associated problems such as congenital heart disease, cleft palate, immunodeficiency, endocrinopathies, central nervous system development, autism, intellectual deficiency, and psychosis. She has been an assiduous advocate for coordinated multidisciplinary care for this patient population, overseeing the largest 22q11.2DS pediatric clinic in the United States and as the corresponding author for the 2011 Journal of Pediatrics paper, "Practical Guidelines for Managing Patients with 22q11.2 Deletion Syndrome."

She has served in key organizational positions within the 22q11.2DS professional community since 1998, including Program Chair for the 2nd Biennial International Conference in 2000; Secretary General for the 8th Biennial International Conference in 2012; Director of the Scientific Program Committee for the 9th Biennial International Meeting in 2014; and most recently as a Founding Board Member and Secretary for the 22q11.2 Professional Society. In addition, she provides essential ties to the lay community, serving as a Founding Board Member for The International 22q11.2 Foundation, Inc. since 2003; acting as an advisor to the UK group Max Appeal and the Canadian Group Chromosome 22 Central; and by initiating 22q at the Zoo – Worldwide Awareness Day. She was instrumental in assembling The International 22q11.2DS Modifier Gene Consortium in 2006 and in establishing The International 22q11.2DS Brain Behavior Consortium in 2012, a group of 22 phenotyping and 5 genotyping sites spanning 4 continents and working collaboratively on an NIMH funded project to identify risk factors for psychosis, where she acts as overall Co-Principle Investigator.

To date, she has been responsible for recruiting >1200 subjects with 22q11.2 related conditions to CHOP; authoring or co-authoring more than 190 peer reviewed publications, many related to 22q11.2DS; along with several book chapters and a handbook for families and professionals. In 2012, Professor McDonald-McGinn was privileged to receive the Angelo DiGeorge Memorial Medal of Honor for her contributions to the 22q11.2DS scientific community.

Educational Day Speaker Profiles

Dr Purnima Hernandez

Dr. Purnima Hernandez is board-certified in pediatric dentistry and behavior analysis. She has been serving the communities of New York and New Jersey for over 20 years.

She is currently pursuing a Masters in Applied Behavior Analysis. Hernandez received her education in Pediatric Dentistry at Columbia University College of Dental medicine. After serving as an assistant professor for many yea rs she decided to pursue a career in the clinical practice of pediatric dentistry. While she delivers care to all children, her special interests are treating children with special health care needs. Her area of focus is on the non-pharmacological management of children's behaviors in the dental office. Hernandez focuses on teaching her patients the skills that will allow them to sit appropriately in an office chair and receive routine treatment. Shaping such skills and foundations are essential in future transitions to adult dentistry. She is currently studying to become a Behavior Analyst to pursue her research interests in the behavior modification of children with disabilities.

Hernandez is also a parent of a child with multiple disabilities including Autism Spectrum Disorder. She is an advocate not just for her child but other children in the community. She has spoken to audiences on various topics related to disability such as health, advocacy, therapy, and special needs dentistry, and has authored and co-authored articles related to disability issues. She serves as Council Member on the Council of Developmental Disabilities in New Jersey and a board member Disability Rights New Jersey. Hernandez was awarded the Solomon Rosenstein Visiting Professorship and Fellowship by the Columbia University College of Dental Medicine for her contribution to the field of special needs dentistry. She was also awarded the Francis Black Humanitarian award in health care by Friends Health Connection, N.J.

Dr Nancy Dougherty

Dr. Nancy Dougherty is a graduate of the University of Pennsylvania School of Dental Medicine, with a Master's Degree in Public Health from the University of Massachusetts, Amherst.

For 12 years, Dr. Dougherty served as the director of the Special Care Dental Program at the Rose F. Kennedy Center (Albert Einstein College of Dentistry). She was the founding director of the Pediatric Dental Residency Program at Jacobi Medical Center in the Bronx, NY. Currently Dr. Dougherty holds a faculty appointment as Clinical Associate Professor at NYU College of Dentistry and is an Attending Dentist in pediatric dentistry at Bellevue Hospital Center in New York.

Professional accreditations include Board Certification in the American Board of Pediatric Dentistry, Fellow in the Academy of Dentistry for People with Disabilities and Diplomate in the American Board of Special Care Dentistry. Dr. Dougherty is also a member of the Task Force on Special Dentistry for the NY State Office of People with Developmental Disabilities (OPWDD).

Dr. Dougherty has done numerous presentations at the local, state and national levels in the areas of special needs dentistry and health literacy. She has been the author of articles published in a number of professional journals, primarily focused on special needs dentistry.

Dr Lisa Shulman

A graduate of Brown University and University of Pennsylvania School of Medicine, Lisa Shulman M.D. completed Pediatric residency training at the Mount Sinai Medical Center of New York and fellowship training in Child Development at the Rose F. Kennedy Center Children's Evaluatio n and Rehabilitation Center (CERC) at Albert Einstein College of Medicine. She is board certified in Pediatrics, Neurodevelopmental Disabilities, and Developmental and Behavioral Pediatrics.

Since 1992, Dr. Shulman has been a member of the Pediatric Attending staff of CERC and an Associate Professor of Pediatrics at the Albert Einstein College of Medicine. From 1996 to the present, Dr. Shulman has been the Director of the Infant/Toddler Team at CERC, a program with a 17 year history as a certified Early Intervention Program performing approximately 300 evaluations per year. Since 2004, Dr. Shulman has been the director of the RELATE program at Einstein, a state of the art evaluation and treatment program for toddlers through teens with autism spectrum disorders. The program follows approximately 1600 children with autism spectrum disorders.

Dr. Shulman's clinical and research interests include: early identification of autism and Asperger's syndrome, language and social regression, overcoming healthcare disparities, use of complementary and alternative medicine in autism, and developmental implications of idiopathic toe-walking.

Assistant Prof Emily A Jones

Emily A. Jones, PhD, BCBA-D is Assistant Professor in the Department of Psychology, Queens College, City University of New York. She teaches courses in applied behavior analysis and developmental disabilities. Dr. Jones›s research involves the development and demonstration of interventions to address impairments in young children with developmental disabilities. She is examining interventions to address joint attention in children with autism and communication, cognitive, and motor skills, as well as aspects of the intensity of intervention in children with Down syndrome. Dr. Jones is also evaluating the effects of support groups and sibling training for siblings of children with autism. This work has been supported by funds from the Professional Staff Congress, City University of New York, Organization for Autism Research, Doug Flutie Jr. Foundation, and Autism Speaks and published in peer reviewed journals such as the Journal of Applied Behavior Analysis, Behavior Modification, Research in Autism Spectrum Disorders, and Research in Developmental Disabilities.

Geri Brewster

Geri Brewster RDN MPH CDN has been a functional nutritional practitioner for over 3 decades, always using diet and nutrient support to create best outcomes in a personalized and supportive fashion.

Among many other honors, she was awarded the 2013 Excellence in Practice Award by Dietitians in Integrative and Functional Medicine (DIFM)

She received her BS in Human Nutrition and Foods from Virginia Tech where she graduated summa cum laude and her MPH at New York Medical College where she received the Sirach award for outstanding achievement in the area of public health. She holds multiple certificates in advanced areas of study.

Her practice is maintained in NYC and Mt Kisco, New York. She is the former Director of Nutrition at the Atkins Center for Complementary Medicine in NYC and currently assists families in the implementation of the Modified Atkins Diet for seizure control.

A highly respected practitioner, researcher and community leader, she has served as an advocate with the Better School Food movement, and is currently a volunteer with her local NAA group and Autism One. Geri speaks frequently on a local and national level on the subjects of healing diets, gut-brain connections, children's health and family nutritional needs. Geri is also an adjunct professor for the University of Bridgeport's Masters in Nutrition program.

She is a contributor to a number of publications and has been quoted in numerous newspaper and magazine articles as well as featured on numerous radio and TV appearances discussing health topics.

Research Symposium Programme.

The 17th SSBP International Meeting:
Developmental Trajectories
of Behavioural Phenotypes

Venue: NYU College of Dentistry, 345 East 24th Street, NY 10010

Day One: Friday, 10th October 2014	
13:00–16:00	**Registration:** At NYU College Of Dentistry (Cod) Septodont Auditorium **Put up Posters in Poster area**
16:00–17:30	**Opening Session:** Developmental Trajectories In Asd (Chair: *Patricia Howlin*)
16:00–16:20	**Opening Remarks:** *Dr Charles Bertolami*, Dean, College of Dentistry *Dr Louis Terracio*, Associate Dean for Research, College of Dentistry
16:20–17.20	**Talk 1: Keynote:** *Catherine Lord* – Developmental Trajectories in ASD
18:00–19:30	**Welcome Reception:** Metropolitan Museum of Art, Patrons Lounge

Day Two: Saturday, 11th October 2014

08:00	**Registration & Coffee**
Session I: Developmental Trajectories in Williams Syndrome (Chair: *Gene Fisch*)	
08:45–09:25	**Introduction**
08:30–08:45	**Talk 2: Keynote:** *Carolyn Mervis* - Developmental Trajectories in Williams Syndrome
09:25–10:00	**Talk 3: Keynote:** *Barbara Pober* – Overview of Williams Syndrome
10:00–10:20	**Talk 4:** *Bishop S.L.* – Early Motor Milestone Markers of Developmental Trajectories : Age of Walking in ASD vs. non-ASD
10:20–10:40	**Morning Refreshments**
Session II : (Chair: Ann Swillen)	
10:40–11:00	**Talk 5:** *Harris J.C.* – Developmental Trajectories in the Extended Lesch Nyhan Disease Phenotype
11:00–11:20	**Talk 6:** *Nærland T.N.* – Age Related Differences in Hyperactivity/Inattention and Peer Problems/ASD among individuals with Down Syndrome
11:20–11:40	**Talk 7:** *Hagerman R.* – Improving the Trajectory of Development in Young Children with Fragile X Syndrome
11:40–12:00	**Talk 8:** *Penhallow J.* – Lifespan Changes in Autism Spectrum Disorder Characteristics in Seven Genetic Syndromes: an 8 Year Follow Up
12:00–12:10	**A short Presentation on:** SSBP 18th International Research Symposium, 3–5 September 2015 In London, UK
12:10–12:40	**SSBP Annual General Meeting**
12:40–13:30	**Box Lunch:** provided by College of Dentistry **Poster viewing**
Session III: Developmental Trajectories in Wolf-Hirschhorn Syndrome and Others (Chair: *Stewart Einfeld*)	
13:30–14:10	**Talk 9: Keynote:** *John Carey* – Principles of Phenotype Analysis in the Assessment of Children with Neurodevelopmental Syndromes
14:10–14:45	**Talk 10: Keynote:** *Agatino Battaglia* – Wolf-Hirschhorn (4P-) Syndrome: Clinical Features and Natural History
14:45–15:05	**Talk 11:** *Loitfelder M.* – Functional Connectivity Changes and Social Behaviour in Neurofibromatosis Type 1
15:05–15:25	**Talk 12:** *Von Gontard A.* – Incontinence in Children with Special Needs
15:25–15:45	**Afternoon Refreshments**
Session IV: (Chair: *Petrus de Vries*)	
15:45–16:05	**Talk 13:** *Howe C.J.* – Intellectual Ability in Tuberous Sclerosis Complex Correlates with Predicted Effects of Mutations on TSC1 and TSC2 Proteins
16:05–16:25	**Talk 14:** *Strydom A.* – Copy Number Variations in Adults with Intellectual Disability and Neuropsychiatric Disorders
16:25–16:45	**Talk 15:** *Samango-Sprouse C.* – Impact of Early Hormonal Treatment (EHT) on the Neurobehavioural Profile of Boys with 47,XXY (Klinefelter Syndrome) at 9 Years of Age
16:45–18:30	**Poster Viewing**
20:00–22:30	**Conference Dinner At The NYU Torch Club**

Day Three: Sunday, 12th October 2014

Session V: Trajectories of Development in Deletion 22Q (Chair: *Chris Oliver*)	
08:30–08:45	**Introduction**
08:45–09:25	**Talk 16. Keynote:** *Ann Swillen* – Developmental Trajectories in 22q11 Deletion Syndrome (22q11.2 DS)
09:25–10:00	**Talk 17: Keynote:** *Donna McDonald-McGinn* – 22q11.2 – Deletions, Duplications, and Atypicals
10:00–10:20	**Talk 18:** *Hidding E.* – Executive Functioning in Relation to Autism and ADHD Symptomatology in 22Q11.2 Deletion Syndrome
10:20–10:40	**Talk 19:** *Evers L.J.M.* – Amino Acids and Cognitive Deterioration in 22Q11 Deletion Syndrome
10:40–11:00	**Morning Refreshments**
Session VI : (Chair: Leopold Curfs)	
11:00–11:20	**Talk 20:** *Brandenburg-Goddard M.N.* – A comparison of Neural Correlates underlying Social Cognition in Klinefelter Syndrome and Autism
11:20–11:40	**Talk 21:** *Roberts J.E.* – Cross-syndrome Infant Developmental Trajectories: Fragile X Syndrome and Autism Siblings
11:40–12:00	**Talk 22:** *Vicari S.* – Adolescents at Ultra-High Risk (UHR) for Psychosis with and without 22Q11 Deletion Syndrome: A Comparison of Prodromal Psychotic Symptoms and General Functioning
12:00–12:10	**Launch of the FIND website :** providing information on genetic disorders and behavioural phenotypes : Chris Oliver, Professor of Neurodevelopmental Disorders, Cerebra Centre for Neurodevelopmental Disorders, University of Birmingham, UK
12:10–12:40	**Lightning Round of 5-Minute Presentations** **(6 presentations)**
	Talk 23: *Howlin P.* – Investigating the Efficacy of the Social Communication Questionnaire for Identifying Autism Spectrum Disorder in Children with Down Syndrome
	Talk 24: *Gray K.M.* – Depression in Adults with Intellectual Disability: Rates and Predictors of Outcome
	Talk 25: *De Maesschalck D.* – Is there a Need for a Neurocognitive Assessment at Key Developmental Time Points in Boys with Klinefelter Syndrome?
	Talk 26: *Raznahan A.*- Neuroanatomically Phenotyping Sex Chromosome Aneuploidies as Models of Genetic Risk for Autistic Behaviors
	Talk 27: *Roozen S.* – Improving Health Promotion Related to Fetal Alcohol Spectrum Disorder (FASD): A Systematic Literature Review
	Talk 28: *Tassone F.T.* – The Multiple Molecular Facets of Fragile X Syndrome and FMR1 Associated Disorders
12:40–13:05	**Talk 29: The Pat Howlin Prize Lecture:** *Crawford H.* – The Effect of Adult Familiarity and Nature of Interaction on Social Anxiety and Motivation in Fragile X, Rubinstein-Taybi and Cornelia de Lange Syndromes
13:05–13:35	**Talk 30: The Tom Oppé Lecture:** *Einfeld S.* – Intervention Strategies for Behaviour Phenotypes
13:35–14:30	**Box Lunch:** provided by CoD
	Posters to be taken down

Abstracts for Oral Presentations:

(in order of presentation)

TALK 1: Developmental Trajectories in ASD

Lord C.
New York Presbyterian Center for Autism and Developing Brain, White Plains, New York 10605, USA

One of the most striking features of autism spectrum disorders are the varying trajectories of development, both across individuals and within individuals across various domains of learning and behaviour. Cross-sectional studies can begin to suggest to us the nature of these patterns of development, but are limited both by recruitment biases at different ages and individual differences in when various changes occur. In this talk, results from longitudinal studies of children referred for possible autism at age 2 years and a comparison group of children with other developmental delays will be presented. In response to a call for the definition of dimensions of behaviour that provide clues to domains of brain function that go beyond diagnosis, a focus will be on the description of dimensions arising from studies of continuities and discontinuities in development.

Keywords: autism, longitudinal, trajectories

TALK 2: Developmental Trajectories in Williams Syndrome

Mervis C.
Department of Psychological and Brain Sciences, University of Louisville, Louisville, KY USA

Williams syndrome (WS) is a neurogenetic disorder caused by deletion of 26 genes on chromosome 7q11.23 and associated with developmental delay and intellectual disability. In this presentation, I focus on three aspects of the WS cognitive/linguistic phenotype and associated developmental trajectories. The first aspect involves the broad relations among verbal abilities, nonverbal reasoning abilities, and visuospatial construction abilities: For children with WS, verbal abilities and nonverbal reasoning abilities are usually at about the same level as each other relative to typically developing same-aged peers, whereas visuospatial construction abilities are considerably weaker. This profile is apparent in young toddlers and continues to characterize individuals with WS throughout childhood and adolescence, as evidenced by patterns of relative strength and weakness in intellectual abilities, academic achievement, and adaptive behavior. The second component involves relations between language and nonverbal communication abilities: For children with WS, language is more advanced than nonverbal communication. This pattern is evident in young toddlers, for whom gestural development lags behind vocabulary development; and throughout childhood and adolescence, with non-pragmatic aspects of language more advanced than sociocommunicative aspects, resulting in overlap with the autism spectrum. The third aspect involves vocabulary acquisition and its relations to other aspects of development. The longitudinal course of receptive concrete vocabulary development from age 4 – 17 years as measured by the Peabody Picture Vocabulary Test-4 will be discussed, along with relations between concrete vocabulary ability and relational vocabulary ability and between relational vocabulary ability and visuospatial construction ability. Finally, variability among young children with WS in early expressive vocabulary growth and the relations between age at attainment of early language milestones such as a 50-word expressive vocabulary and intellectual abilities at age 4 years will be considered, along with implications for early intervention.

Keywords: Williams syndrome, cognitive profile, language development, cognitive development, longitudinal trajectory

TALK 3: Overview of Williams Syndrome

Pober, B.R. [1,2,3]

[1] *Department of Medical Sciences, Netter School of Medicine, Quinnipiac University, North Haven, CT., USA.*

[2] *Department of Pediatrics, Massachusetts General Hospital, Boston, MA., USA.*

[3] *Professor of Pediatrics (Emeritus), Harvard Medical School, Boston, MA., USA.*

Williams syndrome (also referred to as Williams-Beuren syndrome) is a multi-system disorder featuring a characteristic constellation of medical problems in conjunction with a typical cognitive and behavioral profile. The genetic basis of Williams syndrome, discovered in 1993, is a 26–28 gene microdeletion mapping to chromosome 7. The size of the deletion is highly uniform and shows little variation between individuals with Williams syndrome. The presence of a well-defined genetic deletion, in association with a distinctive phenotype, has made Williams syndrome an attractive disorder for efforts to draw genotype-phenotype correlations. In this presentation, I will provide an overview of common medical features, as well as behavioral features such as anxiety, that prominently impact the life and health of those with Williams syndrome. Medical features that will be discussed include cardiovascular disease, multiple endocrine problems (such as hypercalcemia, diabetes, early puberty, and abnormal thyroid function tests), and various gastrointestinal perturbations. Their natural history and genetic connections will be discussed when known.

Keywords: microdeletion, intellectual disability, anxiety, diabetes, vascular stenosis

TALK 4: Early Motor Milestone Markers of Developmental Trajectories: Age of Walking in ASD vs. Non-ASD

***Bishop S.L.*[1], *Farmer C.*[2] *and Thurm A.*[2]**

[1] *Weill Cornell Medical College, White Plains, New York, USA.*

[2] *National Institutes of Health, Bethesda, Maryland, USA.*

Background: Age of walking is recognized as an important marker for identifying developmental disabilities during the first two years of life. Intellectual disability (ID), especially when in the context of neurogenetic disorders, is commonly associated with delayed onset of independent walking. Interestingly, in children with autism spectrum disorders (ASD) and comorbid ID, delayed walking is not generally characteristic. The purpose of this study is to directly examine the relationship between age of walking and later cognitive abilities in children with ASD compared to those with non-ASD developmental disabilities (non-ASD).

Method: Using multiple datasets totalling over 5000 children between the ages of 2 and 18 years with best-estimate clinical diagnoses of ASD or non-ASD, we will examine the relationships between age of walking and nonverbal IQ (NVIQ). We will also explore parental reports of regression and the relationship to age of walking.

Results: Preliminary analyses (ASD: n=1695; non-ASD n=491) indicated significant group differences. Controlling for age at NVIQ assessment, age of walking was negatively associated with later NVIQ in both groups, but this relationship was significantly stronger in the non-ASD group than for children with ASD (p=.002). In children with NVIQ scores less than 70, children with ASD walked 7 months earlier on average (15 months vs. 22 months; p<.001). Furthermore, whereas more than three-quarters of children with non-ASD with IQs less than 70 walked late (i.e., after 16 months), only one-third of children with ASD and ID were reported to be late walkers.

Conclusion: Findings confirm that age of walking, as a proxy for general early gross motor development, is generally conserved in children with ASD with and without ID. However, non-ASD ID groups, walking frequently occurs late. In addition, such gross motor delay relates to nonverbal cognitive development differently in ASD, further differentiating the non-ASD behavioural phenotype of ID.

Keywords: gross motor milestones, walking, intellectual disability, autism spectrum disorder, developmental disability

TALK 5: Developmental Trajectories in the Extended Lesch Nyhan Disease Phenotype

Harris J.C.

The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

Background: Lesch-Nyhan disease (LND) is a metabolic disorder characterized by hyperuricemia, intellectual disability, dsytonic movement disorder, dysarthric speech, and compulsive self-injury. It is caused by deficiency of the enzyme, hypoxanthine phosphoribosyltransferase (HPRT). Nyhan introduced the term behavioural phenotype to describe the characteristic features of self injury (SIB) in LND thus SIB is the paradigmatic behavioural phenotype in LND.

Method: HPRT levels were measured in 21 patients with Lesch Nyhan Disease (level <1%) and 17 variants (LNV) (levels 2% to 20%). Comparisons were made with a control group (HC) of 33 matched subjects. Measures include standardized behavioural rating scales (CBCL, ABS-RC), Fahn-Marsden dystonia scale, NEO personality inventory, Neurocognitive tests and Neuroimaging procedures (MRI voxel-based morphometry PMRS,PET).

