15th SSBP International Research Symposium

Social Phenotypes in Genetic Disorders

11–13 October 2012 • Leuven, Belgium

The Society for the Study of Behavioural Phenotypes

The 15th SSBP International Meeting

Social Phenotypes in Genetic Syndromes

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Welcome

Dear colleagues,

Welcome to the 15th SSBP International Research Symposium and Educational Day. We are honoured to be able to host this meeting in the historical city of Leuven, and hopefully be able to show you some of the facets of its dynamic university.

This year the Society is also celebrating its 25th anniversary and the Committee of the SSBP, under the guidance of its President, Dr Martin Bax, and its chairman, Professor Petrus de Vries, have arranged a session to reflect on the activities of the SSBP the last 25 years.

The theme of this meeting is 'Social Phenotypes in Genetic Disorders', a topic which falls directly in line with the aims of the Society and is relevant to many of the patients and families consulting our clinics today. We hope to address the intricacies of the subject through keynote talks by distinguished invited speakers. Starting with 'What is the Social Phenotype of a Developmental Disorder', exploring 'The Social Brain' and discovering 'The Genetics in Autism', you will journey through 'Targeted Therapies' and 'Refining the Social Phenotypes of Genetic Disorders' and to culminate with 'Developmental Intervention within the Social Phenotype'.

We are delighted to have you participating in the sessions and look forward to stimulating intellectual discussion.

KU Leuven

We take a glimpse at the past...

Situated in the heart of Western Europe, KU Leuven has been a centre of learning for almost six centuries. Founded in 1425 by Pope Martin V, KU Leuven bears the double honour of being the oldest extant Catholic university in the world and the oldest university in the Low Countries.

In its early days, our university was modelled on the universities of Paris, Cologne, and Vienna. In a short time, it grew into one of the largest and most renowned universities in Europe. Its academic fame attracted numerous scholars who made valuable contributions to European culture. In the sixteenth century the humanist Desiderius Erasmus lectured here, where he founded the Collegium Trilingue in 1517 for the study of Hebrew, Latin, and Greek - the first of its kind. The tutor of the young emperor Charles V, Adriaan Cardinal Florensz of Utrecht, was a professor here before being elected in 1522 as the last non-Italian Pope before Pope John Paul II. The philologist, legal scholar, and historian Justus Lipsius taught here for many years.

The mathematician Gemma Frisius helped to lay the foundations of modern science and tutored many famous scientists, including the cartographer Gerard Mercator, whose map projection is still in use, the botanist Rembert Dodoens, and the father of modern anatomy, Andreas Vesalius. In a later period, the theses of the Leuven theologian Cornelius Jansenius provoked a large and heated controversy both inside and outside the Church. In the seventeenth and eighteenth centuries, KU Leuven was an important training centre for Roman Catholic intellectuals from Protestant countries. At the end of the Age of Enlightenment, in 1783, the chemist Pieter Jan Minckelers discovered the suitability of coal gas for lighting. In the nineteenth century, at the instigation of Pope Leo XIII, KU Leuven became an important centre of Thomist philosophy.

Not all has been trouble-free, though, in the university's illustrious history. It has had its share of difficulties during the various social and political upheavals in this region from the sixteenth to the nineteenth centuries. More recently, the two World Wars of the twentieth century deeply scarred the university. In 1914, the University Hall with its precious library was set in flames by German troops and 300,000 books were reduced to ashes. Afterwards, an international solidarity campaign with a major American contribution helped construct a new library on the present Ladeuzeplein. Unfortunately, this library was burned down in 1940 during the Second World War and this time only 15,000 of its 900,000 volumes were saved. Since then, the university library, and in fact the entire university, has undergone a thorough reconstruction.

The university is located in Flanders, the Dutch-speaking northern part of Belgium. With the Dutch language's steady rise to renewed prominence, 1968 saw the university split into two new universities. The French-speaking Université Catholique de Louvain moved to the newly built campus in Louvain-la-Neuve. The Dutch-speaking Katholieke Universiteit Leuven remained in the historic town of Leuven.