Results: LND subjects showed severe self-injury together with problematic aggression, anxious-depressed symptoms, distractibility, motor stereotypes, and disturbing interpersonal behaviours. Patients with LNV were rated as being intermediate between the HC and LND groups on all behaviour scales. Attentional measures were similar in both groups (LND and LNV).The severity of dystonia was correlated with HPRT level. On the NEO. Neuroticism and Extraversion scores were significant for both LND and LNV but higher for LND. Neuroimaging findings on all measures (MRIvoxel-based morphometry, PMRS, and PET) were significantly different from controls and intermediate for LNV.

Conclusion: Examination of the spectrum of HPRT deficiency reveals that the phenotype is far broader than SIB. Self Injurious behaviour only occurs in those with near absence of HPRT. There is consistency of the neurocognitive phenotype across the full HPRT deficiency spectrum making this the most consistent phenotypic feature. The behavioural profile and personality profiles are intermediate for LNV as are imaging findings. This study demonstrates the importance of moving beyond behavioural descriptions of the phenotype and of studying the full spectrum of disease presentations.

Keywords: Lesch-Nyhan, self injury, Neurocognitive

TALK 6: Age Related Differences in Hyperactivity/Inattention and Peer Problems/ASD among Individuals with Down Syndrome

***Nærland T.N.*[1], *Storvik S.S.*[1], *Warner G.W.*[2] *and Howlin P.H.*[2]**

[1] *National Competence Unit for Autism, University Hospital of Oslo, Norway.*

[2] *King's College, London, UK.*

Background: The present study is a collaboration between the National Autism Unit, Oslo and King's College, London. An increasing number of studies report high prevalence of co-morbid conditions in individuals with Down syndrome (DS). Our survey based, cross-sectional study explored differences in rates of these problems with age.

Methods: The Strength and Difficulties Questionnaire (SDQ) and Social Communication Questionnaire (SCQ) were distributed to members of the UK Down syndrome Association and Norwegian parents of DS children; 668 surveys were completed and returned. Response rates were 36% (UK), 41% (Norway). Five age groups were studied: 4–6 yrs (n=58), 7–9 yrs (n=220), 10–12 yrs (n=178), 13–15 yrs (n=188), 16–18 yrs (n=24). Male-female ratio was similar in all groups (approx. 50–60% boys)

Results: SDQ rates of hyperactivity/inattention problems, varied widely among the age groups. Almost half (45%) of 7–9 year-olds scored above cut-off. This proportion gradually declined with age; no-one in the oldest group scored above cut-off. Peer problems (measured by SDQ) and Autism Spectrum Disorder (ASD) symptoms showed the opposite relation with age. In the 7–9 yr. group, 35% scored above cut-off for peer problems and ASD. Among 16–18 year-olds the rates were 62% and 50% respectively.

Conclusion: Although hyperactivity and inattention tend to decline with age among children with DS, peer problems and ASD symptoms are more common in older children. These cross-sectional data support earlier findings (cf SSBP 2012) that highlighted increased passivity levels and loss of functions among adolescents with DS. Clinicians need to be aware that a low score on hyperactivity/inattention may reflect a depression-related passivity. This developmental tendency toward passivity may be relevant when considering both pharmaceutical and pedagogical interventions.

Keywords: Down Syndrome, Attention, Hyperactivity, Passivity, Peer problem, Autism spectrum disorder

TALK 7: Improving the Trajectory of Development in Young Children with Fragile X Syndrome

***Hagerman R.**, Greiss-Hess L., Chitwood K., Hanson A., Polussa J., Bishop L., Siyahian S., Chechi T., Li C.-S. and Mundy P.*

MIND Institute UC Davis Medical Center, Sacramento, California, USA.

Background: Language delays, sensory over-reactivity, impulsivity, anxiety and social deficits are typical problems that emerge in children with fragile X syndrome (FXS) in the second year of life. Studies of young children with autism have demonstrated deficits in the metabolism of tryptophan and diminished production of serotonin, especially in the frontal regions of the brain in the first 5 years of life. Sertraline treatment can increase serotonin at the synapse, stimulate Brain Derived Neurotropic Factor (BDNF) and neurogenesis in the hippocampus, and enhance dopamine levels in the striatum and nucleus accumbens. Our recent retrospective study of sertraline treatment in young children with FXS demonstrated an enhanced trajectory of both receptive and expressive language scores in children with FXS.

Method: Children with FXS (2 to 6 y.o.) were randomized to low dose sertraline or placebo for a 6 month treatment period. Baseline and follow-up testing included the Mullen Scales of Early Learning (MSEL), the Preschool Language Scale (PLS), the Visual Analogue Scale (VAS), the Sensory Processing Measure (SPM), and the Clinical Global Impression Scale-Improvement (CGI-I).

Results: This analysis of the first 30 participants demonstrated significant improvement on the CGI-I (X_2 (3, N=30) = 11.52, p =.009), the VAS overall (F(1,88) = 4.36, p=.040, eta2 =.047) and for subcategories of symptoms falling into Hyperactivity, Impulsivity and Attention (F(1,16) = 6.33, p=.023, eta2 =.284), and on Social Participation of the SPM (F (1,24) = 6.65, p =.016, eta2 =.22). Marginally significant trends for global cognitive improvement were noted for the sertraline group compared to placebo as measured by the MSEL Early Learning Composite (ELC), F(1,28)=3.79, p=.062, eta2 =.119.

Conclusion: Preliminary results suggest that early treatment with low dose sertraline may improve behaviour and cognition in young children with FXS without significant side effects.

Keywords: treatment, fragile X syndrome, sertraline, young children

TALK 8: Lifespan Changes In Autism Spectrum Disorder Characteristics In Seven Genetic Syndromes: An 8 Year Follow Up

***Penhallow J.**[1], Moss J.[1], Wilde L.[1], Eden K.[1], Waite J.[1], Bull L.[1], Crawford H.[1], Heald M.[1], Nelson L.[1] and Oliver C.[1]*

[1] *Cerebra Centre for Neurodevelopmental Disorders, University of Birmingham, Birmingham, UK.*

Background: Currently there is a scarcity of lifespan research relating to rare genetic syndromes. Whilst differential behavioural profiles have been identified for autism spectrum disorder (ASD) characteristics within some of these groups, these profiles have yet to be examined in a comparative longitudinal study. This study aims to describe the changing behavioural phenotype of seven rare genetic syndromes with regard to repetitive behaviour and characteristics of ASD over an eight year period.

Method: Parents of individuals with Angleman (AS; N=47), Prader-Willi (PWS; N=61), Cornelia de Lange (CdLS; N=51), Cri du Chat (CdC; N=30), Lowe (LS; N=26), Smith Magenis (SMS; N=20), and Fragile X syndromes (FXS; N=101), completed the Social Communication Questionnaire (SCQ) and the Repetitive Behaviour Questionnaire (RBQ) on two occasions separated by eight years. We compared children and adults within each syndrome group and reviewed the developmental trajectories of the seven syndromes using reliable change index scores.

Results: Our results indicate patterns of change that are specific to each syndrome group. The FXS group were more likely to show increased impaired on the social communication subscale of the SCQ ($p<.05$). The LS group showed decreases in repetitive behaviour overall ($p<.05$) but increases in repetitive use of language ($p<.05$). The PWS group showed increases in ASD characteristics ($p<.01$) but not repetitive behaviour ($p<.05$). The CdC group showed increased repetitive behaviour ($p<.01$) and ASD characteristics ($p<.05$). The AS group showed decreased ASD characteristics ($p<.05$) and the SMS group showed an increase in compulsive behaviour ($p<.05$) but a decrease in impairment on the sociability subscale of the SCQ ($p<.05$). Although age related differences were found at a syndrome group level, they did not contribute to these differences.

Conclusion: Behavioural phenotypes are not stable and a developmental perspective should be taken when considering diagnosis and prognosis.

Keywords: behavioural phenotype, lifespan changes, genetic syndromes, autism spectrum disorder characteristics, repetitive behaviour

TALK 9: Principles of Phenotype Analysis in the Assessment of Children with Neurodevelopmental Syndromes

Carey, J.C.

Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah.

The designation, phenotype, was proposed as a term by Wilhelm Johannsen in the early 1900s. The word is derived from the Greek, phano (showing) and typo (type), phanotypos. Phenotype has become a widely recognized term in recent years with the identification of human disease genes. It has been used as the "observable constitution of an organism," but sometimes referred to when a person has a particular clinical presentation. There is sparse literature elucidating the principles of phenotype analysis. The purpose of this presentation is to summarize the principles that are used in medical genetics and to facilitate precise and comprehensive phenotype analysis in the investigation of persons with neurodevelopmental syndromes. The proposed principles of phenotype (and its analysis) include: 1. The diagnostic criteria or definition of the phenotype; 2. The spectrum of manifestations and complications; and 3. The natural history and evolution of the features of the condition over time. The challenge for clinical researches is to measure the components of these parameters. Restating and rearticulation of the basic principles of human genetics is helpful here. The application of such principles to neurofibromatosis type 1, as an example, illustrates the concepts and how they can potentially be measured. The standardized examination of the human face also illustrates methods that can be applied to comprehensive phenotype analysis. In recent years, discussions have been occurring about "deep phenotyping" and the "Human Phenome Project." Phenomics is now a more commonly used term and refers to the measurement of phenomes through time. Recent discourse has introduced the idea of a potential Human Phenome Project. In just the last 3 years, we have observed the rapid development of patient registries, a growth in "patient-reported" outcomes, and the creation of numerous resources including PhenoKeeper, the PhenX Tool Kit, and the Human Phenotype Ontology Project. There has never been a more exciting time in the history of medicine surrounding the potential comprehensive assessment of phenotype in all disciplines.

Keywords: phenotype, genotype, syndrome delineation, neurofibromatosis type 1, morphology

TALK 10: Wolf-Hirschhorn (4P-) Syndrome: Clinical Features and Natural History

Battaglia A.

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Wolf-Hirschhorn syndrome (WHS) is a well-known multiple congenital anomalies/intellectual disability syndrome, firstly described in 1961 by Cooper and Hirschhorn. Its frequency is estimated as 1/50,000 to 1/20,000 births, with a female predilection of 2:1. The disorder is caused by partial loss of material from the distal portion of the short arm of chromosome 4 (4p16.3), and is considered a contiguous gene syndrome. No single gene deletions or intragenic mutations have been shown to confer the full WHS phenotype. Only in 1999, were the first data on the natural history brought to the attention of the medical community. WHS is characterized by distinctive craniofacial signs, prenatal and postnatal growth retardation, cognitive impairment, severe psychomotor developmental delay, seizures, and hypotonia. There are skeletal abnormalities such as kyphosis or scoliosis with malformation of the vertebral bodies, fused ribs, club feet and cleft hands. Developmental delay is usually severe: many patients do not learn to control the sphincter, to eat and dress themselves, and less than 50% walk, with or without support, between 2 and 12 years of age. Cognitive impairment is moderate to severe. The language is limited to guttural or bisyllabic sounds and, in some cases, to simple sentences. Seizures are observed in more than 95% of patients, with onset between the neonatal period and 36 months, often triggered by fever. Status epilepticus can occur in half of the patients. Over 30% of children develop atypical absences at the age of 1–6 years. Seizures stop in childhood in about 50%. CNS defects (thinning of the corpus callosum) are often present. Heart defects can be observed in 50%. Hearing, eyes, teeth, and genitourinary anomalies are often detected. There may be recurrent infections of the respiratory tract and otitis media with antibody deficiency. The electroencephalogram shows characteristic features in 90% of patients. WHS individuals reach the adulthood.

Keywords: Wolf-Hirschhorn syndrome, del(4p) syndrome, monosomy 4p, clinical features, natural history

TALK 11: Functional Connectivity Changes and Social Behaviour in Neurofibromatosis Type 1

Loitfelder M.[1,2,3]*, Veer I.M.*[1,4]*, Rombouts S.A.*[1,2]*, Swaab H.S.*[1,2]*, Van Buchem M.A.*[1]*, Schmidt R.*[3] *and Huijbregts S.C.J.*[1,2]

[1] *Leiden Institute for Brain and Cognition (LIBC), Leiden University, Leiden, The Netherlands.*

[2] *Leiden University, Department of Clinical Child and Adolescent Studies, Leiden, The Netherlands.*

[3] *Medical University of Graz, Department of Neurology, Graz, Austria.*

[4] *Charite Universitaetsmedizin Berlin, Department of Neurosurgery and Psychiatry, Division of Mind and Brain Research, Berlin, Germany.*

Background: Children with Neurofibromatosis type 1 (NF1) show impairments in social functioning. However, its functional pattern remained uninvestigated, although it appears likely that suboptimal functioning of brain regions dedicated to social-cognitive functioning exist. We here sought to examine functional connectivity (FC) alterations in areas associated with social-cognitive function in NF1 children.

Method: 14 NF1 patients and 30 healthy controls underwent structural (T1-weighted) and functional (resting state FC) MRI at 3T. Functional imaging data were analyzed with tools from FMRIB Software Library by using a seed based approach. The bilateral amygdala, orbito-frontal cortex, and anterior (ACC) and posterior cingulate cortex (PCC) served as regions of interest. Questionnaires on social skills (Social Skills Rating System), social cognition (subscore of the Social Responsiveness Scale), and social problems (subscore of the Child Behaviour Check List) were conducted in all patients and in a sub-sample of controls (n=9).

Results: NF1 patients show increased FC of the left ACC and the left amygdala with several right hemispheric brain regions. In contrast, controls show increased FC between the left amygdala and the PCC/precuneus and between the left orbito-frontal cortex and frontal and subcortical areas. Moreover, patients showed impairments in social behaviour in all questionnaire scores when compared to controls.

Conclusion: NF1 children show shifts in FC in areas associated with social cognition, and in parallel, deficits in aspects of social behaviour.

Keywords: Neurofibromatosis Type 1,seed based functional connectivity, social functioning, social behaviour

TALK 12: Incontinence in Children with Special Needs

(Originally divided into three abstracts, these were combined at the request of the Scientific Committee. This combined abstract was not published in the JIDR SSBP Special Issue)

Von Gontard A.[1], Niemczyk J.[1], Equit M.[1] Borggrefe-Moussavian S.[1], Pirrung M.[1], L.M.G. Curfs [2]

1 Department of Child and Adolescent Psychiatry, Saarland University Hospital, Homburg, Germany

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Children with special needs require additional medical, psychiatric, psychological and educational assistance. Overall, children with special needs have higher rates of all types of incontinence than typically developing children, i.e. fecal incontinence (FI), daytime urinary incontinence (DUI) and nocturnal enuresis (NE). Intellectual disability (ID) is a major risk factor for incontinence – with increasing rates with decreasing IQ. Incontinence often persists into adolescence and adulthood. Many children, adolescents and adults do not receive appropriate assessment and treatment. The aim of this talk is to present new studies on incontinence in three different subgroups of children with special needs: those with Williams Syndrome (WS), Noonan syndrome (NS) and Autism Spectrum Disorders (ASD). General principles of assessment and treatment shall also be outlined.

Williams Syndrome: WS is characterized by typical facial features, cardiovascular disease, behavioral symptoms and mild ID. 146 children (4–17 years) and 96 adults (18–59 years) with WS were recruited through a German parent support group (51.2% male, mean age 18.6 years). The Parental Questionnaire: Enuresis/Urinary Incontinence (PQEUI), the International-Consultation-on-Incontinence-Questionnaire–Pediatric LUTS (ICIQ-CLUTS), as well as the Developmental Behavior Checklist for parents (DBC-P) or for adults (DBC-A) were filled out by parents or care-givers. 16.1% of the sample had NE, 5.7% DUI and 7.3% FI. NE was present in 44.9% of children (4–12 years), 13.5% of teens (13–17y), 3.3% of young adults (18–30y) and in 3.6% of adults (>30y). DUI was reduced from 17.9% in children, over 2.7% in teens to 0% in (young) adults. FI was present in 21.4% of children, 2.7% of teens, 1.6% of young adults and 0% of adults. 6.2% of children had an ICIQ-CLUTS score in the clinical range. 12.1% of the children and 5.3% of the adults had a DBC score in the clinical range (> 90th percentile). 10.3% of children with NE, 25% with DUI and 7.1% with FI had behavioral problems. There were no significant differences in DBC total scores between continent and incontinent children except for the "self-absorbed" subscale. In summary, the first study shows that children with WS have high rates of incontinence, which decrease with age. Some adults are still affected by NE or even FI. Especially children with DUI are at risk for behavioral problems.

Noonan Syndrome: NS is characterized by short stature, typical facial features, congenital heart defects and behavioral symptoms such as anxiety, obsessive-compulsive behavior, attention deficit and impulsivity. Most children with NS have an average intelligence, one third mild ID. 19 children (5–17 years) and 10 adults (18–48 years) with NS were recruited through a German parent support group (58.6% male, mean age=15.26 years). The PQEUI, and the DBC-P or DBC-A questionnaires were filled out by parents or care-givers. 22.2% of the children had nocturnal enuresis (NE), 21.1% had daytime urinary incontinence (DUI) and 5.9% had fecal incontinence (FI).

No adult was affected by NE or DUI, only one had FI (10%). 23.5% of the children (only boys) had a DBC score in the clinical range (90th percentile), but no adult. 40% of children with any incontinence had a DBC score in the clinical range. Children with NE had significantly more behavioral problems than those without NE (75% vs. 7.7%). 50% of children with DUI had behavioral problems, but no child with FI. In summary, the second study showed that children with NS are more affected by incontinence than typically developing children. Incontinence is a relevant problem in children and adolescents with NS, but does not persist into adulthood. Psychological problems are especially present in Noonan boys with NE or DUI.

Autism Spectrum Disorders: ASD are defined by persistent impairments in reciprocal social communication and interaction, as well as restricted, repetitive patterns of behavior. These are present from early childhood and limit or impair everyday functioning. ASD can be associated with intellectual and language impairment, as well as other disorders. The general heritability is up to 90% and 15% of cases are associated with genetic syndromes. Some studies revealed an increased rate of incontinence in children with ASD. 40 children with confirmed ASD but without ID (85.0% boys; mean age 11.3 years) and 43 controls (60.5% boys; mean age 10.7 years) were assessed. The ICIQ-CLUTS and the Child Behavior Checklist (CBCL/4–18) questionnaires were administered. Child psychiatric ICD-10 diagnoses were based on a structured psychiatric interview (Kinder-Dips). IQ was measured with a one-dimensional intelligence test (CPM or SPM). Children with ASD showed significantly increased rates of NE (30.0% vs. 0%) and DUI (25.0% vs. 4.7%) compared to controls. Rates of FI were increased, too (12.5% vs. 0%), but did not reach statistical significance. Among children with ASD, daytime bladder control (≥ 5 years of age: 20.5% vs. 0%) and bowel control (≥ 4 years of age: 42.5% vs. 7.5%) were significantly delayed compared to controls. The mean LUTS score was significantly higher in children with autism. Rates of children with clinically relevant CBCL externalizing (32.5% vs. 0%) and internalizing symptoms (67.5% vs. 9.3%) and the total problem score (70.0% vs. 2.1%) were higher and IQ was lower (102.2 vs. 110.9) in children with ASD, as well. Children with ASD had significantly more ICD-10 child psychiatric disorders than controls (47.5% v. 4.7%). In summary, this third study showed that ASD are incapacitating, chronic disorders which cause significant impairment in social and everyday functioning. Other behavioral symptoms and disorders co-occur in most cases. In addition, children with ASD are at a high risk to be affected by different forms of incontinence and LUTS.

Conclusions: All three studies show clearly that incontinence is not restricted to persons with moderate or severe ID, but is a major problem in those with mild ID (such as WS), mixed mild ID to normal range IQ (such as NS) and even in those without ID (such as ASD). In addition, co-existing behavioral symptoms and disorders have an influence on the development and persistence of incontinence.
In summary, assessment and treatment of incontinence should be offered actively to children with special needs. Treatment approaches need to be adapted to cognitive level and co-existing behavioral problems and disorders. Combined, multimodal urologic, pediatric and child psychiatric and psychological skills are needed.

Key words: Williams Syndrome, Noonan Syndrome, Autism Spectrum Disorders, urinary incontinence, fecal incontinence

TALK 13: Intellectual Ability in Tuberous Sclerosis Complex Correlates with Predicted Effects of Mutations on TSC1 and TSC2 Proteins

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Background: Tuberous sclerosis complex (TSC) is a multisystem genetic disease, with a range of pathological features, including intellectual disability (ID), and is caused by mutation in either the *TSC1* or *TSC2* genes. We tested if different mutation types were associated with different degrees of severity of ID.

Method: 100 subjects who had an identified *TSC1* or *TSC2* mutation and had evaluation of IQ/DQ were included for genotype-intellectual phenotype correlations. Effects of mutations on *TSC1* or *TSC2* proteins were inferred from sequence data and published biochemical studies.

Results: For *TSC1* all mutations predicted to lead to prematurely truncated protein lay in the region of the gene where expression of the mutant protein would be reduced by nonsense-mediated decay (NMD) of the mRNA. Mutations predicted to lead to mutant *TSC1* protein that would be degraded were associated with higher IQ/DQ than others. There was a negative correlation between length of the predicted aberrant C-terminal tail arising from frameshift mutations in *TSC1* and IQ/DQ. For *TSC2*, by contrast, there was no deficit in the number of mutations predicted to avoid NMD, and there was a positive correlation between length of predicted aberrant tail and IQ/DQ.

Conclusion: Consequences of different mutations for IQ/DQ in TSC can be interpreted in terms of predicted effects on the *TSC1* and *TSC2* proteins. Mutation data may therefore be useful in predicting IQ/DQ outcomes in TSC.

Keywords: genotype-phenotype; tuberous sclerosis complex; mutation; tuberin; hamartin.

TALK 14: Copy Number Variations in Adults with Intellectual Disability and Neuropsychiatric Disorders

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Background: The development of microarray based technologies for comparative genomic hybridisation (array-CGH) analysis has enabled the detection of submicroscopic microdeletions or microduplications referred to as copy number variations (CNVs). Over the past 5 years it has been reported that an enrichment of CNVs are found in neurodevelopmental disorders such as intellectual disability, autism, and schizophrenia. Furthermore, there appears to be overlap between these disorders at the genetic level. We aimed to provide an estimate of the frequency of CNVs in adults with a dual diagnosis of intellectual disability (ID) and one or more additional psychiatric diagnosis.
Methods: We recruited 250 adults with ID from psychiatric clinics across the UK, and conducted detailed clinical assessments. Neuropsychiatric phenotypes were defined using standardised diagnoses and behavioural, cognitive and physical phenotypes were assessed in all participants. Spit samples were collected for aCGH analysis using a NimbleGen platform.
Results: Genomic data were combined with phenotypic data to uncover the genetic risk factors that may contribute to the neurodevelopmental phenotypes. A diagnostic yield of 30% for pathogenic or likely pathogenic CNVs was obtained. CNVs at loci 1p31.1, 1q21.1, 15q11.2, 16p11.2, Xp22.33, were found recurrently in patients with a dual diagnosis of intellectual disability and neuropsychiatric disorders. We will present an overview of cognitive functioning, the neuropsychiatric phenotypes and CNVs found in our study.
Conclusion: CNVs are found in one third of adults with a dual diagnosis of intellectual disability and neuropsychiatric disorders. There is clinical as well as genetic heterogeneity confirming previous studies and suggesting that different causative genes converge in common biological pathways. Adults with ID presenting with neuropsychiatric disorders may benefit from having aCGH done if they have not recently had a genetic work-up.

Keywords: Intellectual disability, psychosis, autism, dual diagnosis, genetics, aCGH

TALK 15: Impact of Early Hormonal Treatment (EHT) on the Neurobehavioral Profile of Boys with 47,XXY (Klinefelter Syndrome) at 9 Years of Age

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Background: 47, XXY is associated with frontal lobe dysfunction and language-based learning difficulties contributing to a complex behavioural phenotype that may include ADHD and atypical social skills. Recent studies have shown the positive effects of early hormonal treatment (EHT) on the neurodevelopmental outcome of boys with 47, XXY in early childhood, but the effects of EHT on behavioural and social development have not been explored at later ages.

Method: 59 prenatally diagnosed 47, XXY boys [22 who received EHT (3 injections of 25 mg testosterone enanthate) and 37 who received no treatment] were evaluated at 9 years of age using the Behaviour Rating Inventory of Executive Function (BRIEF), Social Responsiveness Scale (SRS-2) and Child Behaviour Checklist (CBCL). Significant differences between group scores were tested using appropriate biostatistics.

Results: The EHT treatment group had significantly improved Global Executive Functioning (p=0.038), Monitoring (p=0.027) and Initiation (p=0.0023) on the BRIEF, significantly fewer Aggressive behaviours (p=0.039) affective problems (p=0.002) and Total Problems (p=0.006) on the CBCL and improved social cognition (p=0.0045), social communication (p=0.0175) and fewer autistic mannerisms (p=0.0005) on the SRS-2.

Conclusion: These results provide further evidence of the sustained and positive effects of EHT on the neurodevelopmental outcome and phenotypic presentation of boys with 47, XXY. The significant improvements in social and behavioural skills and executive functioning after EHT presented in this study support the need for continued research and earlier biological treatment interventions for 47, XXY boys.

Keywords: XXY, androgens, sex chromosome disorders, chromosomal variations, Klinefelter syndrome, KS

TALK 16: Developmental Trajectories in 22q11 Deletion Syndrome (22q11.2 DS)

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Chromosome 22q11.2 deletion syndrome, also known as velocardiofacial or DiGeorge syndrome, is a neurogenetic condition affecting 1 in 2,000–4,000 live births and caused in most cases by a hemizygous 3-megabase microdeletion on the long arm of chromosome 22. Its phenotypic expression is highly variable and ranges from severe life-threatening conditions to only a few features. Frequently associated medical conditions include conotruncal cardiac anomalies, palatal anomalies (including velopharyngeal insufficiency), hypoparathyroidism/hypocalcemia, and subtle dysmorphic facial features. The neurocognitive profile is also highly variable, both between individuals and during the course of development. From infancy onward, motor delays (often with hypotonia) and speech or language deficits are commonly observed. During the preschool and primary school ages, learning difficulties are very common. The majority of patients with 22q11.2 deletion syndrome have an intellectual level that falls in the borderline range (IQ, 70–84), and about one-third have mild to moderate intellectual disability. More severe levels of intellectual disability are uncommon in children and adolescents, but are more frequent in adults. In this lecture, we will present and discuss: a) the developmental phenotypic transitions regarding cognitive development in 22q11.2 DS from early childhood to adulthood, b) the changing behavioural/psychiatric phenotype across age, and c) the first large scale longitudinal study on intelligence in 22q11 DS from the International 22q11.2 DS Brain Behavior Consortium.

Keywords: developmental trajectory, intelligence, behavior, psychiatric diagnosis, 22q11 DS

TALK 17: 22q11.2 – Deletions, Duplications and Atypicals

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Since the availability of FISH studies in 1992, the 22q11.2 deletion is now known to be the most common microdeletion syndrome with an estimated prevalence of 1/2000 live births. Etiologically it accounts for the majority of patients with DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome, and a subset of patients with autosomal dominant Opitz G/BBB syndrome and Cayler Cardiofacial syndrome. At present, >90% of deletions are *de novo*, mediated by blocks of low copy repeat sequences, but this figure will likely decrease in association with declining mortality rates and little effect on reproductive fitness. Phenotypically there is wide inter and intrafamilial variability despite the same ~3MB deletion in most. Several genes within this deleted region have been causally related to the more common findings such as T-box transcription factor 1 (*TBX1*) and congenital heart disease, however, with the advent of more sophisticated screening tools such as comparative genomic hybridization and whole genome array, patients with more subtle features of the deletion are now being identified in greater number, as are patients with varying phenotypes and "atypical nested deletions", those which would not have been detected using standard clinically available FISH probes, many of which do not have loss of heterozygosity for key genes such as *TBX1*. Furthermore, these laboratory modalities are also detecting 22q11.2 duplications with greater frequency as compared with metaphase FISH studies. Thus, here we will present data on patients with: the standard 22q11.2 deletion including classic features and rare associations; atypical 22q11.2 deletions; and 22q11.2 duplications. We will compare and contrast all three entities and provide anticipatory guidance, including international consensus health care guidelines, for those clinicians who are now in a position to care for these patients in record numbers. Lastly, we will discuss alternative diagnostic approaches, such as *CHD7* mutational analysis, in those non-deleted patients with symptoms of the 22q11.2 deletion.

Keywords: 22q11.2 deletion, 22q11.2 duplication, DiGeorge syndrome, Velocardiofacial syndrome, TBX1

TALK 18: Executive Functioning in Relation to Autism and ADHD Symptomatology in 22q11.2 Deletion Syndrome

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Background: Children with 22q11.2 deletion syndrome (22q11DS; velo-cardio-facial-syndrome) are at risk for developmental disorders such as attention-deficit-hyperactivity disorders (ADHD) and autism spectrum disorders (ASD). In the present study the relation between executive functioning (EF) and severity of ADHD and ASD symptoms was examined, since EF is known to be important in relation to emotional and behavioural problems.
Method: 63 children (40 females) with a mean age of 13.5(SD 2.6) participated. Standardized assessment was used to evaluate the presence of ASD and ADHD symptomatology. A profile of EF containing cognitive flexibility, inhibition, sustained attention, distractibility, working memory, reaction speed, perseveration, and planning was evaluated.
Results: The profile of EF in 22q11DS was characterized by weaker performance, compared to the norm, on all subdomains of EF, except for performances on perseveration that were within the normal range. Poor cognitive flexibility and inhibition, and high distractibility were found to be related to more severe ASD symptoms, while poor quality of sustained attention and planning, and high distractibility were related to more severe ADHD symptoms.
Conclusion: The degree of impairment on specific EF identified in children with 22q11DS subdomains is related to severity of ASD or ADHD symptomatology. These results may help in defining the mediating role of neurocognitive dysfunctions in the development of social and behavioural problems in 22q11DS.

Keywords: 22q11.2 deletion syndrome, velo-cardio-facial syndrome, executive functioning, autism symptomatology, ADHD symptomatology.

TALK 19: Amino Acids and Cognitive Deterioration in 22q11 Deletion Syndrome

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Background: One of the deleted genes in the 22q11 deletion syndrome (22q11DS) is the PRODH gene, responsible for the formation of glutamate out of proline. Therefore we investigated the relation of psychopathology and IQ with levels of the amino acids proline, glutamate and glutamine.

Method: We included 69 adult patients with the 22q11 deletion syndrome. Among them also patients with lower levels of intelligence and a history of deterioration. Psychopathology and IQ were determined. Out of urine samples levels of proline, glutamate and glutamine were determined. With statistical analysis the relation between psychopathology and IQ, with proline, glutamate and glutamine were investigated.

Results: Hyperprolinemia (proline 316 µmol/l) was found in 20 out of 67 subjects (29.9%), where 6 of them (9% of the total sample) could be classified having a severe hyperprolinemia (proline 550 µmol/l). Proline was not associated with intelligence levels or psychopathology. 2 out of 55 subjects had a Glutamine level below normal range (344–743 µmol/l) and 3 out of 55 subjects had a Glutamate level above the normal range (<121 µmol/l). Glutamate was significantly negatively related to IQ (p=.013), with higher levels of glutamate in patients with lower IQ. Age was also related with glutamate, with higher glutamate levels in patients with increasing age, which is remarkable, because glutamate is most of the time neutral or negatively related with age.

Conclusion: Because the observed clinical deterioration in 22q11DS comes with increasing age, we hypothesize that higher glutamate levels should be taken into account as a modulating factor of cognitive deterioration. As a possible explanation we think that in some patients excessive levels of glutamate can act as a neurotoxin, causing cognitive deterioration. Hyperprolinemia was a common finding in this sample, but could not be related to psychopathology or intelligence scores.

Keywords: 22q11 deletion syndrome, proline, glutamate, glutamine, amino acids, cognition.

TALK 20: A Comparison Of Neural Correlates Underlying Social Cognition in Klinefelter Syndrome and Autism

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Background: Klinefelter Syndrome (KS) is a genetic syndrome characterized by the presence of an extra X chromosome that appears to increase the risk of psychopathology, such as autism spectrum disorders (ASD). It is important to determine what underlying mechanisms cause this risk. It may be especially relevant to study this in terms of functioning of neural circuitries underlying social information processing, and compare these between children with KS and ASD. The current study used functional MRI to gain insight into neural mechanisms behind social-cognitive dysfunction in KS and ASD.

Method: Fourteen boys with KS, seventeen boys with ASD and nineteen non-clinical male controls aged 10–18 were scanned while matching and labelling facial expressions (face processing and affect labelling, respectively).

Results: There were no differences in ASD symptoms between the KS and ASD groups. No group differences in neural activation were found during face processing. However, during affect labelling the ASD group showed increased amygdala activation compared with controls. The KS group showed increased activation in the middle frontal gyrus, compared with the control and ASD groups, during affect labelling.

Conclusion: Although speculative, the boost in amygdala activation in the ASD group might be explained by the hypothesis that during face processing they apply a perceptual feature-based approach, which is impossible during affect labelling. The latter requires social information processing, which may lead to increased amygdala activation. Boys with KS may not label incoming social information intuitively, but rather attempt to use a 'reasoning' or more rational approach, which involves frontal areas. No group differences in task performance were found. These results imply the X chromosome may significantly impact brain development, and social difficulties associated with KS may be anchored in dysfunction of neural networks underlying social information processing in a way that might be different from children with idiopathic ASD.

Keywords: Klinefelter; autism; social cognition; fMRI; facial affect processing.

TALK 21: Cross-Syndrome Infant Developmental Trajectories: Fragile X Syndrome and Autism Siblings

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Background: Despite the high association of intellectual disabilities and autism spectrum disorder (ASD) in fragile X syndrome (FXS), few studies have examined the emergence of these conditions in FXS, and no work has contrasted the developmental profiles of infants with FXS to those at established risk for ASD or developmental delays. In this study, we examine broad indicators of early development in infants with FXS contrasted to infants at high risk for ASD and infants with non-specific developmental delays.

Method: A total of 321 infant boys ranging in age from 3 to 25 months participated. Of the 321 participants, 97 had FXS, 32 were ASD siblings, 59 had no developmental concerns and 133 had non-specific developmental delays (DD). The Mullen composite and domain scores were the primary dependent variables with age and group and their interaction as the predictors.

Results: Regression results for the Mullen composite revealed an age by group interaction ($p < .0001$) with the DD group ($B = -2.47$, $p = < .0001$) showing a decline across age, and the ASD siblings group showing no differences from the typical reference group ($p = .24$). The FXS group showed declines across age with divergence from the typical reference group at 9.3 months and divergence from the ASD sibling group at 10.6 months of age. Discriminant function analyses suggested accurate prediction of group membership was moderate to high with an overall cross-validated classification rate of 81%. Genetic factors will also be reported.

Conclusion: Our findings suggest that etiologically distinct profiles of early development can be detected by 10 months in infants with FXS contrasted to those with DD and ASD siblings in addition to typical controls. Fine motor delays in the FXS group appear to be the primary differentiating factor.

Keywords: fragile X syndrome, autism, early detection, developmental trajectories, infants

TALK 22: Adolescents at Ultra-High Risk (UHR) for Psychosis With and Without 22q11 Deletion Syndrome: A Comparsion of Prodromal Psychotic Symptoms and General Functioning

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Background: Genetic syndromes related to psychosis have become increasingly important for exploring the trajectory that leads to psychosis onset. Among these genetic syndromes, a very significant opportunity for mapping earlier phases of the trajectory can be found in 22q11.2 deletion syndrome (22q11DS). Comparative studies have shown that schizophrenic disorder in 22q11DS largely resembles schizophrenia in the general population. Nevertheless, only few studies have investigated the features of prodromal symptoms in patients with 22q11DS. The aim of the present study was to investigate differences and similarities between two samples: patients with 22q11DS clinically at risk for psychotic onset (UHR+22q11DS group) and patients at clinical high risk for psychotic onset (UHR group).

Method: The study was conducted on a sample of 30 individuals with 22q11DS at UHR of psychosis and 81 individuals at UHR of psychosis but without 22q11DS. The two groups were compared on positive, negative and depressive symptoms, level of general functioning and IQ.

Results: There was a significant group difference in negative symptoms, but no significant differences were found for positive, global and total symptoms. The UHR+22q11DS group showed a lower level of general functioning. The clinical profile of the UHR+22q11DS group appeared clearly more homogeneous.

Conclusion: Even if the two UHR groups are comparable in terms of positive symptoms, the UHR+22q11DS seem to have a specific clinical pattern characterized by higher negative symptoms, lower general functioning and an older age of onset of the UHR state. This finding may be of clinical value for the development of specific therapeutic intervention for UHR+22q11DS, and of theoretical value since the two groups may share only some underlying etiopathogenetic mechanisms.

Keywords: 22q11.2 deletion syndrome, Ultra-High Risk, Schizophrenia, Early Intervention, Prodrome

TALK 23: Investigating the Efficacy of the Social Communication Questionnaire for Identifying Autism Spectrum Disorder in Children with Down Syndrome

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Background: The Social Communication Questionnaire (SCQ) has been used in a number of studies to identify autism spectrum disorders (ASD) among children with Down syndrome (DS). However, although the SCQ is a widely used and recommended screening measure for ASD, it was originally developed to identify idiopathic autism and has not been validated for use in other developmental disorders.

Method: Fifty children with DS (aged 8–17 years) were assessed on a number of measures including the SCQ, Autism Diagnostic Observation Schedule (ADOS-G), Developmental Behaviour Checklist (DBC) and Vineland. The association between scores on the ADOS and SCQ was assessed and factors related to "misclassification" on the SCQ (compared with meeting threshold on the ADOS) were explored.

Results: Although most children who scored positive for ASD on the SCQ scored above cut off on the ADOS, there were some discrepancies between the two measures. Within this sample, the most effective cut-point on the SCQ was =19, (sensitivity =.74, specificity=.74). Fifteen SCQ items differentiated significantly (p<. 01) between children who scored positive for ASD on the ADOS and those who did not; using only these 15 items resulted in increased sensitivity (.83) although specificity was reduced. Factors related to discrepancy between SCQ and ADOS ratings included hearing impairments and levels of anxiety and disruptive behaviour. Adaptive behaviour levels were related to both SCQ and ADOS scores.

Conclusions: The SCQ can be of value in identifying the presence of autism symptomatology in children with DS. However, this should not be used alone as a diagnostic tool and the need for a more comprehensive assessment post-screening is crucial.

Keywords: Down syndrome, autism spectrum disorder

TALK 24: Depression in Adults with Intellectual Disability: Rates and Predictors of Outcome

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Background: A significant number of adults with intellectual disability (ID) present with mental health problems, including depression. However, little is known about the childhood predictors of symptoms of depression in adulthood. This study aimed to examine rates of depression symptoms in adults with ID, and to investigate role of individual childhood factors (e.g. age, gender, IQ, behaviour and emotional problems) and the environment (e.g. socio-economic disadvantage) in terms of adult outcomes.

Method: Rates and predictors of symptoms of depression in adulthood were explored in a representative population of 578 children and adolescents with ID, and comparison samples of children with autism, Fragile X, Williams, Down, and Prader Willi syndromes. Participants were followed over 18 years with five waves of data collection. Symptoms were measured using the depression screening items of the Developmental Behaviour Checklist for Adults (DBC-A).

Results: Approximately 75% of Time 1 participants were followed up at Time 5. Rates of symptoms of depression in adulthood (Time 5) were compared across the representative population sample with ID and the samples of adults with autism, Fragile X, Williams, Down, and Prader Willi syndromes. A series of regression analyses were used to investigate the associations between childhood, adolescent and environmental factors, and later evidence of depression symptoms.

Conclusion: Results are discussed in terms of risk factors for the development of depression in adulthood and potential targets for intervention and prevention strategies. Better identification of risk for depression should lead to improved identification and diagnosis, and access to treatment.

Keywords: Depression symptoms, adults, childhood and adolescence, predictors, longitudinal.

TALK 25: Is There a Need for a Neurocognitive Assessment at Key Developmental Time Points in Boys with Klinefelter Syndrome?

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Background: Boys with Klinefelter syndrome (KS) are at increased risk for psychosocial, motor, language and learning difficulties, resulting in lower levels of education. The multidisciplinary KS team at our center has developed an integrated follow-up protocol, including comprehensive assessment at key developmental time points: infancy, preschool, pre-middle school, adolescence, and early adulthood. We illustrate the value of this multi-disciplinary approach.

Methods: Two young KS men, aged 19 and 20 years, were evaluated for cognition (WAIS-IV-NL), attention/executive (Stroop, 15 words, Figure of Rey), motor (Movement ABC), visual-spatial (DTVP-A), language (CELF-4-NL) and academic skills. Socio-emotional functioning was evaluated through interviews and observations.

Results: The first man did a bachelor degree in office management. He reported difficulties with formulating concise answers in written or oral assessments and wanted to improve his organizational skills. The second young man finished a professional education in electricity. Parents reported problems with time management, poor sense of duty and episodes of verbal and physical aggression, which had a major impact on the family functioning. Both men had verbal, performance and working memory scores within the normal range, but had a low processing speed. Their interpretation of complex language tasks was moderately impaired, resulting in a low Language Content Index on the CELF-4-NL. This influenced overall processing speed for completing tasks with auditory information. Both had fine motor difficulties with sluggish motor tempo and limited coordination skills. Neuropsychiatric evaluation in the second case showed rigid behaviour, mood instability, and difficult social interaction with peers. Individualized management strategies were developed for both students and their families.

Conclusion: The value of a formal assessment of neuropsychological functioning in older KS adolescents is illustrated. Management strategies should be based on the profile of each patient. Early interventions for neurocognitive and psychiatric symptoms might prevent lower levels of education and employment in KS.

Keywords: Klinefelter syndrome, neurodevelopment.

TALK 26: Neuroanatomically Phenotyping Sex Chromosome Aneuploidies as Models of Genetic Risk for Autistic Behaviors

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Background: Sex Chromosome Aneuploidies (SCAs) are often accompanied by impairments of language and social communication, and provide a unique opportunity to compare phenotypic effects of varying X and Y chromosome dosage. Therefore, characterizing alterations of brain development in SCAs may advance our understanding about the brain bases of autism spectrum disorders (ASD), and the potential contribution of differences in sex chromosome dosage to the increase risk of ASD in males relative to females.

Method: Here, by studying a rare neuroimaging cohort of people with varying sex chromosome complement (80 XX, 89 XY, 28 XXX, 58 XXY, 26 XYY, 20 XXYY, 5 XXXXY), we carry out the first direct comparison of X and Y chromosome dosage effects on human brain development, focusing on the two biologically dissociable determinants of cortical volume (CV): cortical thickness (CT) and surface area (SA). We consider X and Y dosage effects on global as well as local measures of cortical anatomy: complementing the latter structural analysis with large-scale online meta-analysis of functional imaging data.

Results: We find that X and Y-chromosomes have opposing effects on overall brain size (smaller vs. larger respectively), but highly convergent effects in local anatomy. This property of locally-convergent effects generalizes across both CT and SA, and centres on several cortical sub-regions that have previously been implicated in ASD. Online meta-analysis of functional neuroimaging data in typically-developing controls links foci of convergent X-Y effect to socio-cognitive and socio-emotional domains of information processing.

Conclusion: These findings specify a distributed system of cortical regions that may mediate the increased risk for impairments of language and social cognition in SCA. Locally convergent sex chromosome effects implicate genes that are shared between X and Y-chromosome and therefore less likely to explain sex-differences in ASD risk.