...to understand the present and face the future

Such a rich history of nearly six hundred years has provided KU Leuven with its own dynamic international dimension. Today, international co-operation is regarded as essential for a modern university. Top-level research is judged according to international standards and implies interaction, co-operation, and exchange, both of researchers and results. As such,

KU Leuven is a charter member of the League of European Research Universities, and European surveys rank KU Leuven among the top ten European universities in terms of its scholarly output. Likewise with regard to teaching, several quality surveys demonstrate that KU Leuven stands on par with internationally respected institutions in a large number of fields.

This academic reputation attracts students from all over the world. KU Leuven has been involved in the Erasmus student exchange programme since its launch in Europe in the late 1980s; the growing success of the Erasmus programme later on led to the launch of the Socrates programme, and today the University of Leuven has over 300 contracts under this programme. Each year around 600 international Erasmus students spend part of their study programme in Leuven, while more than 500 of our students share the same European experience at another university. The TEMPUS-PHARE programme was set up for students and researchers from Eastern Europe, while contacts with universities in the former Soviet Union are being built up through the TEMPUS-TACIS programme. The co-operation with universities in Latin America falls within the scope of the ALFA programme.

Besides these exchange programmes, the university has set up a number of international academic programmes aimed both at Belgian and international students. Unlike the regular Dutch-language programmes, the international academic programmes are taught in English. Most of these programmes confer master's degrees: full bachelor's degree programmes in English are offered only in the fields of theology and philosophy.

At present, KU Leuven caters to more than 40,000 students, around 15% of whom are international students from more than 120 nations. In terms of its personnel, there are 6,781 academic staff, 3,219 administrative and technical staff, and 8,775 university hospital staff members. On the academic side, the university is composed of fourteen faculties, fifty departments and about 240 sub-departments. Further, its network of thirty auxiliary libraries now houses a total of 4.3 million volumes, 14,500 magazines and journals, and 7,492 full text electronic magazines. And concerning its medical facilities, KU Leuven supports five hospitals and three affiliated hospitals, with a total of 2,057 hospital beds for the acutely ill.

KU Leuven's rich history can be read not only from the city's street names, but also from the dozens of historical university buildings. The medieval cloth hall, near the famous gothic town hall, is the university's administrative centre. The beautifully restored Great Beguinage houses students and guest professors. And numerous other old colleges and residence halls give Leuven the stylish face of a university town with a tradition. Where else can you find a university within a town, and indeed a 'town' within a university, so dynamically integrated? Its rich historical tradition continues to serve as a solid foundation for top-level research and centres of academic excellence. To this day, KU Leuven thrives as a bustling student town with a strong international allure, where various cultures meet and experiences are exchanged.

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

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

Forthcoming Meetings of the SSBP

2013	Stellenbosch, South Africa	16th International
2014	New York, USA	17th International

The SSBP Executive Committee

Elected President	Dr Martin Bax (London) (m.bax@imperial.ac.uk)
Chair	Professor Petrus de Vries (Capetown) (petrus.devries@uct.ac.za)
Hon. Secretary	Professor Leopold Curfs (Maastricht) (curfs@msm.nl)
Hon. Treasurer	Professor Christopher Howe (Cambridge) (ch26@cam.ac.uk)
Committee	Dr Honey Heussler (Brisbane) (h.heussler@mater.org.au)
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	USA (East Coast) - Professor James Harris (Baltimore) (jharrisd@jhmi.edu)
	USA (West Coast) - Professor Randi Hagerman (Sacramento) (randi.hagerman@ucdmc.ucdavis.edu)
Administrator	Dr Heather Windram (hfw30@cam.ac.uk)

Tom Oppé and the Tom Oppé Distinguished Lecture

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

2012	Chris Oliver
2011	Tony Holland
2010	Randi Hagerman
2009	Alcino Silva
2008	Hans-Christoph Steinhausen
2007	Petrus J de Vries

Chris Oliver

Chris Oliver is Professor of Neurodevelopmental Disorders at the University of Birmingham and director of the Cerebra Centre for Neurodevelopmental Disorders. He trained as a clinical psychologist at Edinburgh University before completing a PhD on self-injurious behaviour in people with intellectual disability at the Institute of Psychiatry, London. He is currently researching early intervention, behaviour disorders in people with severe intellectual disability, behavioural phenotypes in genetic syndromes, neuropsychological and behavioural assessment for people with severe intellectual disability and Alzheimer's disease in adults with Down syndrome. Sadly, he supports Luton Town Football Club.