Keywords: Aneuploidy, Cortical Thickness, Surface Area, Pseudoautosomal

TALK 27: Improving Health Promotion Related to Fetal Alcohol Spectrum Disorder (FASD): A Systematic Literature Review

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Background: Alcohol use during pregnancy is one of the leading preventable causes of intellectual or developmental disability. FASD is the non-diagnostic umbrella term used to characterize the full range of damage caused by prenatal alcohol exposure, varying from mild to severe, and encompassing a broad array of physical defects and cognitive, behavioural, emotional, and adaptive functioning deficits. This situation clearly warrants intervention. Development of a focused, effective and evidence based intervention requires insight in the burden of FASD and the underlying dynamics. The current literature synthesis aims to provide the required evidence base by compiling the literature on FASD, specifically addressing what we know of the prevalence of FASD, which behaviours contribute to FASD, and which preventive measures have been recommended so far.
Method: A search was conducted in multiple electronic bibliographic databases up to May 2014, including PubMed, PsychInfo, PsychArticles, ERIC, CINAHL and EMBASE. A query was generated and the resulting hits were exported and screened by two independent screeners. The constructed query yielded 395 hits. After the first screening round on the basis of titles, 153 records (39%) remained; after the second round on the basis of abstracts, 143 records (36%); and after the third round on the basis of full-texts, 54 records (14%). Resulting articles are examined to determine whether meta-analysis is feasible or whether a systematic review will be conducted. All materials, data, and analysis scripts will be made available publicly.
Results: Results of the systematic literature search will be presented and specific recommendations for prevention efforts will be discussed.

Keywords: Fetal Alcohol Spectrum Disorder, health promotion, prevalence, intervention, drinking behaviour, systematic literature review

TALK 28: The Multiple Molecular Facets of Fragile X Syndrome and *FMR1* Associated Disorders

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Background: Absence of *FMR1* mRNA and FMRP causes Fragile X syndrome, the most common inherited cause of intellectual disabilities. Carriers of fragile X premutation alleles, with 55–200 CGG repeats within the FMR1 gene, are considered at risk for a number of clinical phenotypes, including cognitive problems, developmental delay, autism spectrum disorders, seizure, psychiatric disorders and of major concern, fragile X-associated tremor/ataxia syndrome. These clinical involvements likely arise from a toxic gain-of-function due to the elevated levels of expanded *FMR1* transcripts observed in premutation carriers, although how this RNA can lead to neuronal cell dysfunction is unknown. However, a number of other molecular events are triggered by the presence of a CGG repeat expansion including altered expression of long non coding RNA within the *FMR1* locus, abnormal alternative splicing, dysregulated miRNA landscape, protein sequestration, genomic changes, non AUG translation and to CGG size and methylation mosaicism.

Method: Southern Blot and PCR analysis were utilized to determine CGG size and methylation status. qRT-PCR and Western blot analyses were used to measure *FMR1* mRNA and FMRP expression levels. A long-read single molecule real time sequencing was utilized to determine the expression levels of FMR1 isoforms.

Results: *FMR1* CGG size and methylation inter and intra-tissue mosaicism was observed in individuals with a full mutation and in premutation carriers. FMRP expression was CGG dependent. An unbalanced abundance of select isoforms, accounting for the elevated *FMR1* mRNA levels, was identified in premutation carriers compared to typical controls.

Conclusion: In addition to increased *FMR1* mRNA production and decreased expression of FMRP, a number of non-exclusive molecular mechanisms have likely downstream effects and contribute to the observed variability in clinical presentation observed in both fragile x syndrome and in *FMR1* associated disorders.

Keywords: ***FMR1*** mRNA, FMRP, alternative splicing, miRNA, clinical phenotype

TALK 29: *The Pat Howlin Lecture Prize Winner:*
The Effect of Adult Familiarity and Nature of Interaction on Social Anxiety and Motivation in Fragile X, Rubinstein-Taybi and Cornelia De Lange Syndromes

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Background: Increased social anxiety, alongside a willingness to interact, has been reported to describe the social impairments in individuals with Fragile X (FXS) and Cornelia de Lange (CdLS) syndrome, whereas typical social interest and intact social skills are reported in individuals with Rubinstein-Taybi syndrome (RTS). Understanding situations in which social anxiety may be induced is important for intervention planning. In this study, the effects of adult familiarity and type of social interaction on anxiety and motivation were investigated.
Method: Individuals with FXS (n = 20), RTS (n = 20), CdLS (n = 20) and Down syndrome (DS; n = 20) participated in four social tasks, each with a familiar and unfamiliar adult. Social anxiety and motivation were assessed using the Social Anxiety and Motivation Rating Scale, developed for this study.
Results: To assess social anxiety, a 4 (condition) x 2 (familiarity) x 4 (syndrome) mixed ANOVA revealed a three-way interaction (p =.003). Further analyses revealed that whilst participants with FXS and RTS exhibited high levels of social anxiety during all interactions, participants with CdLS showed increased social anxiety only during interactions with an unfamiliar adult, particularly when this involved a focussed discussion. A three-way interaction was also revealed for social motivation analyses (p =.014). Further analyses revealed that social motivation was similarly influenced by the social interactions with familiar adults in all groups. During unfamiliar interactions, participants with CdLS showed reduced social motivation during a focussed discussion.
Conclusion: These results indicate social anxiety is high but consistent across interactions with familiar and unfamiliar adults in individuals with FXS and RTS. However, in CdLS, social anxiety is more likely to be influenced by the social situations and interacting adult. Furthermore, the results show that whilst social anxiety and motivation are related constructs, they are not dependent on one another.

Keywords: social anxiety, social motivation, social impairments, fragile X syndrome, Cornelia de Lange syndrome, Rubinstein-Taybi syndrome.

TALK 30: *The Tom Oppé Lecture Award:* **Intervention Strategies For Behaviour Phenotypes**

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Background: There are no researched models for providing clinical services to address behaviour problems which are features of behaviour phenotypes. Potential service models could include care by individual expert clinicians, multidisciplinary syndrome-specific clinics, as part of treatment research programs, through disability specific mental health services, or through generic mental health services. The advantages and disadvantages of such approaches will be discussed. We will describe a different approach, namely providing specialist support through a population-wide public health intervention.

Method: Stepping Stones Triple P (SSTP) is a public health strategy delivered to parents of children aged 0–12 with developmental disabilities (DD). The current research aims to enhance Stepping Stones with modules for specific causes of DD, namely Down, Fetal Alcohol, Fragile X, Prader-Willi and Williams syndromes. Syndrome specific modules and materials will be developed to complement the multilevel SSTP five-tiered program. The enhanced SSTP program will be offered to families across three Australian states. The public health impact will be assessed at a population level using the RE-AIM strategy (Reach, Efficacy, Adoption, Implementation, Maintenance).

Results: Examples of the syndrome-specific modules will be presented

Conclusion: If effective, the validation of a multilevel public health strategy for parents of children with DD and emotional and behavioural problems, that includes novel behavioural interventions for psychopathologies associated with particular causes of DD, will significantly reduce the burden of mental ill-health for families carers and community.

Keywords: Behavioural phenotype, Stepping Stones Triple P, behavioural problems, developmental disabilities, intervention.

Abstracts for Poster Presentations

(in alphabetical order of primary author)

POSTER 1: Aggressive and Self-Injurious Behaviors in MECP2-Related Syndromes

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Background: Loss- and gain-of-function mutations of the X-linked methyl-CpG-binding protein 2 gene (MECP2) cause Rett syndrome (RTT) and MECP2 duplication syndrome (Dup), respectively. The two syndromes share several important clinical features, including repetitive midline hand movements, communication and motor impairments, and epilepsy. Self-injurious (SIB) and aggressive behaviours have been reported in both syndromes. To date no studies have directly compared the frequency of caregiver-reported SIB and aggression among individuals with RTT and Dup using the same measurement tool.

Method: The caregivers of 26 females with classic RTT (aged 2–33 years), and 11 males with Dup (aged 2–22 years) participated. Data on SIB, aggression, other behaviours, and health problems were collected via paper surveys.

Results: The majority of caregivers reported the occurrence of SIB (RTT = 85%, Dup = 55%). In RTT, the most frequent topographies were biting hands/arms (50%), and rubbing/scratching (46%). In Dup, the most frequent topographies were biting hands/arms (27%), and poking eyes/ears (27%). Rates of aggressive behaviour were lower, and did not significantly differ across groups (RTT = 35%, Dup = 45%). Relationships between problem behaviours and parent-reported health and mood problems were also examined.

Conclusion: This study extends previous reports of the occurrence of SIB and aggression in RTT and Dup. These results suggest that SIB and aggression are frequent problems in both syndromes, although the specific topographies varied between the groups. Additional research is needed to identify specific risk factors, and effective intervention strategies for challenging behaviors among individuals with MECP2-related syndromes.

Keywords: Rett syndrome, MECP2-duplication syndrome, self-injurious behaviour, aggression

POSTER 2: A Mixed-Methods Approach to Investigate Attitudes Pertaining to Sexuality and Relationships for People with Genetic Developmental Disabilities

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Background: Historically, people with intellectual and developmental disabilities (IDD) have experienced widespread discrimination and stigma. The rights of people with IDDs are now protected by laws and policies but there is still some way to go to ensure equal opportunities. One complex area is that of sexuality and parenting, with the majority of people with IDD not having experienced romantic relationships, enjoyed intimacy, or having had children.

Method: We investigated attitudes to sexual rights using a mixed-method design including interviews of young women with, and parents of women with 22q.11.2 deletion syndrome analysed using interpretative phenomenological analyses in conjunction with a survey directed at people in the general community, healthcare professionals and parents of children with genetic IDDs.

Results: The young women in the study expressed a desire to have romantic relationships, and to have children. They overestimated the risks of heritability; and expressed as a commitment to meeting the individual needs of future children. The women expressed beliefs that their parents would be supportive if they chose to become parents. Whilst all parents expressed support for their children to have relationships, they expressed concerns about their children becoming parents. There had been little discussion between parents and their children about sexuality, relationships and parenting. Overall the survey indicated that people's attitudes towards sexual rights were positive, and most strongly related to their political ideology, overall liberal attitude to sexuality and for females the quality of interactions with a person with a genetic IDD was also important.

Conclusions: Whilst attitudes in the community generally are positive, there is a need for sexual education and a need to promote discussions about sexuality, relationships and parenting in families in which there is a young person with a genetic IDD.

Keywords: sexuality, relationships, parenting, attitudes.

POSTER 3: An Unusual Floppy Infant

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Background: We report a 13-month-old female infant with hypotonia since birth, developmental regression, pallor and apathy. She was exclusively breastfed. She was born at 41+3 weeks of g.a. APGAR score 9–10. She lost ability to smile at 9 months of age and she developed generalized tremors at 11 months of age! Her mother was healthy, non vegetarian but deeply depressed. Family history was unremarkable. Parents non-consanguineous.
Methods and Results: Physical examination showed pallor, hypotonia, normal tendon reflexes, she was apathetic, with poor eye contact, unable to smile, to support head and to sit without support. Her weight and length were on the 50th percentile, head circumference was on 25th percentile. Laboratory tests: Hb 9.4 g/dL, MCV 117 fL, RBC 2.120.000/cmm, LDH 946 U/L, serum cobalamin undetectable, serum folate slightly increased, urinary methylmalonic acid 1950 mM/M ur. creat. (normal < 2); normal serum methylmalonic acid, homocysteine and methionine.! Brain MRI: diffuse delay of myelination and a severe cerebral atrophy! We started i.m. hydroxocobalamin 1000ug/day for two weeks, followed by 4 weekly injection and successive oral administration. After the second injection the patient began to smile starting weaning regularly. One week later: Hb 11,5 g/dL, MCV 110 fL, serum cobalamin 2000 pg/mL. Seven months later the expressiveness improved, she was able to walk with support and to interact with people. General intelligence quotient was 45 on Griffith Scale.! Patient's mother tests: serum cobalamin 155 pg/mL, Hb 15.7 g/dL, MCV 87.4 fL, serum homocysteine slightly increased, positive APCA. At gastric biopsy: chronic atrophic gastritis. She started i.m. hydroxocobalamin replacement.
Conclusion: The most frequent cause of cobalamin deficiency in breastfed infant is dietary deficiency. It's important monitoring maternal storage to prevent deficiency and considering cobalamin deficiency in infants with severe neurological problems.

Keywords: hypotonia, cobalamin, developmental regression, macrocytic anemia, methylmalonic aciduria

POSTER 4: Neurodevelopmental Profile and Cognitive Variability in Two Females with the Rare 48, XXXX Chromosomal Disorder

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Background: 48, XXXX is a rare chromosomal aneuploidy associated with neurocognitive deficits, speech and language disorders and executive dysfunction but the scarcity and variability of reported cases limit our understanding of the 48, XXXX phenotype. To our knowledge, this is the first study to report on the neurodevelopmental, cognitive and behavioral profile of two females with 48, XXXX of similar ages.

Method: Patient 1 (age=11.0) and patient 2 (age=10.9) were evaluated using the Wechsler Intelligence Scale for Children (WISC-IV), the Leiter International Performance Scale (LIPS-R), Expressive and Receptive One-Word Vocabulary tests (ROWPVT-4/EOWPVT-4) the Beery Visual Motor Integration tests (Beery-VMI-5th), the Child Behavioral Checklist (CBCL) and Behavioral Rating Inventory of Executive Function (BRIEF).

Results: Verbal IQ's were 44 and 68 on the WISC-IV and 56 and 80 on the LIPS-R for patient 1 and 2, respectively. Overall vocabulary was stronger in patient 2 than patient 1, but receptive vocabulary was stronger than expressive in both patients (Patient 1: 62 / 55; Patient 2: 83 / 79; ROWPVT-4, EOWPVT-4). Both 48, XXXX girls had significantly impaired visual motor capacities in graphomotor and perceptual domains (<5th percentile Beery-VMI subtests) as well as significant executive dysfunction and behavioral/social deficits (<10th percentile on CBCL and BRIEF subtests).

Conclusion: Patient 1 had an extensive history of family learning disabilities (FLD) likely contributing to her delayed cognitive development relative to patient 1. We hypothesize that the co-existing ADHD in both subjects compounded their existing social and behavioral deficits. The visual-motor deficits in both subjects is a novel finding and likely to be a contributing factor in the cognitive delays associated with 48, XXXX. These distinct and overlapping features are characteristic of other sex chromosome variations and may be of great use in the diagnosis, treatment and counseling of 48, XXXX patients and families.

Keywords: XXXX, tetrasomy X, chromosomal variations, sex chromosome disorders, case-report, rare diseases

POSTER 5: ASD Symptoms in Children with 16p11.2 Deletions and Duplications and Those with Idiopathic ASD

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Background: The pediatric prevalence of Autism Spectrum Disorder (ASD) among those with copy number variations (CNVs) of chromosome region 16p11.2 is between 15--25%. However, it is unclear whether (a) individuals with 16p11.2 CNVs +/- a clinical diagnosis of ASD differ on standardized measures of ASD symptomatology and (b) those with 16p11.2 CNVs differ from those with idiopathic ASD on these same measures.

Methods: Ninety children with 16p11.2 CNVs ages 6 to 17 who participated in the Simons Variation in Individuals Project (SVIP) were evaluated using the Autism Diagnostic Observation Schedule-2 (ADOS-2), the Autism Diagnostic Interview-Revised (ADI-R), the Behaviour and Sensory Interests Questionnaire (BSIQ), the Child Behaviour Checklist (CBCL), and developmentally appropriate cognitive assessment. Linear mixed models and nonparametric tests were run to test the effect of ASD diagnosis on outcome variables. Analyses with idiopathic ASD cases from the Simons Simplex Collection are currently underway.

Results: Fifteen (24.2%) children with deletions and 6 (21.4%) children with duplications had received an SVIP-based ASD diagnosis. Deletion cases +/- ASD demonstrated significant differences across ADOS calibrated severity scores (CSS) for the Social Affect and raw domain total scores (ASD+ vs. ASD- means: 6.6 vs. 3.0 for SA, 6.1 vs. 2.3 for total, p p = 0.47). Duplication cases +/- ASD exhibited significant differences on the Reciprocal Social Interaction domain of the ADI-R (ASD+ vs. ASD- means: 19.3 vs. 10.5, p = 0.04), across all ADOS CSS domains (ASD+ mean range: 6.5--7.3, ASD-: 2.2--3.1, p <0.01) and the Repetitive and Stereotyped Mannerisms domain of the BSIQ (10.2 vs. 3.0, p = 0.01).

Conclusion: Children with 16p11.2 CNVs +/- ASD were most consistently distinguished from one another on core ASD symptoms per the ADOS yet were not different on most other indices of ASD characteristics, IQ, or psychiatric symptoms.

Keywords: ASD, 16p11.2, ADOS, ADI-R

POSTER 6: Psychological Growth in Parents of Children Affected by Developmental Disabilities: Preliminary Results

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Background: Having unexpected and difficult experiences such as caring for a child affected by a developmental disability can cause psychological distress for parents. However families can improve and even thrive as a result of their child, often constructing meaningful stories surrounding their journey, or discovering new happiness and spirituality. This phenomenon is known as psychological growth; that is experiencing a positive change, for example changing life values.

Method: We aimed to examine psychological growth (and the factors affecting it) in parents of children affected by developmental conditions including 22q11.2 deletion syndrome, Williams syndrome, or multiple congenital anomalies without a known aetiology. An online survey was utilised to investigate the experiences of 255 parents and caregivers. The survey included standardised questionnaires of coping, social support, family-centred services, and perceived changes as a result of their child.

Results: The majority of participants were female (96%) and from North America (53%), Australia/New Zealand (23%), and Europe (21%). Initial analyses indicate 80% of participants perceived some positive change as a result of their child (i.e., they received a score greater than 54 out of 90 on the Psychological Well-Being - Post-Traumatic Changes Questionnaire) and 30% perceived a high level of positive change (i.e., a score greater than 72 out of 90). Participants tended to utilise positive reappraisal (M = 9.80, SD = 4.99), seeking social support (M = 7.81, SD = 4.29), and planful problem solving (M = 7.22, SD = 3.69) styles of coping. However, those who exhibited high levels of positive change appeared to use positive reappraisal more than those who perceived less or no positive change.

Conclusion: As expected, a proportion of parents experienced positive growth or change. Growth was associated with positive reappraisal. Hence, interventions to promote specific adaptive coping mechanisms may be useful to promote parental psychological wellbeing.

Keywords: Psychological growth, developmental disability, 22q11.2 deletion syndrome, parents

POSTER 7: Social Cognition in 22q11.2 Deletion Syndrome in Relation to Autism and ADHD Symptomatology

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Background: Children with 22q11.2 deletion syndrome (22q11DS; velo-cardio-facial syndrome) experience social problems that are part of the symptomatology of autism (ASD) and attention-deficit-hyperactive disorder (ADHD). This study aimed to examine the relation between social information processing and ASD and ADHD symptom severity in children with 22q11DS.

Method: Psychiatric and psychological assessment in a sample of 46 children with 22q11DS (28 females) aged 9 to 18.5 years was used evaluating the presence of ASD and ADHD symptomatology. Quality of social cognition (face recognition, identification of facial emotions) was evaluated and compared to processing of abstract visuospatial information. Relations with ASD and ADHD symptom severity were assessed.

Results: Slower, less accurate face and emotion recognition, as well as less accurate abstract visuospatial information processing was found in children with 22q11DS as compared to the norm. Processing of complex social information (faces and negative emotions) and complex abstract stimuli were most severely impaired. While accuracy of visuospatial information processing was related to ASD and ADHD symptom severity, such correlation did not exist between quality of social cognition and autism and ADHD symptomatology.

Conclusion: Impairments in processing of complex social and abstract visuospatial information seem to be part of a specific endophenotype of 22q11DS. Moreover, evidence suggests that larger impairments in visuospatial information processing is associated with increased social behavioural problems in this population.

Keywords: 22q11.2 deletion syndrome, velo-cardio-facial syndrome, social cognition, autism symptomatology, ADHD symptomatology

POSTER 8: Decision Making Skills and Relationships with Executive Function in Cornelia De Lange Syndrome

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Background: Anecdotal reports from parents suggest that people with Cornelia de Lange syndrome (CdLS) struggle with making decisions and this difficulty leads to anxiety, challenging behaviour and self injury. Additionally, there is evidence of executive function deficits in rare genetic syndromes. Literature suggests a relationship between executive function and decision making skills, which could provide an explanation for decision making difficulties in CdLS. This study aims to empirically investigate decision making skills in CdLS and their relationship with executive function.

Method: Participants with CdLS (N=25; Mage 18.60), fragile X (FXS) (N=25; Mage= 18.48) and Rubinstein-Taybi syndromes (RTS) (N= 25; Mage= 18.60) and 20 typically developing (TD) children (Mage= 6.90) completed direct EF assessments suitable for people with intellectual disabilities. Participants also completed a novel decision making task in which they were presented with pictures representing 8 decision making scenarios counterbalanced for familiarity (familiar or unfamiliar), number of options (2 or 5) and visibility (picture cards of options were either covered over or visible). Videos of these assessments were coded for behaviours related to memory, decision making difficulties and anxiety.

Results: Preliminary results show no significant effects of familiarity (p=.67), visibility (p=.74) or number of options (p=.57) in decision making time between participants with CdLS and RTS, however participants with CdLS showed significantly more behaviours indicative of memory difficulties when options were not visible (p=.02). Furthermore, participants with CdLS also showed significantly higher anxiety scores in conditions placing a higher memory demand compared to participants with RTS (p=.01).

Conclusion: Preliminary results point to memory-related demands being highly anxiety provoking in CdLS. Data will be analysed further to include FXS and TD groups and to examine relationships with the EF profiles in the groups. Results have the potential to inform development of interventions to aid decision making in CdLS in the future.

Keywords: Decision making, Executive function, Anxiety, Intellectual Disabilities

POSTER 9: Dissociations in Cortical Thickness and Surface Area in the Developing Brain in Down Syndrome: A Pediatric Neuroimaging Investigation

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Background: Despite the fact that Down syndrome (DS) is the most common genetic cause of intellectual disability, surprisingly little is known about the developing cortex in youth with the syndrome. Thus, the current pediatric neuroimaging study sought to (a) provide group-level descriptions of deviations in cortical thickness (CT) and surface area (CSA) in DS quantified at ~81,000 vertices across the cortex; and (b) begin to investigate developmental trajectories for CT and CSA in DS cross-sectionally.
Method: Participants included 31 youth with DS and 45 typically developing (TD) age- and sex-matched peers (M Age=15; Range=5–24 years; 40 females). All MRI scans were obtained on the same GE 3T scanner and processed with Montreal Neurological Institute's CIVET pipeline.
Results: A dissociation between CSA and CT was found: CSA was largely reduced while CT was largely increased. These findings were observed at the whole cortex and vertex-level. Pronounced areas of CSA reduction were identified in the superior temporal and frontal lobes; in contrast, CT was largely increased, particularly in more anterior and posterior brain regions. The one notable exception was that of thinner cortex in DS in the parahippocampal gyrus. Age trajectories for total CSA and mean CT were largely parallel for the DS and TD groups (i.e., no statistically significant group X age interactions).
Conclusion: These results suggest that cortical volume reductions in DS are driven by reduced CSA, particularly in the frontal and temporal lobes, consistent with executive function and language weaknesses associated with the syndrome. On average, the cortex was thicker in DS, with the exception of thinner cortex in the parahippocampal gyrus, an area relevant for the precocious onset of Alzheimer's disease. Lastly, this preliminary cross-sectional examination of age effects suggested largely similar degrees of CT and CSA deviation from same age-peers across this age range.

Keywords: Down syndrome, brain, magnetic resonance imaging, cortical thickness, cortical surface area, neuroimaging

POSTER 10: Effect of Adapting Early Reading Interventions Based on the Down Syndrome Behavioural Phenotype

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Background: The behavioural phenotype of Down syndrome (DS) is characterized by a heightened probability of strengths in visual versus auditory processing, deficits in expressive language and speech articulation, and challenges with motivation and persistence. This profile of behaviour may be useful for guiding adaptations of reading interventions provided to individuals with DS.

Method: Two multiple baseline across participant, single-case design studies were conducted to evaluate the effect of adapting two reading interventions (i.e., phonological awareness, decoding) based on the behavioural phenotype. Eleven children and adolescents with DS (6–13 yrs) received intervention (4x/wk) for four months. Participants began the intervention in a non-adapted reading intervention baseline condition. Participants were entered into the treatment phase (i.e., adapted intervention) in a staggered manner. Mastery of targeted skills (e.g., letter sounds, word reading) was assessed daily.

Results: A functional relation was found between the adapted phonological awareness intervention and targeted skills (i.e., phonological awareness, target words). Additionally, three out of five participants demonstrated an increased rate of learning of letter sounds. Results were less consistent for the decoding intervention. Three out of six participants appeared to have increased rates of learning (i.e., target words, phonetically regular words, and sound-symbol correspondences) in the adapted decoding intervention.

Conclusion: Adaptations based on the DS behavioural phenotype appeared to enhance the response to a phonological awareness intervention. Similar adaptations applied to a decoding intervention appeared to produce a less consistent effect on learning. Results indicate that adaptations were most effective for students who entered the study with lower reading skills. Implications for future research will be discussed.

Keywords: Down syndrome, reading, phonological awareness, decoding.

POSTER 11: Functional Brain Connectivity in Neurofibromatosis Type I

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Background: Neurofibromatosis, Type 1 (NF1) is the most common monogenetic disorder affecting the human nervous system. Many different abnormalities have been observed in the brains of NF1 patients. As cognitive and social deficits have also been observed across many different domains, it appears increasingly likely that, rather than abnormalities in specific neural structures, suboptimal functioning in networks of brain regions might underlie the varied social-cognitive phenotype in NF1. This is the first study to examine intrinsic functional network alterations in NF1.

Method: Eighteen NF1 patients and 34 healthy controls underwent structural and resting state-fMRI (Philips, 3 Tesla Achieva MRI). After data-denoising using FIX (FSL software), multi-session temporal concatenation and dual regression using ten previously reported functional networks (three visual networks, the default mode network (DMN), an auditory network, a sensorimotor network, an executive function network, two fronto-parietal networks and a cerebellar network) were used to identify group differences.

Results: Intrinsic functional connectivity increases of NF1 patients when compared to healthy controls were identified in a visual networks, the DMN, the auditory network and the left fronto-parietal network. In contrast, decreased functional connectivity were found within another visual network and the sensorimotor network.

Conclusion: This is the first study to report on differences in resting state functional connectivity in NF1. Widespread differences in functional connectivity between controls and NF1 patients were found. These abnormalities might underlie the varied and widespread problems experienced by individuals with NF1.

Keywords: resting state functional connectivity, Neurofibromatosis Type 1, network changes

POSTER 12: Microstructural White Matter Alteration in Neurofibromatosis Type 1 and its Association with Executive Functioning

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Background: Neurofibromatosis Type 1 (NF1) is characterized by brain volumetric increases and cognitive deficits (particularly executive dysfunction). Moreover, widespread micro-structural white matter changes (WM) have been reported, but their relation to executive function has not been investigated so far. We here seek to examine the relation between micro-structural alterations and executive function in patients and highlight WM group differences.

Method: We performed diffusion tensor imaging analyses using tract-based spatial statistics in 16 NF1 patients and 32 controls and used a whole brain as well as a region of interest based approach (using bilateral anterior thalamic radiation, ATR), to determine micro-structural group differences. Grey (GM) and white matter volume were calculated using FSL. Sub-scores of the Memory-Search-2-Dimensions (MS2D, one of the Amsterdam Neuropsychological Tasks) were correlated with diffusion-parameters.

Results: Bilateral fractional anisotropy (FA), an index of general WM integrity, and the right-hemispheric axial diffusivity (DA), a measure of axonal integrity, of the ATR correlated with MS2D correct responses (FA: right: r=.695, p=0.008; left: r=.615, p=0.025, DA: right: r=.513, p=0.037). In line with previous literature, we identified decreases in FA, and increases in mean diffusivity, radial diffusivity and axial diffusivity in NF1 patients disseminated over the whole brain. Group differences were found significant within ATR for all four measures (p-range: <0.001–0.004). Volumetric differences were found for WM (p=0.001), but not for GM (p=0.225).

Conclusion: We here report for the first time on the association between aberrant WM-microstructure within the ATR and executive function in NF1. However, its association with increased WM needs to be further determined.

Keywords: Neurofibromatosis Type 1, diffusion tensor imaging, white matter integrity, executive function

POSTER 13: Association of Motor Skills with Adaptive Functioning in Children with XXY And XXYY Syndromes

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Background: XXY/Klinefelter and XXYY syndromes are associated with cognitive, motor, and adaptive functioning (AF) delays. The aim of this study was to evaluate motor skills and their association with adaptive functioning in these groups.

Method: Males with XXY (n=64) age 4–21 were evaluated for motor using the Beery Test of Visual Motor Integration and the Bruininks-Oseretsky Test of Motor Proficiency, BOT-2), cognitive assessments (WASI; WISC-IV) and adaptive skills (Vineland-II).

Results: Mean scores for XXY were significantly higher than XXYY for both VMI and BOT-2 composites (***M*** VMI Score XXY 92.3 (sd 14.4), XXYY 81.5 (sd 11.3), t(106)=4.239, p=0.00; ***M*** BOT-2 Composite XXY 45.7 (sd 9.45), XXYY 38.1 (sd 7.63), t(59)=2.944, p=.005). In both groups, there was a significant positive correlation between motor skills and overall adaptive functioning scores (XXY R=0.33, p=0.013; XXYY R=0.38, p=0.013). This correlation remained significant after controlling for age and IQ for the VMI.

Conclusion: Motor skills are associated with adaptive functioning in males with XXY and XXYY. Evaluation and treatment of motor deficits is important for adaptive functioning in this patient group.

Keywords: XXY, XXYY, Klinefelter syndrome, motor skills, visual motor integration, adaptive functioning

POSTER 14: Association of Social Communication, Expressive Language and Motor Skills with Therapeutic Horseback Riding Intervention with Children with Autism

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Background: Autism spectrum disorders (ASD) are associated with motor, speech, social and adaptive functioning delays. The aim of this study was to evaluate the effects of 10 weekly Therapeutic Horseback Riding (THR) or barn activity group (BA) (with no animal-human interaction).

Method: Children with ASD were randomized to a 10-week THR intervention (n=52) or a BA (n=48). Children were evaluated using the Peabody Picture Vocabulary Test (PPVT), the Systematic Analysis of Language Transcripts (SALT), Bruininks-Oseretsky Test of Motor Proficiency, Postural Praxis and Verbal Praxis on Command, (SIPT), self-regulation behaviours (Abberant Behaviour Checklist), adaptive skills (Vineland-II), and Social Responsiveness Scale (SRS).

Results: There was a significant improvement in receptive language (PPVT *M* 7.8, sd 9.8), and expressive (SALT p=.001) language, and fine motor (BOT p=.001), sit ups (p=.015) and postural praxis performance (p=.001) in the THR group. Social Communication (SRS p=.0065) improved in both THR and BA groups. This finding remained significant after controlling for age and IQ.

Conclusion: Social communication and motor skills are associated among children with autism. Evaluation and treatment of communication and motor deficits are important for social communication.

Keywords: autism, social communication, motor skills, language, therapeutic horseback riding

POSTER 15: Behavioural Phenotype of the Classic Adult Form of Myotonic Dystrophy Type 1 (DM1)

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Background: Myotonic Dystrophy Type 1 (DM1) is an autosomal dominant myopathy caused by an unstable expansion of trinucleotide repeats (CTG) in chromosome 19q. The classic adult form of DM1 has an onset between 10 and 30 years. The mutation and associated symptoms continue to progress throughout life. Congenital and childhood forms of DM1 have a strong association with autism spectrum disorder (ASD). The present study is based on a comprehensive assessment of Norwegian DM1 patients. Psychiatric and neurodevelopmental problems were investigated. We explored how these problems are related to mutation size, inheritance mode, IQ, onset and duration of disease and other somatic symptoms.

Method: 31 DNA confirmed classic DM1 patients (Age 21–61 years; 18 male 13 female) participated. All could walk independently and were of average IQ. Expansion size reassessment was performed using Southern Blot analysis of lymphocytes. Measures included the Beck inventories for depression (BDI) and anxiety (BAI); the Autism Quotient (AQ) and the WASI for IQ.

Results: High rates of depression were identified; 50% scored above BDI cut-off for mild depression; 25% for moderate or severe. The ratio between affective and somatic items indicated true depression. Paternal inheritance, small mutation size and high IQ increased the likelihood of depression. Mean AQ score was 18; one participant scored above the ASD cut-off of 32. 37% scored above BAI cut-off for mild anxiety, 19% for moderate or severe. Large mutation size was related to Anxiety.

Conclusion: A high prevalence of psychiatric problems was identified. Compared with individuals with comparable mutation sizes, but with onset in early childhood, rates of ASD were relatively low. More information about how the behavioural phenotype changes and is related to the progressing mutation will be presented at the meeting.

Keywords: Myotonic Dystrophy type 1, Inheritance mode, Depression, Anxiety, Autism Spectrum Disorder

POSTER 16: The Effects of Intervention Intensity on Acquisition of Communicative Skills in Children with Down Syndrome

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Background: To best meet the needs of learners with Down syndrome requires an approach to intervention delivered at some level of intensity. Intervention intensity refers to the quantity and quality of intervention including the environment in which intervention occurs, number of opportunities, frequency of sessions, and overall duration of intervention.

Method: In a series of preliminary studies we manipulated different aspects of the dose of intervention. Intensity varied in terms of number of opportunities per session, session duration, and spacing of opportunities (inter-stimulus interval). Matched responses within a skill area were randomly assigned to a level of intensity and acquisition compared within single subject experimental designs (multiple-baseline and alternating treatments).

Results: Children showed differential responding to the various intervention intensities. Results show the complexity of examining treatment intensity, revealing issues with respect to aspects of intensity to manipulate and how, selecting experimental designs, measuring multiple outcome measures, and the influence of learner characteristics.

Conclusion: Through this approach we may begin to tease apart the relative contributions of different aspects of intensity on skill acquisition and determine the most effective intensity of early intervention for children with Down syndrome.

Keywords: Intensity, Down Syndrome, Research Design, Intervention

POSTER 17: Developmental Lag of Visuospatial Attention in Duchenne Muscular Dystrophy

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Background: Children with Duchenne Muscular Dystrophy (DMD) present a specific deficit of voluntary attention but to date there has been no clear characterization of their attentional skills. The present study investigated the hypothesis that DMD patients present deficits of both voluntary and automatic visuospatial attention systems and that their performance could be equivalent to that of younger healthy males.

Method: Twenty males (mean age 10y) with diagnosis of DMD, 20 age-matched healthy males (10y, 3 mo) and 20 healthy younger males (7y, 6 mo) were required to perform two visuospatial attention tasks: voluntary and automatic.

Results: In the voluntary task, the performance of the DMD group was significantly worse than that of the age-matched group, and equal to that of the younger controls. In the automatic attention task also, the performance of the DMD patients was less efficient than that of the age-matched controls and equal to that of the younger children.

Conclusion: This study confirms the previous report of voluntary attention deficit in DMD and extends the evidence to include also an automatic attention system deficit. The development level of attention in DMD patients is below that expected for their age and corresponds to a delay of about three years. These results reinforce the statement that the absence of full-length dystrophin expression in the brain, genetically determined in DMD, is associated with a delayed maturation of visuospatial attention skills.

Keywords: Duchenne muscular dystrophy, dystrophin, automatic and voluntary visuospatial.

POSTER 18: Brain Imaging in Prader Willi Syndrome

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Background: Prader Willi syndrome (PWS) temper outbursts are often described as unpredictable episodes of intense emotion that cannot be managed with behavioural intervention alone. Individuals with PWS and parents often describe a 'loss of control' and need for the outburst to run its course before the individual can calm down. This, along with the high frequency of outbursts in PWS suggests that there is a genetic and neurobiological base predisposing individuals with PWS to temper outbursts. To date PWS brain imaging studies have focused primarily on obesity and hyperphagia. The aim of this study is to investigate the structure, connectivity and neurochemistry of the PWS brain in relation to temper outbursts and other maladaptive behaviour.
Method: 12 participants with PWS will be compared to 12 typically developing age- and gender-matched controls, and 12 participants with an intellectual disability of an unknown cause matched by age, gender and IQ. Whole brain magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) will be conducted to investigate possible structural and connectivity abnormalities and magnetic resonance spectroscopy (MRS) will be used to examine GABA, glutamate and glutamine concentrations in the thalamus and prefrontal cortex. Cognitive and behavioural skills will be assessed using the Wechsler Abbreviated Intelligence Scale (WASI), the Developmental Behaviour Checklist (DBC) and a temper outburst survey designed by the authors.
Results: Preliminary findings will be presented at the conference.

Keywords: Prader Willi syndrome, magnetic resonance imaging, diffusion tensor imaging, magnetic resonance spectroscopy, GABA, temper outbursts.

POSTER 19: Phenotypic Differences Between Adults with Autism and Lesch-Nyhan Disease Based on the Five-Factor Model of Personality

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Background: Lesch-Nyhan disease (LND) and autism (ASD) are neurodevelopmental disorders that are both characterized by varying degrees of cognitive dysfunction, aberrant behaviours, and motor neurological abnormalities. However, while persons with ASD show markedly impaired social cognition, those with LND show good social cognition. We sought to determine whether LND and ASD are associated with different personality profiles under the five-factor model of personality.

Method: A knowledgeable informant rated the personality traits of 17 adults with autism spectrum disorder (ASD), 28 with Lesch-Nyhan disease (LND), and 22 healthy controls (HC) using the NEO Personality Inventory or Five-Factor Inventory. The participants (65 male, 2 female) ranged from 18 to 68 years of age.

Results: Multivariate analysis of variance revealed significant ($p<0.0001$) overall effects of group on personality trait ratings. Post hoc tests showed significant ($p<0.05$) pair-wise group differences on 4 of 5 factors. Patients with ASD and LND were rated as higher in Neuroticism and lower in Openness and Conscientiousness than HCs. Neither group differed from HCs in Agreeableness. However, adults with LND were higher in Extraversion than both ASD and HC groups, which did not differ from each other. Finally, adults with ASD were rated as lower in Openness than patients with LND (who were lower than HCs). Stratifying patients by IQ (below versus above 70) had little impact on personality trait ratings in either LND or ASD.

Conclusion: Adults with ASD and LND are rated by caregivers as much less emotionally stable, open to change or novelty, and dependable than healthy adults. They are not rated as less agreeable in general, even if they might be in some contexts. Finally, patients with ASD crave greater routine than those with LND, and patients with LND are much more extraverted than both patients with ASD and most healthy adults.

Keywords: Autism, Lesch-Nyhan disease, personality

POSTER 20: Putative Neural Substrates of Social Cognition in Adults with Autism or Lesch-Nyhan Disease Compared to Healthy Controls

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Background: Lesch-Nyhan disease (LND) and autism (ASD) are neurodevelopmental disorders that share some phenotypic features, such as cognitive dysfunction, motor neurological abnormalities, and self-injury. However, while persons with ASD show markedly impaired social cognition, those with LND show good social cognition.
Method: We explored neural substrates of this phenotypic difference by comparing the gray matter volume (GMV) of three brain regions that are closely linked to social cognition in 8 adults with LND, 10 with ASD, and 11 healthy controls (HC). Each participant received a brain MRI scan and completed the Benton Facial Recognition Test of facial discrimination. Using region-of-interest masks, we extracted GMVs of the amygdala, fusiform, and superior temporal regions from each scan.
Results: Overall, the groups differed in facial discrimination ($F=11.06$, $p<0.001$). Adults with LND performed more poorly than HCs ($d=2.09$) and those with ASD ($d=1.53$). The ASD group performed worse than HCs, though not significantly. Three ANCOVAs (covarying for total gray matter) revealed group differences for the amygdala ($F=4.97$, $p= 0.015$) and fusiform ($F=4.39$, $p=0.023$) but not superior temporal ($p0.05$) region. Post hoc comparisons showed one pattern of group differences (HCASD=LND) for the amygdala and fusiform, and another for the superior temporal region (ASD slightly but not significantly smaller than LND and HC).
Conclusion: Both LND and ASD groups showed significantly reduced GMVs in brain regions that participate in social cognition (Pelphrey *et al*, 2014). Whereas both groups showed reduced amygdala and fusiform GMV, those with ASD showed slightly smaller superior temporal GMV. While abnormalities of facial processing, social perception, and fear response might contribute to common features of the phenotype, the mechanism by which these phenotypes arise may differ. The superior temporal gyrus is particularly relevant to social attention and directed eye contact, impairments of which are more characteristic of ASD than LND.

Keywords: Lesch-Nyhan disease, autism, brain MRI

POSTER 21: Understanding How Cognitive and Emotional Functioning Affect Mental Health in Children With 22q11.2 Deletion Syndrome

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Background: Children with chromosome 22q11.2 deletion syndrome (22q) struggle with impairments in several domains of cognitive functioning, which likely increase stress and anxiety. It is now clear that negative emotional stimuli interact with anxiety and impair attention and inhibition in typical adults and children. We report new data showing how cognitive functioning and emotional processing interact to alter the ability to self regulate in children with 22q.

Method: Children with 22q and typical (TD) children completed tasks where difficulty of judging space and time was varied to find their thresholds for accurate performance. They were also assessed for anxiety and adaptive functioning and completed attention and inhibition tasks where neutral or emotional (happy/angry) faces were used as stimuli. Ability to control attention and inhibit responses was compared for negative or non-negative emotional states.

Results: Children with 22q required much bigger differences between spatial and temporal quantities than did TD children to perform very accurately on the experimental tasks. This disadvantage likely causes stress, anxiety and avoidance in everyday life. We also found that, when negative emotions were presented, cognitive processing was more significantly impacted in the 22q than the TD the group

Conclusion: Impaired spatial/temporal information processing ability likely induces stress, anxiety and avoidance in children with 22q. This reduces learning opportunities and likely creates negative emotional states that further impair these children's ability to function. The degree of coping or struggling might modulate the risk for psychopathology. To help these children cope and not struggle in school and life, it is necessary to adjust cognitive demands to match their abilities. This will help them self-regulate and possibly reduce symptoms associated with diagnoses such as ADHD, anxiety and schizophrenia.

Keywords: 22q11.2, cognition, emotion, anxiety, adaptive function, psychopathology

POSTER 22: Improving Outcome Measures for Fragile X Syndrome Clinical Trials: Development of Fragile X Syndrome-Specific Rating Scales

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Background: Fragile X Syndrome (FXS) is a genetically determined neurological disorder in which affected individuals show intellectual disability to varying degrees and display a variety of associated psychiatric symptoms. High quality outcome measures are a critical component to well-designed clinical trials for individuals with FXS, and these trials also provide an opportunity for assessing novel interventions for Autism Spectrum Disorder (ASD). To complement existing validated measures used in studies of FXS, we designed an experimental scale and a FXS-specific, clinician-rated visual analog scale (VAS) following a paradigm of elaboration from natural history studies of genetically determined orphan conditions. The objective was to develop a Fragile X Syndrome Rating Scale for assessing the FXS phenotype. Development of the scale acknowledged that some but not all individuals with FXS fulfill diagnostic criteria for ASD.

Method: We retrieved 948 Pub Med "hits" relating to "Fragile X Syndrome" and "phenotype". Using this literature and expert input from consulting clinical practitioners and the FRAXA Research Foundation, we derived 10 items specific to Adult and Child FXS phenotype, 6 items relating to FXS plus ASD, and 18 nonspecific items associated with FXS, all rated on 4 point Likert scales. We developed a Domain Specific VAS allowing clinician ratings of behaviors reflective of Repetitive or Stereotyped Behaviors, Speech and Language, Anxiety, Phobias or Social Withdrawal, Motor Performance, Sensory Sensitivity and Cognition. These scales were subject to a preliminary test of face validity.

Results: Data presented show preliminary psychometric properties and feasibility of the Fragile X Syndrome Rating Scale. The relevance of the FXS with Autism subscale will be presented, as will clinician feedback on the Domain Specific VAS.

Conclusion: The Fragile X Syndrome Rating Scale and clinician Domain Specific VAS assess the FXS phenotype and may be useful assessment tools in intervention studies.