Patricia Howlin and the Patricia Howlin Prize Lecture

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.

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.

An award certifcate will be presented to the winner during the SSBP Research symposium.

Patricia Howlin Lecturers

2012	Sheena Grant
2011	Leah Bull
2010	Debbie Allen

Acknowledgments

We are grateful for all the help and support received during the preparation of this Meeting, and will receive throughout and after the event. Without the endless hours of reflection, of planning, of executing and of revision by numerous willing minds, this Meeting would not have so smoothly arrived where it is today.

Thank you to Mrs Marleen Van Leemputten, Mrs Rita Logist and Mrs Veerle Mattheus from the Department of Human Genetics at the KU Leuven for their constant attentiveness, their willingness to help and their patience in sharing their administrative skills and networking knowledge in support of the Local Organizing Committee.

Dr Heather Windram, last year you took on an enormous challenge in accepting to be the Administrator at the SSBP office in Cambridge. You have mastered all the facets of the Society. Through your attention to detail and sensitivity to every need, you have been a great support every step of the way. Thank you.

We are grateful to the members of the Local Organizing Committee, its Scientific Committee, and the SSBP Committee for their input in bringing us all here today. Thank you all for coming to Leuven to share your knowledge. See you in Stellenbosch in 2013!

Ann, Thomy and Petrus

Sponsors

SSBP 2012 is extremely grateful to its sponsors:

Fonds Wetenschappelijk Onderzoek Vlaanderen
The Scientific Research Foundation of Flanders
http://www.fwo.be/Default.aspx

Foundation Marie Marguerite Delacroix
http://www.stichtingdelacroix.be

Keynote Speaker Profiles

(in order of presentation)

Eric Legius

Eric Legius is a clinician scientist and currently the Head Department of Human Genetics at the KU Leuven.
His research is targeted towards neurofibromatosis type 1 and related conditions. The research group contributed successfully towards the understanding of the molecular etiology of a number of tumors in NF1 such as benign neurofibromas, gastrointestinal stromal tumors (GIST), and glomus tumors. The group is also involved in the molecular and cognitive characterization of the NF1 microdeletion region.
In 2007 his research team identified a new condition resembling neurofibromatosis type 1, now known as Legius syndrome (autosomal dominant condition caused by a heterozygous mutation in *SPRED1*). The group is using animal models (mouse and Drosophila) to gain insight in the importance of SPRED and the RAS-MAPK pathway for cognition.
Other ongoing projects are NF1-related oncogenesis (molecular oncology of malignant peripheral nerve sheath tumors) and a clinical trial to improve cognitive aspects in children with NF1 using Simvastatin treatment (NFSIMCODA-trial together with Erasmus University Rotterdam).

He is recipient of the Collen Research Foundation, Blackwell Public Service Award for neurofibromatosis (NNFF), Scientific Prize NFKONTAKT, NF-Holland Award, Sidmar prize from the Royal Academy of Medicine, Belgium.

Ype Elgersma

Prof. Ype Elgersma received his PhD '*Cum Laude*' in 1995 at the University of Amsterdam on the study of peroxisome biogenesis and protein trafficking in *S.cerevisae.* He then worked as a Post-doc in UC San Diego, Cold Spring Harbor Laboratory and UC Los Angeles, USA. During this time he switched his interest towards Neuroscience, and received training in the laboratory of Alcino Silva.
In 2002, Ype Elgersma started his own laboratory at the Department of Neuroscience, Erasmus MC University Medical Center in Rotterdam. The Netherlands. His laboratory seeks to get insight in the molecular and cellular basis of cognitive disability, and to use this knowledge to develop treatments. The laboratory is particularly interested in developmental disorders that are associated with learning disabilities, with a specific focus in disorders in the RAS-ERK and TSC-MTOR pathways and in Angelman Syndrome. Central to the approach is the use of genetically engineered mice. These mice are studied at the biochemical, cellular and behavioral level. In this way the lab hopes to understand the specific function of these genes and proteins in neuronal function, and to develop therapies.
To translate these findings to the clinic, Ype Elgersma was co-founder of the *ENCORE* expertise center for neuro-developmental disorders, which includes the national referral center for TSC, Angelman Syndrome and Neurofibromatosis. Several clinical trials are currently

ongoing in this center. The *ENCORE* expertise center is an inter-departmental collaboration involving 9 departments, but with a particular strong participation of the departments of Pediatrics, Child Neurology, (Child) Psychiatry, Clinical Genetics and Neuroscience. Ype Elgersma is currently the scientific director of *ENCORE.*