Keywords: Fragile X, outcome measures, clinical trials

POSTER 23: Evaluating ASD Characteristics in Males with Sex Chromosome Aneuploidy using the ADOS-2

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Background: The behavioural phenotype of children with sex chromosome aneuploidies (SCA) includes an increased risk for social cognitive deficits, language disorders, and autism spectrum disorders (ASD). Our previous research has shown that ASD occurs in approximately 5–10% of males with XXY/Klinefelter syndrome, 30% of XYY and 45% of XXYY when evaluated using the ADOS and ADI-R. The ADOS-2 was released in 2012 with revised algorithms and the addition of clinical comparison scores that characterize autism severity. The aims of this study were: (1) to determine differences in results when applying the ADOS-2 algorithms, and (2) to further classify and compare ASD severity scores in subgroups of males with SCA.

Method: ADOS results from 121 males age 4–26 with SCA (XXY n=38; XYY n=55; XXYY n=28) were scored using ADOS-2 algorithms and the clinical comparison score was calculated. Results were analyzed using Fisher's exact test and ANOVA with post-hoc Tukey.

Results: The revised ADOS-2 algorithms led to more scores in the ASD range in comparison to the ADOS-G for all SCA subgroups (XXY: from 8% to 13%, XYY from 33% to 43%, XXYY from 43% to 52%). In 88% of cases in which classification changed, the inclusion of stereotyped behaviours in the ADOS-2 algorithms accounted for the change. CSS scores were significantly higher in the XYY and XXYY SCA groups compared to XXY when analyzed both for overall group (p=0.008) and within the subset that met criteria for ASD (p=0.03).

Conclusion: The ADOS-2 algorithms lead to increased results in the ASD range in comparison to the ADOS. Consideration of all aspects of the behavioural phenotype (including language, learning, and social cognitive deficits) of SCA is important when evaluating ASD in males with SCA. ASD severity is increased in males with an extra Y chromosome in comparison to XXY/Klinefelter syndrome.

Keywords: sex chromosome aneuploidy, XXY, Klinefelter syndrome, XXYY, XYY, autism

POSTER 24: The Developmental Course of Effortful Control in Fragile X Syndrome

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Background: Although attention problems are among the most impairing features associated with fragile X syndrome (FXS), few studies have examined longitudinal change and stability of symptoms across early childhood. In Study 1, we examined one component of attention, effortful control, in children with FXS compared to chronological age (CA) and mental age (MA) controls. To inform the developmental course of symptoms, Study 2 examined longitudinal changes in effortful control in an expanded FXS sample.
Method: Study 1 included 14 males with FXS (CA=48.59 months, MA=29.89) and CA (n=14) and MA (n=14) control groups. Study 2 included 41 males with FXS assessed on 1–3 occasions (84 observations). Both studies examined effortful control using both an experimental snack delay task and parent-reported attention problems (Child Behaviour Checklist [CBCL]). Data were analyzed using nonparametric Wilcoxon and Fisher's exact tests (Study 1) and multilevel models (Study 2).
Study 1 Results: Compared to both CA and MA controls, the FXS group failed the snack delay task at higher rates (FXS=57%, CA=0%, MA=7%) and received elevated scores on both CBCL attention subscales, with particular difficulties on items measuring concentration, coordination, and sitting still.
Study 2 Results: Growth analyses indicated the proportion of failed trials in the FXS improved by.60% per month. Higher MA predicted lower proportion of failed trials across ages. Participants who were rated as having more severe attention problems also showed greater behavioural improvements over time.
Conclusion: Effortful control impairments were evident in FXS and persisted in comparison to both CA and MA controls, suggesting difficulties were not solely attributable to intellectual disability. Importantly, more severe parent-rated profiles in FXS did not predict greater deficits over time, but rather indicated greater opportunity for improvement. These findings underscore the importance of complementing cross-sectional comparisons with longitudinal analyses to inform within-individual patterns and growth.

Keywords: fragile X syndrome, effortful control, attention, longitudinal, development, snack delay

POSTER 25: Narrative Skills in Children with 22q11.2 Deletion Syndrome: A Cross-Syndrome and Cross-Linguistic Comparison

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Background: The ability to tell a story involves a number of language and cognitive skills. In order to tell a good story a child needs to understand cause-effect relationships, outline events and use precise vocabulary to convey ideas to aid a listener in comprehending the tale. Children with some genetic syndromes seem to have difficulties acquiring these skills, which has impact on their everyday social communication. Cross-syndrome and cross-linguistic research on this topic is rare.

Method: A cross-syndrome comparison of the narrative skills of Dutch speaking school-aged children with 22q11.2 deletion syndrome (22q11.2 DS) and children with Williams Syndrome is presented. These children are compared with (a) mental age matched control groups of children with an intellectual disability (ID) with unknown etiology, (b) children with ID with unknown etiology and co-morbid autism spectrum disorder and (c) typically developing children. In addition, a cross-linguistic Dutch-English comparison is summarized highlighting story (re)telling characteristics in children with 22q11.2 DS. A fine-grained story analysis based upon samples of the Bus Story Test and the Expression, Reception and Recall of Narrative Instrument was carried out.

Results: The results indicate cross-syndrome and within-syndrome variability in narrative skills. Cross-linguistic profiles are discussed and the impact on everyday communication is highlighted.

Conclusion: Evaluating pragmatic and more specifically narrative language skills across syndromes can contribute to the understanding of the communicative behavioural phenotype. Detailed language assessments may improve intervention targeting communication, and lead to specific parental advices for these groups of children.

Keywords: narrative skills, 22q11.2 deletion syndrome, Williams syndrome

POSTER 26: The Social Behavioral Phenotype in Boys and Girls with An Extra X Chromosome (Klinefelter Syndrome and Trisomy X): A Comparison with Autism Spectrum Disorder

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Background: The present study aimed to gain more insight in the social behavioural phenotype, and autistic symptomatology, of children with an extra X chromosome in comparison to children with Autism Spectrum Disorder (ASD).

Method: Participants included 60 children with an extra X chromosome (34 boys with Klinefelter syndrome and 26 girls with Trisomy X), 58 children with ASD and 106 controls, aged 9 to 18 years. We used the Autism Diagnostic Interview-Revised, Social Responsiveness Scale, Social Anxiety Scale and Social Skills Rating System.

Results: In the extra X group, levels of social dysfunction and autism symptoms were increased, being in between controls and ASD. With regard to early autism symptoms, 19.2 % of the children with an extra X chromosome scored above cut-off on all three ADI-R diagnostic domains of autism symptomatology. Within the extra X group, 25 % had autism traits in the severe range (T>75) based on the SRS. Children with an extra X who did not show high levels of autism symptoms at an early age (retrospectively), still went on to display significantly increased levels of autism traits compared to typically developing children at time of the study. In contrast to the ASD group, the extra X group showed high levels of social anxiety. Across all measures, the social behavioural phenotype was similar for boys and girls with an extra X chromosome, and not dependent on recruitment strategy (i.e. prenatal follow-up cases or referred cases).

Conclusion: The findings indicate that Klinefelter syndrome and Trisomy X can be associated with an increased vulnerability for social dysfunction and symptoms that belong to the autism spectrum. High levels of social anxiety may be distinctive for children with an extra X chromosome and call for studies comparing the underlying cognitive and neural mechanisms driving social dysfunction to children with ASD.

Keywords: Klinefelter, Trisomy X, autism, social functioning, X chromosome, sex chromosomal aneuploidies.

POSTER 27: Social Attention, Affective Arousal and Empathy in Men with Klinefelter Syndrome (47,XXY): Evidence from Eyetracking and Skin Conductance

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Background: Individuals with an extra X chromosome (Klinefelter syndrome) are at risk for problems in social functioning and have an increased vulnerability for autism traits. In the search for underlying mechanisms driving this increased risk, this study focused on social attention, affective arousal and empathy.

Method: Seventeen adults with XXY and 20 non-clinical controls participated in this study. Eyetracking was used to investigate social attention, as expressed in visual scanning patterns in response to the viewing of empathy evoking video clips. Skin conductance levels, reflecting affective arousal, were recorded continuously during the clips as well. Empathic skills, i.e. participants' understanding of own and others' emotions in response to the clips was also assessed.

Results: Results showed reduced empathic understanding, decreased visual fixation to the eye region, but increased affective arousal in individuals with Klinefelter syndrome.

Conclusion: We conclude that individuals with XXY tend to avoid the eye region of faces. Considering the increased affective arousal, we speculate that this attentional deployment strategy may not be sufficient to successfully downregulate affective hyper-responsivity. As increased affective arousal was related to reduced empathic ability, we hypothesize that own affective responses to social cues play an important role in difficulties in understanding the feelings and intentions of others. This knowledge may help in the identification of risk factors for psychopathology and targets for treatment.

Keywords: Klinefelter, empathy, eyetracking, social cognition, arousal, emotion, autism

POSTER 28: Late Diagnosis of 7q11.23 Deletion/ Duplication

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Background: Clinical variability has been described in 7q11.23 deletion/duplication. In many cases physical manifestations may not be apparent at an early age, making diagnosis difficult in infants and young children. We described five adults with intellectual disability (ID) diagnosed using CGH-ARRAY.

Method: Four patients had 7q11.23 deletion (three F) (mean age 33.7 years) and one male patient (37 years) had 7q11.23 duplication. The deletion was inherited from the mother in one case, de novo in the others. Two female were monovular twins. They have been evaluated from clinical, neurophysiological, neuroradiological and psychometric point of view.

Results: Language delay requiring speech therapy was present only in the 4 deleted patients. All the female subjects presented early puberty. All subjects presented hypostaturality (the duplicated patient received GH treatment). No patient presented supravalvular aortic stenosis, but all the female presented a mild mitral prolapse. No hypercalcemia neither iris stellata were detected. Neurosensorial hypoacusia was detected in 3/5 patients. All the patients presented dysmetric saccadic movements. MRI showed Arnold Chiari 1 malformation in the deleted male, and cerebellar tonsillar ectopia in the females. MRI in the duplicated patient documented marked cranio-encefalic asymmetry, hypoplasia of the left hemisphere, hypoplasia of the corpus callosum and of the cerebellar vermis, failure of subversion of the hippocampal structures. Mean TIQ in the deleted subjects was 55,75 (range 45–76) VIQ 57 (45–75) PIQ 56,5 (<45–81) TIQ in the duplicated was 64 (VIQ 69,PIQ 63) VABS documented more marked compromission of the socialization skills in all the subjects. Autism Behaviour Checklist confirmed socialization difficulties in the two deleted twins and in the duplicated one, who showed also aggressive behaviour and obsessive compulsive disorder.

Conclusion: Moderate to mild ID and behaviour difficulties seem to be the more constant symptoms in our 7q11.23 deletion/duplication subjects.

Keywords: 7q11.23 deletion/duplication, intellectual disability, CGH-ARRAY

POSTER 29: Neurodevelopmental Outcomes of Children with Down Syndrome and Congenital Heart Defects

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Background: Nearly half of all children with Down syndrome (DS) are born with a congenital heart defect (CHD), the most significant of which is an atrioventricular septal defect (AVSD). Herein, we compare the developmental trajectories of children with DS + AVSD to age-matched children with DS without CHD (DS-CHD) and examine factors that may impact these trajectories.
Method: We ascertained 58 subjects (17 with DS+AVSD and 41 with DS - CHD). The Bayley Scales of Infant and Toddler Development III was administered at three time points between 3 -24 months of age. We also administered the Parenting Stress Index (PSI) and the Disability-Adapted Infant/Toddler Home Observation for Measurement of the Environment Developmental Delay (HOME-DD).
Results: The DS+AVSD group performed significantly worse compared to DS-CHD on expressive language ($p=0.01$) and gross motor ($p=0.02$) at T_1 only. At T_2, DS+AVSD and DS-CHD did not perform significantly differently in any domains. At T_3, the DS+AVSD performed significantly worse compared to DS-CHD for receptive language ($p=0.008$). Further, the trajectory of expressive language across the three time points significantly differed between DS+AVSD and DS-CHD ($p<0.01$). For the PSI, parents of children with DS+AVSD consistently reported more stress than those of DS-CHD. Groups differed significantly for HOME-DD scores for verbal and emotional responsiveness ($p=0.01$) and total score ($p=0.03$), with the DS + AVSD group having lower overall HOME-DD scores, indicative of a lower quality of the child's home environment.
Conclusion: Our longitudinal data document that children with DS+AVSD have greater developmental deficits, especially in the language domain and higher risk of parenting stress and lower quality of the child's home environment compared to children with DS-CHD. Finding that CHDs may account for part of the variation in language delay and possibly parent-child interactions may be useful for clinicians in providing developmental surveillance and interventional services.

Keywords: Down syndrome, congenital heart defects, neurodevelopment, parenting stress

POSTER 30: The Impact of Child Characteristics on Parental Perceptions of Challenging Behaviour in Adults with Rare Genetic Syndromes - Applying the Self-Regulatory Model

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Background: A high proportion of adults with genetic syndromes display challenging behaviour (CB: self-injury, aggression and property destruction) and live at home with their parents. There is a dearth of research exploring parental perceptions of challenging behaviour in *adults* with genetic syndromes. In this study, the Self-Regulatory Model was applied to explore associations between parental perceptions of CB and parental wellbeing, and whether child characteristics, in particular, markers for behavioural dysregulation (impulsivity, hyperactivity, repetitive behaviour), affected these associations.

Method: This was a cross-sectional correlational study. Sixty-five parents of adults with eight genetic syndromes (Angelman, Cornelia de Lange, Cri du Chat, Fragile-X, Prader-Willi, Smith-Magenis, and Lowe syndromes) completed the Illness Perception Questionnaire-Revised (IPQ-R); adapted to measure perceptions of self-injury, aggression and property destruction. Parents completed questionnaires of parental locus of control, attributions about behaviour and psychological distress. Questionnaire data on child characteristics associated with CB were included in the analysis. Correlations and simultaneous linear regressions were employed.

Results: Inter-correlations between IPQ-R subscales supported the use of the Self Regulatory Model for exploring perceptions of CB. A large proportion of parents endorsed current situational and biological factors as underpinning CB. Few parents endorsed operant reinforcement as a cause of CB. Parental psychological distress was associated with a belief in *child control over parent***.** CB and child impulsivity were independently related to parental perceptions. Higher impulsivity scores were associated with lower parental responsibility for child behaviour and a belief that CB comes and goes unpredictably.

Conclusion: The Self-Regulatory Model is promising for further research on parental perceptions of CB. Research is needed that differentiates between perceptions related to CB (self-injury and aggression), and perceptions associated with markers of behavioural dysregulation. Parental perceptions and behaviour will be discussed in relation to impact on family functioning, interventions for CB and support seeking.

Keywords: Self-Regulatory Model, parental perceptions, challenging behaviour, impulsivity

POSTER 31: Increased Cortical Thinning in Autism Spectrum Disorder During Adolescence: A Longitudinal Study

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Background: Previous magnetic resonance imaging (MRI) studies implicate atypical early brain development, marked by excessive brain growth, in autism spectrum disorders (ASD). However, recent cross-sectional research suggests that cortical development during the adolescent and young adulthood years might also be aberrant. Therefore, we completed the first longitudinal study examining highly localized differences in multiple components of cortical development (i.e., cortical thickness and surface area) among adolescents and young adults with high functioning ASD.

Method: Youths with ASD (n=17) and typically developing (TD) youths (n=18) provided two high-resolution 3-Tesla anatomic MRI scans (n=70) ~2 years apart. Groups were matched on age (scan 1 mean=17 years, scan 2 mean=19 years), IQ (mean=116), sex ratio, and duration between scans. The FreeSurfer image analysis suite was used to quantify vertex-level cortical thickness and surface area values and to complete longitudinal analyses.

Results: There was greater cortical thinning for the ASD group as compared to the TD group, particularly within left posterior fusiform and left superior parietal cortices (cluster corrected $p<.01$). In the ASD group, increased thinning in these regions was associated with greater everyday executive function impairments and more repetitive behaviours, respectively. In contrast, longitudinal changes in surface area did not differ between groups after cluster correction for multiple comparisons. Including IQ and age as covariates, or reanalysing the data including only males did not alter the pattern of findings reported above.

Conclusion: The present study extends prior cross-sectional research by showing increased cortical thinning (in temporal and parietal regions) in ASD during adolescence and into young adulthood. This contrasts with cortical surface area, which appears to exhibit comparable rates of change for TD and ASD individuals during this age range. These findings suggest that there is a protracted window of atypical cortical development in ASD extending beyond early development into late adolescence/young adulthood.

Keywords: autism, brain, longitudinal, cortical thickness, executive function

POSTER 32: SRGAP3-/- Mice Present a Neurodevelopmental Disorder with Schizophrenia-Related and Autism-Related Intermediate Phenotypes

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Background: Mutations in the SRGAP3 gene residing on chromosome 3p25 have previously been associated with intellectual disability. SRGAP3 regulates cytoskeletal dynamics through the RHO protein RAC1. RHO proteins are known to be involved in cytoskeletal reorganization during brain development to control processes such as synaptic plasticity.

Method: To elucidate the importance of SRGAP3 in brain development, we generated Srgap3-knockout mice.

Results: Ten percent of these mice developed a hydrocephalus and died before adulthood. Surviving mice showed various neuroanatomical changes, including enlarged lateral ventricles, white matter tracts, and dendritic spines together with molecular changes, including an increased basal activity of RAC1. Srgap3-/-mice additionally exhibited a complex behavioural phenotype. Behavioural studies revealed an impaired spontaneous alternation and social behaviour, while long-term memory was unchanged. The animals also had tics. Lower locomotor activity was observed in male Srgap3-/- only. Srgap3-/- mice showed increased methylphenidate stimulation in males and an impaired prepulse inhibition in females.

Conclusion: Together, the results show neurodevelopmental aberration in Srgap3-/- mice, with many of the observed phenotypes matching several schizophrenia-related and autism spectrum disorder-related intermediate phenotypes. Mutations of SRGAP3 may thus contribute to various neurodevelopmental disorders.

Keywords: neurodevelopmental disorder, RHO proteins, schizophrenia, autism

POSTER 33: Molecular Subtypes and Neurodevelopmental Status Influence Behavioral Phenotype in Angelman Syndrome

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Background: Angelman syndrome (AS) is a neurodevelopmental disorder caused by lack of expression of the maternally inherited *UBE3A* gene. There are four molecular subtypes, viz. maternal chromosome 15q11q13 deletion, paternal uniparental disomy (UPD), imprinting defects, and maternal *UBE3A* mutations. The NIH Rare Diseases Clinical Research Network Angelman Syndrome Natural History study is a longitudinal study in which individuals with AS undergo medical and developmental evaluations annually. Maladaptive behaviours are frequently reported by parents. We seek to determine whether maladaptive behaviours are influenced by an AS individual's molecular subtype and current developmental functioning.

Method: 129 individuals with AS participated in this study, out of which 15 participants returned for two visits. Maladaptive behaviours were assessed using the Aberrant Behaviour Checklist (ABC). Developmental evaluations were performed using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) or the Mullen Scales of Early Learning and generated a Developmental Quotient (DQ).

Results: Of the 129 participants, 87 had a deletion, 28 had UPD / imprinting defect, and 14 had a *UBE3A* mutation. Mean age was 9.9 years old (SD: 6.2 years) and 53% were female. Participants with a *UBE3A* mutation had higher ABC Irritability (ABC-I) subscale scores than those with a deletion ($p<0.001$); participants with a deletion had higher ABC Social Withdrawal (ABC-SW) lethargy scores than those with UPD / imprinting defects ($p=0.029$). Developmental functioning was positively correlated with the domains of ABC-I ($r=0.311$, $p=.001$), ABC Hyperactivity ($r=0.229$, $p=0.012$) and negatively correlated with ABC-SW ($r=-0.194$, $p=0.033$) and ABC Stereotypy ($r=-0.180$, $p=0.049$). Among the 15 participants who were seen twice, there were no significant changes in their scores on any ABC subscales over time.

Conclusion: In individuals with AS, maladaptive behaviours are strongly influenced by their molecular subtype and current level of developmental functioning.

Keywords: Angelman Syndrome, Behavioural Phenotype, Aberrant Behaviour Checklist, Bayley Scales of Infant and Toddler Development, Mullen Scales of Early Learning

The 2014 SSBP Educational Day

How to Succeed with Children with Intellectual Disability (ID) and Autism Spectrum Disorders (ASD) in a Clinical Setting: Oral Health, Diet and Behavioural Issues

Venue: NYU Kimmel Center, Room 914, 70 Washington Square S, NY 10012

Educational Day Programme: Monday 13th October 2014	
8:00 – 9:00	**Registration & Coffee**
Monday Morning Session : **Working with Children with Special Needs : Autism Spectrum Disorder and Self-injurious Behaviour** (Chair: *Amr Moursi*)	
9:00	**Introductory Remarks** *Mark Wolff,* Professor & Chair of the Academic Chairs of the NYU College of Dentistry
9:15 – 10:30	**Educational Day Talk 1:** *Purnima Hernandez* – Autism Spectrum Disorder: Increasing Successful Outcomes Utilizing Procedures From Applied Behavior Analysis In A Dental Setting
10:30 – 11:00	**Morning Coffee and Snacks**
11:00 – 12:15	**Educational Day Talk 2:** *Nancy Dougherty* – Oral Self-Injurious Behaviors in Autism
12:15 – 13:15	**Box Lunch provided**
Monday Afternoon Session: (Chair: *Patricia Brooks)*	
13:15 – 14:00	**Educational Day Talk 3:** *Lisa Shulman* – Overview and Updates on Autism Spectrum Disorders
14:45 –15:15	**Afternoon Coffee and Snacks**
14:00 – 14:45	**Educational Day Talk 4:** *Emily Jones* – Down Syndrome: Behavioral Phenotype And Early Intervention
15:15 – 16:00	**Educational Day Talk 5:** *Geri Brewster* – The Alimentary Canal and Beyond
	Conference Wrap-up

EDUCATIONAL DAY TALK 1: Autism Spectrum Disorder: Increasing Successful Outcomes utilizing Procedures from Applied Behavior Analysis in a Dental Setting

Hernandez P.
23–00 route 208 South, Fair Lawn, NJ, USA

Dental procedures can be anxiety provoking for many typically developing children and adults. For individuals with Autism Spectrum Disorder (ASD) even a routine cleaning may evoke problem behavior that may interfere with the provision of dental care safely. Core social communications issues such as deficits in joint attention, imitation skills, empathy, and language impairment may render current pediatric dental basic behavior guidance procedures ineffective. Additionally behavioral characteristics such as unusual responses to sensory stimuli and generalization issues may evoke problem behavior during engagement in oral health care procedures both in the dental and home settings. Understanding of behavior and its principles is key in the successful management of any patient in a dental practice. Procedures and tactics from Applied Behavior Analysis have been shown to be effective in a variety of settings in managing problem behavior and for acquisition of adaptive skills. This lecture will discuss home and in-office preparation to help patients acquire the skills to accept routine dental procedures, which increases the likelihood of positive outcomes for patients with ASD. A behavioral interview will be discussed to develop a behavioral profile of a child with ASD and how this profile may be used to reduce problem behavior.

Keywords: Autism Spectrum Disorder, Dentistry, Pediatrics, Behavior, Applied behavior analysis

EDUCATIONAL DAY TALK 2: Oral Self-injurious Behaviors in Autism

Dougherty N.
New York University College of Dentistry

Self-injury is a common and potentially devastating behavior seen in people with autism. The persistence of self-injurious behaviors (SIB) despite intervention can prove frustrating to health care providers as well as parents and caregivers. A significant percentage of SIBs involve the head and neck region, including the mouth and dentition. This talk will provide an overview of SIB with a focus on oral involvement. Theories concerning the etiology of SIB, along with a discussion of various treatment modalities, will be presented.

Keywords: autism, self injury, SIB, oral health

EDUCATIONAL DAY TALK 3: Overview and Updates on Autism Spectrum Disorders

Shulman, L.

Neurodevelopmental Pediatrician, Infant and Toddler Services and the RELATE program, Children's Evaluation and Rehabilitation Center, Rose F. Kennedy Center, Albert Einstein College of Medicine, USA

The talk will cover a review of the DSM 5 ASD criteria, a discussion of the rationale and strategies for making an early diagnosis. We will review the current thinking on the causes of ASD, the components of an evidence-based work up, and medical comorbidities. We will finish up with a discussion of controversial topics relating to ASDs including complementary and alternative medicine interventions, the role of vaccinations, and the increasing prevalence rates.

Keywords: autism, early identification, DSM 5, causes, controversies

EDUCATIONAL DAY TALK 4: Down Syndrome: Behavioral Phenotype and Early Intervention

Jones E.A.
Department of Psychology, Queens College, City University of New York, USA.

The Down syndrome behavioral phenotype is characterized by impairments in communication, motor, and cognitive development, but relative strengths in social development and visual processing. These early impairments may be pivotal behaviors that, when improved through intervention, increase the infants' exposure to new contingencies and result in changes in related skill areas. There is a need for examination of interventions that specifically address these impairments, while building on characteristic strengths. Drawing on the extensive literature demonstrating the effectiveness of behavior analytic interventions to address core areas of impairment in children with autism, we will explore how similar interventions could be developed and tailored for learners with Down syndrome. We will discuss interventions for early communication, motor, and cognitive impairments and review current research about the optimal intervention intensity conditions to employ when implementing these interventions.

Keywords: Down syndrome, intervention, communication, behavior analysis

EDUCATIONAL DAY TALK 5: The Alimentary Canal and Beyond

Brewster G.
Clinical Nutritionist, Private Practice

Ms Brewster will highlight current literature regarding the various microbiota and biofilm communities in the oral cavity and GI tract and how food influences them. She will also discuss the influence of food and the gut terrain on the immune and neurological systems and how these physiological underpinnings can impact behavior. She will also review the studies of the various subtypes of autism and the various gut microbial differences and accompanying GI symptoms as characterized by distinct and less diverse gut microbial compositions compared to non-autistic children. Ms. Brewster will also discuss various therapeutic diets recommended for reducing inflammation, stabilizing blood sugar, controlling seizures, and influencing behavior.

Keywords: microbiota, biofilm, inflammation, ketosis, behavioral-subtypes

SSBP Syndrome Sheets

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

Angelman Syndrome

Alternative names

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

First description

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

Genetic aspects

Angelman syndrome is caused by a disruption of the maternally inherited proportion of chromosome 15q11.2–13 (Clayton-Smith & Laan, 2003; Knoll *et al*., 1989) via four known genetic mechanisms (Jiang *et al*., 1998). Approximately 70% of cases are caused by a de novo deletion (Knoll *et al*., 1989). The deletion can be further categorised as a 'Class I' or 'Class II' depending on the amount of information missing (Sahoo *et al*., 2006), with Class I deletions representing a larger deletion, encompassing Class II. The majority of deletions in Angelman syndrome are Class II, with an estimated prevalence of between 55 and 60% of de novo deletions (Christian *et al*., 1995). 2–7% of cases are caused by Uniparental Disomy (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 non-verbal 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.

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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 well-established 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 first-degree 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 peri-natal 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 gene-environment 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 my 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, non-verbal 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

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Patricia Howlin, 2013

CHARGE Syndrome (or Association)

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, was 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 the mutation in 65–75% of cases, but in >90% of "typical" CHARGE cases based on clinical diagnosis.

Incidence/prevalence

Most common estimate is 1/10,000 births. Recent national surveillance study in Canada found 1/8,500 live births.

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/index.htm - UK support group
- http://www.chargesyndrome.org.nz/ - Australasian support group
- www.chsbs.cmich.edu/timothy_hartshorne - CHARGE research lab focused on behaviour

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Timothy S. Hartshorne, April, 2010

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

Incidence / Prevalence

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

Physical features and natural history

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

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

Available guidelines for behavioural assessment/ treatment/management

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

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André Hanauer, June 2010

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 5th Fingernails".

Genetics and molecular biology
The biochemical and molecular cytogenetic etiology of Coffin Siris syndrome is unknown. McPherson *et al.* (1997) describes a 1 male to 3 females distribution, but Fleck *et al.* (2001) found the distribution to be 10 males to 8 females. Both autosomal dominant and autosomal recessive inheritance have been suggested by various studies (McPherson *et al.* 1997). Studies have examined the candidate region for Coffin Siris. An infant with findings consistent with Coffin Siris syndrome was reported to have an apparently balanced translocation with breakpoints at 1q21.3 and 7q34 (Mcpherson *et al.* 1997). Other research suggested a candidate region for Coffin Siris at 7q32->34 (McGhee *et al.* 2000). A partial trisomy 9p gene change has also resulted in a Coffin Siris phenotype (Temtamy *et al*. 2007). Coffin Siris investigations continue.

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

Physical features and natural history
Minimal clinical criteria for the diagnosis of Coffin Siris syndrome include developmental delay, hirsutism, coarse facies, feeding problems, and hypoplasia or aplasia of the distal fifth digits and nails. Additional characteristics of Coffin Siris syndrome include feeding or sucking difficulties, wide mouth, thick lips, hypotonia, flat nasal bridge with broad nose, sparse scalp hair, thick and laterally placed eyebrows, microcephaly, abnormal ear placement, abnormal or delayed dentition, high arched palate, delayed bone age, coxa valga, frequent otitis media, and respiratory infections (Fleck *et al.* 2001). Head circumference-for-age percentile is generally reported to be less than the 3% to 10%. There are several reports of individuals with Dandy-Walker malformations or Dandy- Walker variants. Seizures are infrequently reported.

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

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

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

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

Useful Websites

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

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Judith Hiemenga, Srinivasan Sathyanarayanan & Joann Bodurtha, 2010

Cornelia de Lange Syndrome

First description and alternative names

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

Incidence/prevalence

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

Genetics

CdLS is caused by a deletion in the NIP-BL gene on chromosome 5 (locus 5p13) in 20% to 50% of cases (Gillis *et al.*, 2004; Krantz *et al.*, 2004; Miyake *et al.,* 2005; Tonkin *et al.*, 2004). Additional mutations on the SMC3 gene on chromosome 10 (Deardorff *et al.*, 2007) and X linked SMC1 gene (Musio *et al*., 2006) are reported to account for 5% of cases. The NIP-BL gene is expressed in the developing skeleton and soft tissue of the limbs, hands, spinal column, face and head including the ear canal, the atrial and ventricular areas of the heart, oesophagus, trachea and lungs (Tonkin *et al.* 2004). Individuals with NIP-BL mutations show large variability in presentation but a larger proportion of these individuals appear to be more severely affected by the syndrome with more severe intellectual disability and limb abnormalities (Gillis *et al.* 2004; Bhuiyan *et al.* 2006). In contrast, mutations in SMC1A and SMC3 have currently been found to result in a milder presentation of the CdLS phenotype with less severe intellectual disability and fewer physical abnormalities (Deardorff *et al.* 2007).

Physical features and natural history

Individuals with CdLS typically have a low birth weight, small stature, upper limb abnormalities (25%) and hirsutism, although those with a milder presentation seem less affected by these problems (Deardorff *et al.* 2007; Kline *et al.* 2007). Distinctive facial features, including: synophrys, long, thick eye lashes, a long and prominent philtrum, a thin upper lip; and a downturned mouth appear characteristic of most individuals with the syndrome (Kline *et al.* 2007). CdLS is associated with many health problems. Some of the most commonly occurring problems include: gastro-intestinal disorders, hearing and eye abnormalities, cardiac and genito-urinary problems. Gastro-intestinal disorders are particularly problematic in CdLS.
Little is known about the life expectancy of individuals with CdLS, although recent research studies have included participants aged 40 years and above (Moss *et al* & Oliver *et al.*, both in submission). Gastro-intestinal disorders associated with CdLS create an increased risk of early mortality due to aspiration, leading to pneumonia in some cases. Early assessment and intervention of gastro- intestinal difficulties is of utmost importance in individuals with CdLS.

Behavioural characteristics

Self-injurious behaviour is generally thought to be more common in people with CdLS than in the general intellectual disability population (Sloneem *et al.* 2009) and reported to be influenced by social reinforcement for some individuals (Arron *et al*., 2006). There is a notable association between self-injurious behaviour and associated medical conditions, particularly gastrointestinal reflux (Luzanni *et al*., 2003). Self-restraint behaviours are common (Hyman *et al*., 2002) and this has led to suggestions that individuals with CdLS may be at risk for self-injurious behaviour to become difficult to regulate. The increased frequency of compulsive like behaviours within the syndrome such as tidying up and lining up behaviours (Hyman *et al.*, 2002; Moss *et al.* 2009) also indicates that individuals with CdLS may be at risk for difficulties with behaviour regulation.

An association between CdLS and autism spectrum like characteristics has recently been recognised (Basile *et al.,* 2007; Berney *et al.*, 1999; Bhyuian *et al*., 2006; Moss *et al.*, 2008). This association with ASD is not solely accounted for by associated intellectual disability (Moss *et al.*, 2008). 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 (Collis *et al.*, 2006).

Early pilot research investigating the developmental trajectory of CdLS has indicated that there may be some age related changes in mood and behaviour in CdLS. In particular, increases in autistic like characteristics, lower mood and increased difficulties in self-injurious and aggressive behaviour have been reported. These changes appear to be particularly prominent during transitional periods for example during a move from school to college or from home to residential placement. Identifying the most appropriate environment and slow introduction to new settings has been found to be helpful for some individuals (Collis *et al.*, 2006)

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).

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.
- Useful websites/associations for more information
- CdLS Foundation UK and Ireland: www.cdls.org.uk
- CdLS World: www.cdlsworld.org
- 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.

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J Moss & C Oliver, July 2010.

Cri du Chat Syndrome

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

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

Genetics and Molecular Biology
CdCS is predominantly caused by a partial deletion on the tip of the short-arm of chromosome 5 (with a critical region of 5p15). The size of the deletion ranges from the entire short arm to the region 5p15 (Overhauser *et al*., 1994). A de novo deletion is present in 85% of cases; 10 to 15% are familial with more than 90% due to a parental translocation and 5% due to an inversion of 5p (Van Buggenhout *et al*., 2000). Neibuhr first identified the specific chromosomal region implicated in the syndrome as 5p15.1–5p15.3, using cytogenetic analysis (Niebuhr, 1978). More recent work has mapped specific critical areas within this region as being responsible for the expression of the core clinical features of the syndrome. For example, the characteristic high pitched 'cat-like' cry from which the syndrome derives its name has been mapped to the proximal part of 5p15.3, the speech delay to the distal part of 5p15.3 and severe intellectual impairment to 5p15.2 (Overhauser *et al*., 1994). This distinctive cry is considered the most prominent clinical diagnostic feature of the syndrome (Mainardi *et al*. 2006). Though relatively rare, CdCS represents the most common deletion syndrome in humans (Cornish *et al*, 2001).

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

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

marked with age.

Self-injurious and aggressive behaviours are a common behavioural feature of CdCS (Collins & Cornish, 2002; Cornish & Munir, 1998; Cornish & Pigram, 1996; Dykens & Clarke, 1997). Self- injury is reported to occur in between 70% and 92% of individuals (Arron *et al*., in review; 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*., in review; Collins & Cornish, 2002). Aggressive behaviour has been reported in between 52% and 88% of individuals with CdCS (Arron *et al*., in review; Cornish & Pigram, 1996; Collins & Cornish, 2002) with an odds ratio of 2.7 compared to a matched contrast group (Arron *et al*., in review). 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).

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.

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P Tunnicliffe, J Moss, & C Oliver, July 2010.

Down Syndrome

First description

Original description was by J. Langdon Down in 1887. Trilogy 21 was first reported in association with Down Syndrome (DS) by Jejune and colleagues in 1958.

Incidence/prevalence

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

Genetics

Three types of abnormality affecting chromosome 21 occur. In about 95% of cases the DS is caused by primary non-disjunction leading to trilogy 21. The origin of supernumerary human chromosome 21 (HSA21) in free trilogy 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 trilogy 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 trilogy 21.

Physical features

Two types of phenotypes are observed in trilogy 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 . 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 tiroiditis, 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 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. Iris Brushfield spots are present in 55%. 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 abnormalities 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.

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 behavioural problems compared to controls with cognitive disability have been described in DS

but more frequent than in sibling or in controls with normal IQ. 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%). 25.6% of adults with DS have 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.

Cognitive characteristics

Cognitive disability is present in all patients with DS. Most children and adult with DS function in the mild or moderate range of intellectual disability. About 10% have a low average-borderline degree of intellectual disability (cognitive impairments that are not so severe as to be classifiable as a learning disability). A minority have a severe or profound cognitive impairment.

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 typically more advanced than nonverbal cognition. Cognitive 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 trilogy 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) may be the cause of dementia in DS.

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%).

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

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Annapia Verri, 2005

Foetal Alcohol Syndrome/ Alcohol Related Neurodevelopmental Disorder

First description and alternative names

FASD 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 (FASD) by Streissguth & o'Malley in 2000 (4,5).

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.

Incidence/ prevalence

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

Physical features and psychiatric characteristics

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

Infants can demonstrate Primary Regulatory Disorders characterized by difficulties in tolerating environmental stimuli (i.e. habituation problems), co-ordinating 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 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 Behavioural Scale (VABS) shows Functional Deficits in daily living skills, socialization and communication (3, 5, 8,9,10, 13).

Brain structural abnormalities

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

Brain neurotransmitter and neurophysiological abnormalities

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

Available guidelines for behavioral assessment/ treatment/management strategies

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

Useful websites /associations for more information

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

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Kieran D O'Malley, Raja Mukharjee, July 2010

Fragile X Syndrome

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. There is enhanced metabotropic glutamate receptor 5 (mGluR5) activity leading to enhanced long term depression (LTD). Treatment with an mGluR5 antagonist is a form of targeted treatment to reverse this neurobiological abnormality and studies are underway to assess treatment efficacy in behaviour and cognition.

Genetic aspects

Sex-linked transmission, 80% of males with a full mutation (>200 CGG repeats) have intellectual disability and the rest having learning and or emotional problems. In full mutation 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 but DNA studies are essential to identify the CGG repeat expansion. Carriers have a small CGG expansion of 55 to 200 CGG repeats. They are typically unaffected cognitively although in approximately 10 to 20% intellectual disability or autism can occur in carriers. 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%, primary ovarian insufficiency in 20% of female carriers and neurological problems in a subgroup of aging male and female carriers. These neurological problems include neuropathy, 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) do not occur in those with a full mutation because they usually do not have elevated *FMR1*-mRNA levels.

Variants of fragile X syndrome (FraX-A) have now been identified. FraX-E is related to a similar abnormal DNA expansion on the X chromosome, slightly nearer the tip of the chromosome's long arm than FraX-A. Initial reports suggest that the characteristic behavioural phenotype associated with FraX-A is not present in these variants, but learning disability may still be associated, as may speech and language difficulties and autism.

Incidence/Prevalence

The allele frequency of the full mutation is 1 in 2500 of the general population, however many 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.

Institutionalised 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. 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, typically in adults. Seizures occur in approximately 30% 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. Aging studies in individuals with fragile X syndrome have documented a high rate of Parkinsonian symptoms in the 50s and beyond.

Behavioural characteristics

Intellectual impairment is very variable and may relate to the molecular findings. Those with higher levels of FMRP, such as females and those with an unnmethylared 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 disorganised speech, poor topic maintenance, and tangential comments. Social impairments, autism and ADHD. Social anxiety with aversion to eye contact is present in the majority of children and adults. Approximately 30% will have autism and an additional 30% will have an autism spectrum disorder (including PDDNOS or Asperger's syndrome). 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 scratching provoked by frustration, anxiety and excitement is 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 behaviour is seen in the majority. Approximately 30% have aggression, and anxiety associated with hyperarousal is a component of this aggression. Hyperactivity is seen in about 80% although attention problems and impulsivity without hyperactivity can be seen especially in girls with the full mutation.

Individuals with fragile X syndrome typically respond well to a stimulant medication after 5 years of age. Selective serotonin reuptake inhibitors (SSRIs) help anxiety and can be used even in those under 5 y, 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 preliminary data suggests improvement in the majority of patients. Arbaclofen, a GABAB agonist has also been shown to benefit patients with fragile X syndrome particularly those with autism or high levels of irritability. Preliminary data from mGluR5 antagonist treatment of adult with fragile X syndrome suggests benefits also.

Resources

- The Fragile X Society, 53 Winchelsea Lane, Hastings, East Sussex, TN35 4LG. 01424 813 147
- The National Fragile X Foundation, P.O. Box 37, Walnut Creek, California, 94597, USA. 800–688–8765

- FRAXA Research Foundation, 45 Pleasant St., Newburyport, MA 01950, USA. 978–462–1866

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Randi Hagerman, September 2010

Klinefelter Syndrome (49,XXY)

First description and alternative names

"Klinefelter Syndrome" or "Klinefelter's Syndrome", sometimes abbreviated as KS, was first described by Dr. Hans Klinefelter in 1942 as an endocrine disorder characterized by small firm testes, hypogonadism, gynaecomastia, and increased levels of follicle-stimulating hormone. Patricia Jacobs determined in 1959 that the clinical phenotype was due to a 49,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. 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.

Available guidelines for behavioural assessment/ treatment/management

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

Useful websites/associations for more information

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

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Rhoshel K Lenroot, 2010

Lesch-Nyhan Disease (LND)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Treatment:

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

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

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

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

Life expectancy:

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

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

First description and alternative names

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

Incidence/prevalence

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

Genetics

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

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

Physical features and natural history

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

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

Other facial features include:

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

Behavioural characteristics

A recent study (Evans *et al*., 2012) reported that the behaviors associated with MWS include a very high rate of oral behaviors (in particular, chewing or mouthing objects or body parts and grinding teeth), an increased rate of repetitive behaviors (such as

switching lights on and off; flicking, tapping or twirling objects), and an under-reaction to pain. Other aspects of the MWS behavioral phenotype are suggestive of a happy affect and sociable demeanour. Despite this, those with MWS displayed similarly high levels of behavioral problems as a control group with a similar level of intellectual disability from other causes, with over 30% showing clinically significant levels of behavioral or emotional disturbance.

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

Neuropsychological characteristics

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

Useful websites/associations for more information

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

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

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 a half of all cases arise in unaffected families.

Incidence/prevalence

About 1 in 3,000 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.

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 is associated with autism spectrum disorder but no robust epidemiological data are available to indicate the exact rates of ASD in NF1.

Cognitive characteristics

The global intellectual abilities of individuals with NF1 fall on a normal distribution, shifted downwards with thirty to fifty percent showing global intellectual disability (IQ<70). In addition, there are high rates of specific neuropsychological deficits including language, visuo-spatial, attentional, organisational and other executive deficits (Rowbotham *et al*., 2009).

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Noonan Syndrome

First description

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

Associated conditions

Noonan syndrome is -incorrectly- also 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 examples of distinct syndromes with partially overlapping phenotypes include Cardio-Facio-Cutaneous (CFC) syndrome, Costello syndrome, and LEOPARD 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). The mutations associated with NS result in a gain of function of SHP-2 (Tartaglia *et al*., 2001). Recently, activating mutations in other genes of the Ras-MAPK pathway (*SOS1, KRAS, RAF1, MAP2K2, NRAS, SHOC2*) were found as the causative mutations in NS. These findings establish hyperactive Ras as a cause of developmental abnormalities seen in NS (Schubbert *et al*., 2006).

Incidence/prevalence

The incidence of NS is estimated as 1 in 1000 to 1 in 2500 live births (Mendez & Opitz, 1985).

Physical features and natural history

Key characteristics are 1) short stature, 2) typical facial dysmorphology (hypertelorism with down- slanting palpebral fissures, ptosis 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 pectus carinatum/excavatum, cryptorchidism, lymphatic dysplasia and a webbed neck. There is substantial variability in expression, and improvement of the physical phenotype occurs with increasing age. The diagnosis is made on clinical grounds, by observation of key features. The most widely used scoring system has been developed by Dr. Ineke van der Burgt (1994). In 2010, this scoring system was updated by adding a few features (Dyscerne, Noonan Syndrome Guideline Development Group, 2010). Neural complications that have been described more frequently in NS are Arnold-Chiari malformations and hydrocephaly. 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 and psychiatric characteristics

A distinctive pattern of behavioural characteristics can not be recognized, although there are indications for an increased risk for behavioural problems in children, characterized by social problems, stubbornness, restlessness, and impulsivity. Classical psychiatric syndromes have only incidentally been described for NS and mainly concern cases of anxiety disorders, obsessive-compulsive disorders and mood disorders. In adults, alexithymia seems to be present more often and with respect to personality, friendliness, agreeableness and a tendency to a socially desirable attitude have been noted. Because of this combination of problems in expressing emotions and amenable

traits, psychopathology may remain underreported (Verhoeven *et al*, 2008; Wingbermühle *et al*, 2009).