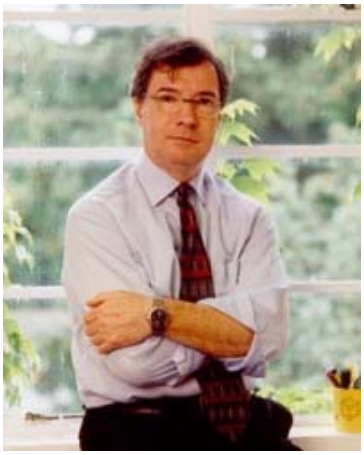
Annick Vogels

Annick Vogels obtained her Medical Degree at the KU Leuven and trained in child psychiatry at the University Hospitals of Leuven and the Royal Hospital for Sick Children in Bristol. She is currently a child psychiatrist and is specialised in children and adults with a genetic disorder and/or intellectual disability and psychiatric problems.
Her main interest is the behaviour and psychiatric problems in Prader-Willi Syndrome. In 2001, she completed her PhD on “Psychosis in Prader-Willi Syndrome” at the KU Leuven. Her research interests remain in that of Prader-Willi Syndrome with an emphasis on their behaviour and psychiatric problems, and also other children and adults with a dual diagnosis of intellectual disability and psychiatric problems.

Kris Dierickx

Kris Dierickx is full professor of biomedical ethics and a staff member of the Centre for biomedical ethics and law, Faculty of Medicine (KU Leuven, Belgium). His research and publications focus on ethics in genetics, research ethics, regenerative medicine, and biobanks.
Kris Dierickx was also the coordinator of the EC funded FP6 project GeneBanC :Genetic bio and dataBanking: Confidentiality and protection of data. Towards a European harmonisation and policy.
He was and is partner in several national and international research consortia (eg. EuroPHEN, GeneBanC, EuroCareCF, STPES, Eurogentest, Disk Regeneration).
Kris Dierickx is member of several ethics committees, editorial boards, and acts as an ethics reviewer for FP7 projects and ERC grants.

Anthony J. Holland



Tony Holland trained in Medicine at University College and University College Hospital, London, qualifying in 1973. After some years in General Medicine he then trained in Psychiatry at the Maudsley Hospital and Institute of Psychiatry in London. He held a senior academic post at the Institute of Psychiatry from 1987. In 1992 he moved to the Department of Psychiatry at the University of Cambridge and in 2002 he was appointed to the Health Foundation Chair in Learning Disability at the University of Cambridge.

He leads the Cambridge Intellectual and Developmental Disabilities Research Group (www.CIDDRG.org.uk) in the Department of Psychiatry, University of Cambridge. This is a multidisciplinary group that undertakes a broad range of research relevant to people with intellectual disabilities. His specific interests include the eating, behavioural and mental health problems associated with having Prader Willi Syndrome; the relationship between Down's syndrome and Alzheimer's disease, and also clinical/legal issues relevant to the needs of people with intellectual disabilities. He leads one of the clinical research themes of the NIHR Collaborations in Leadership for Applied Health Research and Care (CLAHRC) for Cambridgeshire and Peterborough that is specifically investigating the needs of adults with learning disabilities and acquired brain injury, and the nature and function of specialist services that support them. In 2010 he was elected a Fellow of the Academy of Medical Sciences and appointed a Senior Investigator by NIHR. He is editor of the Journal of Intellectual Disability Research (JIDR).

Ilse Noens

Ilse Noens is associate professor at the Parenting and Special Education Research Unit of the KU Leuven, staff member of the interdisciplinary KU Leuven Autism Research (LAuRes) consortium, and visiting researcher at the Psychiatric and Neurodevelopmental Genetics Unit of Massachusetts General Hospital in Boston. Her primary research area concerns autism spectrum disorders. A first line of research focuses on the antecedents, nature and consequences of autism spectrum disorders and other developmental disorders in an educational perspective. A second, more applied research line involves the development and evaluation of diagnostic instruments and intervention strategies, e.g. regarding augmentative communication and parenting behaviour.