Neuropsychological characteristics

Neuropsychological findings show intelligence scores in a wide range, with only a mildly lowered average intelligence. In about one-third of the patients mild mental retardation is found (Allanson, 2005). Verbal and performal capacities are divided more or less equally. Language and motor development are often delayed, but are in general no longer dysfunctional in adulthood. Mild attention problems have been found, as well as problems in executive functioning (i.e. slightly diminished organization skills and compromised abilities to structure complex information). As a result, learning difficulties may be present, requiring special educational attention. As described above, social cognitive functions (recognizing and expressing emotions) may be impaired as well (Wingbermühle *et al*, 2010).

Available management guidelines

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

More information

- www.dyscerne.org. For the 2010 NS guideline PDF-document as developed by the Dyscerne Network of Centres of Expertise for Dysmorphology.
- www.ncbi.nlm.nih.gov/omim/163950. For the information on NS in OMIM, an online database of human genes and genetic disorders.
- www.noonansyndrome.org For the Noonan syndrome support group.

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Ellen Wingbermühle, Ineke van der Burgt, Jos Egger and Willem Verhoeven, June 2010

Prader-Willi Syndrome (PWS)

First description

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

Genetics and molecular biology

PWS results from the absence of expression of the paternal allele of paternally expressed/maternally imprinted genes at the chromosomal locus 15q11-q13 (the PWS critical region). The commonest genetic mechanisms leading to PWS are: a) a *de novo* deletion at the PWS critical region on the chromosome of paternal origin (~ 70% of cases) and b) maternal uniparental disomy (mUPD) of chromosome 15 where both chromosomes are derived from the mother (~ 25% of cases). Other rarer causes of PWS include imprinting centre defects and unbalanced translocations. A number of paternally expressed/maternally imprinted genes have been identified within the PWSCR of which the largest is *SNRPN* (containing the imprinting centre) which codes for a small nuclear ribosomal protein involved in the control of synthesis of proteins related to hypothalamic function. Other paternally expressed/maternally imprinted genes in this region include *Necdin*, *MAGEL2*, *MKRN3*, *IPW*, *PAR-1* and snoRNAs including *HBII-85* and *HBII-438*. As yet, no single gene mutation has been identified as a cause of PWS, other than a mutation of the imprinting centre which itself influences the expression of several genes.

Incidence/prevalence

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

Natural history

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

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

Behavioural and psychiatric characteristics

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. 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).

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). 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.

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 comprehensions, abstract reasoning, recognising emotions and appreciating the concept of time.

Available guidelines for behavioural assessment/ treatment/management

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. Supplementation of the sex hormones assists the development of secondary sexual characteristics and improves bone mineral density and content.

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).

Many features of the behavioural phenotype are thought to be serotonin mediated e.g. skin picking, mood swings, obsessional symptoms. Selective serotonin reuptake inhibitors (SSRIs) may be useful in addressing these problems. Antipsychotic, antidepressant and mood stabilising medications have all been shown to be of benefit in those with severe psychiatric disorders.

Useful websites/associations for more information

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

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Sarita Soni, April 2010

Rubinstein-Taybi Syndrome (RTS)

Prevalence

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

Genetics

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

Physical features

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

Behavioural characteristics

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

Cognitive characteristics

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

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

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

Rett Syndrome/ Rett Disorder / RTT

First description

The first full description of the disorder, by the Viennese neurologist Andreas Rett, was published in 1966.

Genetics and Neurology

The disorder is due to mutations on *MECP2*, (Xq28), a gene which appears to control the activities of other genes. It is expressed throughout the body but particularly in neurones during early brain development and in maturity. The first neurones to be affected, at 10–14 weeks gestation, are those in the brain stem and the Cajal-Retzius neurones which appear to have a role in determining the later function of pyramidal neurones. Since female cells acquire two X chromosomes but use only one in each cell, a wide range of clinical severity is to be expected, according to the proportion of cells using the affected gene. In affected XY males, severe disease is to be expected. The mutation commonly occurs in a sperm, less often in an ovum of an apparently healthy adult and rarely in the zygote leading to mosaic expression. For these reasons the disorder is much more often seen in females than males. Family recurrences are unusual. A figure of 1 in 300 has been proposed. Prenatal diagnosis is possible and mutation testing of parents and female siblings of affected people is advisable. The brain is reduced in size, the cortex being particularly affected with neurones smaller and more closely packed than normal with poor dendritic development but no evidence of degeneration. There is early disturbance of the neurotransmitters serotonin, glutamate and acetylcholine.

Incidence/prevalence

The disorder occurs worldwide with female childhood prevalence at least 1 in 10,000. It has seldom been found in males in whom early deaths have been reported.

Life expectancy/ mortality

The annual death rate in rate in the UK is 1.2% with the most physically disabled at increased risk and the most able commonly surviving into adulthood in good health. A number of sudden deaths (probably at least 20%) are thought to be related to the central autonomic dysregulation. Some deaths are related to epilepsy, to aspiration pneumonia or nutritional difficulties but less severely affected people are likely to die from causes unrelated to the Rett disorder.

Physical features and natural history

Gestation and birth are usually unremarkable and the infant looks normal and makes initial developmental progress. Smiling, sitting, reaching, self-feeding, walking and a little speech may develop although the later milestones tend to be delayed and poorly accomplished. However signs of the disease may also be detected from birth. These are placidity, disturbance of spontaneous movements and reduced exploration by the child. An experienced parent will often recognise a difference as compared with other children. Head circumference, although commonly within the centiles at birth, fails to increase at a normal rate. Developmental stagnation is common around 9–10 months and regression in hand use and communication follows, usually around 1–2 years but occasionally months or even years later. Sleep disturbance and hyperactivity are common. A relatively stable state is then reached and some developmental progress possible. About half of the children can walk and communication and voluntary hand use may improve. Facial appearance is pleasant and not frankly dysmorphic. The fourth metatarsals and metacarpals may be short. Stature is reduced. Epilepsy is present in over 50% and this may be generalised or focal. Early hypotonia gives way to hypertonia with the risk of contractures. Scoliosis develops in most people. Episodes of dystonia are common. Abnormal oral movements may make feeding difficult. Gastric reflux, aerophagy and constipation are common. Poorly regulated central autonomic function leads to disturbed cardio-respiratory control with episodes of breath-holding, shallow breathing, hyperventilation and valsalva breathing, It is important to appreciate the wide range in severity of this disorder, such that

all the above features may appear soon after birth, proving rapidly lethal or may appear late and remain mild.

Cognitive and Behavioural characteristics

Babies are quiet and placid unless in pain. Sleep disturbance, crying spells and withdrawal are usual during the regression period and may persist. After regression there are periods of agitation associated with the labile respiratory rhythm, hyperventilation and breath-holding and aerophagy.

The non-epileptic vacant spells may be accompanied by altered attention, specific movements, pallor, cyanosis or fainting. A range of involuntary movements includes stereotyped movements of the hands with squeezing or patting finger action and voluntary hand use is commonly absent or poor. Bruxism and head banging occur in some people. Injury may result to the individual or to others, from these repeated movements. Although speech is uncommon, non-speech communication is enjoyed, as is quiet face-to-face contact. Intellectual disability is usually severe or profound but the range of severity is wide with a few people only mildly affected and others very severe from birth. A few people can speak, write and draw. Typically people with Rett disorder have charm and show interest and enjoyment of the company of familiar people. Music is particularly enjoyed and the choice of music is often personal and emphatic.

Differential Diagnosis

In most cases the genetic test confirms the clinical diagnosis but around 5% with the classical signs have not been shown to have the mutation and a few cases have been reported with a *MECP2* mutation but without the clinical signs of the disorder, so that the clinical diagnosis is still paramount.

In the very early stages there may be confusion with the degenerative disorders of infancy.

The repetitive movements of the hands has sometimes led to confusion of Rett disorder with Autism and some have recommended classification within the 'autistic spectrum'. However the sociability of people with Rett disorder and their highly characteristic genetic and physical features should make the distinction.

Mutations in the genes CDKL or FOXG1 have been separately reported as leading to very severe developmental disorders, still to be fully characterised but with similarities to Rett disorder.

Management

Progress is being made towards genetic and pharmacological treatment for the Rett disorder thanks to the development of mouse models for the disease, but this is still for the future.

Due to their complex physical and psychological needs these people require careful periodic multidisciplinary assessment and monitoring throughout life. The family or carers also require emotional and physical support. Adequate provision for an individual with Rett Disorder is likely to involve specialist assessment and management of feeding and nutritional, epilepsy and non-epileptic autonomic attacks, movement and posture and communication support. Music therapy is particularly valuable in facilitating interaction. Both child and adult will require a protected environment with safe opportunities for active movement, such as walking, hydrotherapy and riding for the disabled and interesting activities.

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Alison M Kerr, 2010

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 institutions, asylums and forensic psychiatric hospitals (Olanders 1975). In 1974 200,000 newborns were screened 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 one X chromosome is silenced . The extra X chromosome in triple-X women is also silenced through Lyonization. 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 found on the second X chromosome. In cases of an extra X chromosome there is another late-replicating chromosome, so replication time increases during each cell division (Barlow 1973). The extra X chromosome might also have some influence on the nuclear architecture and on epigenetic processes (Kelkar and Deobagkar 2010). The question of 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 (Jacobs 1979).

Physical features and natural history

Tartaglia *et al*. (2010) reviewed the physical findings in triple-X syndrome. Since most of these findings (such as clinodactyly, epicanthal folds or hypertelorism) were minor, the majority of cases remain undiagnosed. Tall stature is common, and especially the arms and legs are longer. Girls have their growth spurt earlier than do controls. Clinically speaking, decreased head circumference is probably the most important common feature; a relationship has been reported between head circumference and level of cognitive functioning (Ratcliffe *et al.* 1994). Motor and coordination abilities seem to be somewhat impaired, 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 exceed the population prevalence numbers. But some disorders seem to be more common in triple-X cases: urogenital anomalies, (partial) epilepsy and Premature Ovarian Failure (POF) (Tartaglia *et al*. 2010).

Behavioural and psychiatric characteristics

Low self-esteem seems to be the most common feature, and shyness is also common in triple -X females. Receptive and expressive language disorders are common. These language disorders may be responsible for social problems, as is challenging behaviour, although this behaviour is less common. Both individuals living in a stable family and controls in unstable families function better than triple-X girls do (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 cases of less severe global intellectual disability. More specifically, there is a higher prevalence of psychotic disorders and adjustment disorders (Olanders 1975). Newborn-

screening studies have not continued to the age at which psychotic disorders could have become noticeable. Further psychiatric research with standardised psychiatric diagnostic tools is warranted in these females.

Neuropsychological characteristics

Neuropsychological, physical and developmental data on triple-X syndrome have recently been reviewed by Leggett *et al.* (2010), Tartaglia *et al.* (2010) and Otter *et al.* (2010).

Data on intelligence are consistent, indicating that Full Scale IQs are almost 20 points lower than would be expected in the family. Whether the girls show problems in reading or arithmetic is not uniformly reported in the case reports. Mild or serious academic problems are quite common. In individual cases support may be necessary and beneficial. Further research is needed to determine whether there are attention problems due to receptive language disorder, auditory processing disorders or attention deficit disorder (ADD). 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 English, French, Spanish, German and Dutch.
- http://www.rarechromo.org/information/Chromosome%20X/Triple%20X%20FTNW.pdf provides a syndrome sheet with information on physical and behavioural developmental issues.
- The KS&A (Klinefelter Syndrome and Associates) website http://www.genetic.org .

Parents and triple-X-girls/women in the United States have the opportunity to meet experts, other parents and triple-X girls/women.

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Maarten Otter, summer 2010

Tuberous Sclerosis Complex (TSC)

First description and alternative names

Even though earlier cases exist, the first detailed description of the disorder was by Désiré-Magloire Bourneville, a French Physician, in 1880 when he described the case of a young girl with severe intractable epilepsy, intellectual disability and a 'confluent vesiculo-papular eruption on her nose, cheeks and forehead'. Neuropathology showed white, potato-like growths in the brain, referred to by Bourneville as 'tuberous sclerosis of the cerebral convolutions'. The term *tuberous sclerosis complex* was introduced by Moolten in 1942 to describe the multi-system nature of the disorder. The abbreviation TSC is used (Kwiatkowski *et al*., 2010).

Genetics and Molecular Biology

Occurs as a spontaneous mutation in 70% of cases. Autosomal dominantly inherited in the remaining 30% of familial cases. The disorder is associated with mutations in one of two genes, *TSC1* (on 9q34) or *TSC2* (on 16p13.3). The TSC1–2 protein complex acts as a heterodimer linking 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).

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, bones, 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 (Roach *et al*., 1998). 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 (AML) may be causes of death.

Behavioural and psychiatric characteristics

Tuberous sclerosis complex 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 (Prather & de Vries, 2004; 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 (Prather & de Vries, 2004; 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).

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 (de Vries, 2010), but these should not be used outside formal trials.

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

Useful websites/associations for more information

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

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Petrus de Vries, August 2010
Revised 10/07/2013

Turner Syndrome

First description

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

Genetics and molecular biology

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

Incidence and prevalence

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

Physical features and natural history

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

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

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

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

Because of the small stature, which is almost invariable relative to the height of the parents, it has become usual to treat with human growth hormone.

The average stature after treatment is increased by a few centimeters, although the condition is not associated with growth hormone insufficiency and high doses are needed to achieve any significant benefit. There is no evidence that treatment with growth hormone benefits psychosocial adjustment, although it may improve self-esteem.

Behavioural and psychiatric characteristics

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

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

Neuropsychological characteristics

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

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

Available guidelines for behavioural assessment/ treatment/management

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

Useful websites/Associations for more information

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

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David H Skuse, 2014

Velo-Cardio-Facial Syndrome

Alternative names

22q11.2 deletion syndrome, Sedlackova syndrome, DiGeorge syndrome, Shprintzen syndrome, Conotruncal anomaly face syndrome.

Genetics / aetiology

85–90% of individuals with VCFS are found to have an interstitial deletion of approximately 3 million bases pairs on the long arm of chromosome 22 although smaller deletions have also been reported. In a minority of individuals, no deletion can be detected. Several groups have reported that the T-box transcription factor gene Tbx-1 is responsible for the cardiovascular defects found in VCFS using a mouse model of the disease (2–4). Other genes deleted in the 22q11 region include COMT (5) and PRODH (6).

Incidence / prevalence

It is the most frequent known interstitial deletion syndrome found in man and occurs in approximately 1 in 4000 live births (1).

Physical phenotype

The usual features are a characteristic facial appearance (a long face, small ears with over-furled helices, upslanting eyes, a widened nasal bridge with a prominent nasal tip and a small mouth), cleft palate/ cleft lip and congenital heart disease (particularly conotruncal heart defects). It is important to stress that there is considerable variability of expression of the phenotype, even within members of the same family. In addition to the usual physical features, over 100 other physical features of the syndrome have also been reported.

Psychiatric/behavioural disorder

Several common temperamental features have been described in studies of children and adolescents with VCFS including behavioural excitation, an exaggerated response to threatening stimuli, and an enduring fearfulness of painful situations (7). In addition, children with VCFS are reported to have poor social interaction skills, a bland affect with minimal facial expression, attentional difficulties and high levels of anxiety and depression (7–8). As the first cohort of children with VCFS was followed into adolescence and early adulthood, evidence began to accumulate for a high prevalence of major psychiatric disorder in these individuals. Specifically, several studies have reported high rates of bipolar disorder (64%), attention deficit disorder (ADD/ADHD) (36%) and psychosis (10–30%) (9–11). In a large series of VCFS adults, Murphy and colleagues (1999) found that VCFS individuals have very high rates of psychosis (30%), the majority of which was schizophrenia (25%) (12). Higher rates of autistic spectrum disorder in VCFS have also been reported (13).

Neuropsychological deficits

Early reports of children with VCFS described language abnormalities including immature language usage, poor development of numerical skills and significant impairments in reading and spelling (14). In a study of 37 VCFS children, Swillen and colleagues (1997) reported a wide variability in intelligence ranging from moderate learning disability to average intelligence with a mean full-scale

IQ (FSIQ) of approximately 70 (15). 45% of individuals (n=17) had a learning disability, the vast majority (82%) of which was mild. Similarly, Moss and colleagues (1999) reported that the mean FSIQ of their sample of 33 children and adults was 71, with 17 (52%) of their sample demonstrating learning disability (16). VCFS individuals with a familial deletion are found to have a lower mean FSIQ than individuals with a de novo (non-inherited) deletion (15).

A specific neuropsychological profile has also been described in children with VCFS with verbal IQ exceeding performance IQ on tests of general intellectual functioning (15–16). This discrepancy may relate to difficulties in planning ability, visuospatial ability and non-verbal reasoning in addition to deficits in novel reasoning and concept formation.

More recently, deficits have been highlighted in memory regulation and VCFS individuals are more likely to demonstrate false recognition deficits in the

suppression of irrelevant content. Trait-like deficits of memory regulation may also occur in VCFS and can be observed during the retrieval stage, while selective encoding remains intact (17).

Further elaboration of numerical skills in children with VCFS showed that they had preserved number reading abilities and retrieval of arithmetic facts indicating that the verbal subsystem is not impaired in VCFS. In contrast, children with VCFS showed difficulties in number comparison, the execution of a calculation strategy and word problem solving, all of which involve the semantic manipulation of quantities. This may provide evidence for a specific deficit in the quantity subsystem in children with VCFS (18).

Brain structural abnormalities:

Neuroanatomical differences reported in people with VCFS include an increased incidence of white matter hyperintensities and developmental midline abnormalities (e.g. septum pellucidum defects) (19–20) and a significant reduction in volume of posterior brain structures (especially in the cerebellum, temporal and parietal lobes), which is largely accounted for by decreased WM volume (20–22). Further, these quantitative neuroimaging studies report relatively reduced volumes of total brain, left parietal lobe grey matter and right cerebellar white matter volumes but increased volumes of both frontal lobes, mid-sagittal corpus callosum areas and enlarged Sylvian fissures. In terms of Diffusion Tensor Imaging, people with VCFS are reported to have a significantly reduced fractional anisotropy of white matter in frontal, parietal and temporal regions and, in WM tracts connecting the frontal and temporal lobes (23).

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Kieran C Murphy & Frederick Sundram, September 2008

Williams Syndrome (also known as Williams-Beuren Syndrome)

First descriptions

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

Genetic aspects

Williams syndrome is a genetically determined neurodevelopmental disorder caused by a heterozygous deletion of about 1.6 Mb (approx. 25–28 genes) on chromosome 7 (7q11.23). A deletion of the elastin gene (ELN) which occurs in >99% of individuals with WS) is associated with congenital heart disease and connective tissue abnormalities e.g. hernias and premature ageing of the skin. Several genes are also associated with the intellectual disabilities and cognitive deficits observed in WS, including GTF2I, LIMK1 and CYLN2 (see Skwerer & Tager-Flusberg, 2011, for review) Transmission is autosomal dominant and although most cases are de novo occurrences, some instances of parent to child transmission have been reported (Donnai & Karmiloff-Smith, 2000).

Incidence

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

Physical phenotype and natural history

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

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

Behavioural and psychological characteristics

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

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

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

Further information

- www.williams-syndrome.org.uk

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Patricia Howlin, 2014

Wolf-Hirschhorn Syndrome

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

Genetics and Molecular Biology

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

Prevalence and Mortality

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

Physical Features

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

Behavioral and Neuropsychological characteristics

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

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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,XXY is currently estimated at approximately 1/1000 males. As it is typically not associated with marked phenotypic characteristics it is frequently undetected.

Physical features and natural history

Physical phenotypic differences associated with XYY syndrome are usually mild. Boys have increased growth velocity during childhood, and adult height is usually increased approximately 7cm above what is expected. Puberty, testicular function and fertility are usually normal.

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, 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 symptoms, although these were within clinically referred populations and may not be indicative of individuals with XYY syndrome overall.

Neuropsychological 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. Speech delay is common and many boys require speech therapy and special education. Reading may be particularly affected. Delayed motor development and impaired fine and gross motor function have been reported. 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.

Available guidelines for behavioural assessment/ treatment/management

Formal guidelines are not currently available. Current recommendations usually include neuropsychological assessment and early intervention for learning disorders or behavioral problems.

Useful websites/associations for more information

- KS & A (Knowledge, Support and Action), www.genetic.org
- www.rarechromo.org

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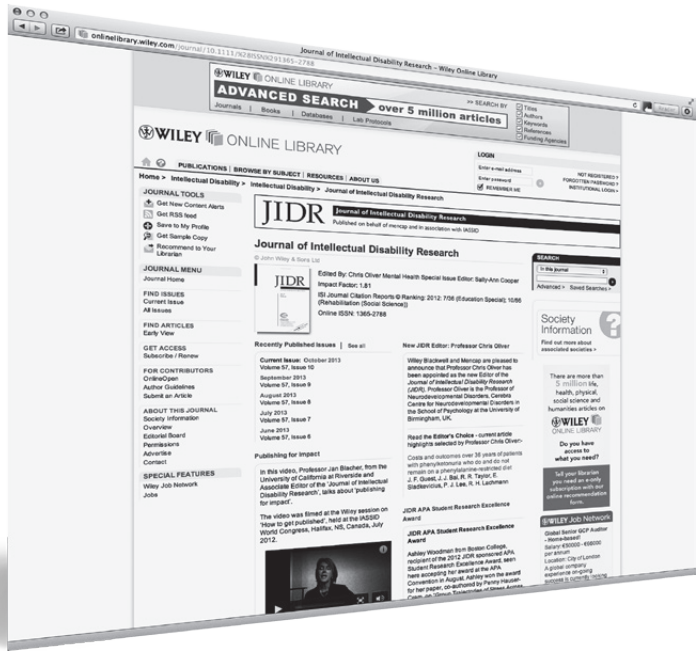

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