Peter C. Mundy

Peter Mundy is presently Professor and Lisa Capps Chair in Neurodevelopmental Disorders and Education at the School of Education and Department of Psychiatry and Behavioural Sciences, University of California at Davis, and Director for Educational Research at UC Davis M.I.N.D. Institute. He is also Adjunct Professor of Psychology at the University of Miami, Florida. Professor Mundy had read for his BA in Psychology at Stockton State College, New Jersey before obtaining an MS and PhD in Developmental Psychology at the University of Miami. His Postgraduate Research and Clinical Fellowships were carried out at the UCLA Neuropsychiatric Institute. Professor Mundy is a member of various advisory committees, review panels, Editorial Boards and presently chairs the Data Safety Monitoring Board for NIMH collaborative RO1 "Interventions for Communication in Autism". Recent awards include The Princeton Lecture Series Fellowship award (2009), The Leonard and Frances Blackman Lecture Award (2010), The Simpson-Ramsey Lecture Award (2010) and in 2011 his publication on 'The Early Social Communication Scales' was selected by Autism Speaks for the recommended list of

measures appropriate for clinical trials with ASD in the areas of Social Communication and Repetitive and Restricted Behaviors.

Professor Mundy is presently investigating virtual reality applications for attention and learning in children with autism and ADHD, the hypothesis being that impaired social attention inhibits learning, academic success and social success in 8 to 18 year old students with ASD. He is developing new methods for social-cognitive neuroscience research and evaluation with higher functioning children with autism, whilst also looking at biomarkers of processes that lead to individual differences in the social learning of HFA children. He is interested in developing a curriculum of instruction to address impairments in reading comprehension in middle school students with ASD and examining the effectiveness of these methods in a large randomized control study. A study of the degree to which preschool development, intervention, neural growth, RNA expression and immunological factors help to explain variance in elementary school learning and academic competence in students with ASD is also being planned.

Kevin A. Pelphrey

Kevin Pelphrey is presently the Harris Associate Professor of Child Psychiatry at the Yale Child Study Center, Yale School of Medicine in New Haven, Connecticut, USA. He also holds an appointment as Faculty member at the University College London and the Anna Freud Center in London , UK. He had obtained his BA in Psychology and in Architecture at the North Carolina State University and his PhD in Psychology at the University of North Carolina at Chapel Hill thereafter which he was a post-doctoral fellow in Neuroscience at Duke University. He has received numerous awards including the Harriet Rheingold Fellowship, The John Merck Scholars Award in the Biology of Developmental Disabilities in Children (2006), The Richard Newton Breakthrough Research Award (2008) and the Boyd McCandless Award for a distinguished early career theoretical contribution in Developmental Psychology (2008). In 2008 he was appointed as a Chartered Member of the child Psychopathology and Disabilities Study Section of the NIH, and in 2011 elected as Treasurer of the International Society for Autism Research.

Professor Pelphrey's research thrust, amongst others, is in identifying sex differences in brain structure, function, connectivity and temporal dynamics in autism spectrum disorders, characterizing associations between DNA sequence and copy number variants and brain structure and function in female ASD and female typically developing children versus male counterparts. He is also investigating brain differences in structure, function and temporal dynamics in relation to heterogeneity in ASD behaviour and genetics. Using multi-modal neuro-imaging he is investigating biomarkers of risk for autism. Longitudinal functional neuro-imaging and eye tracking studies are used to identify the development of anxiety disorders in children.

Thomas Bourgeron

Thomas Bourgeron is geneticist and Director of the Human Genetics and Cognitive Functions Unit in the Department of Neuroscience at the Institute Pasteur in Paris, France. Professor Bourgeron's primary research interests involve the genetic origin and evolution of human cognitive functions. His team of geneticists, neurobiologists and clinicians explore the relationship between genetics and the susceptibility to psychiatric conditions. They are especially interested on autism spectrum disorders, and their previous studies have revealed the implication of a synaptogenetic pathway including the synaptic cell adhesion molecules NLGN3, NLGN4X, and NRXN1 and the scaffolding protein SHANK3 - all crucial for the maintenance of functional synapses. Their aim is to identify new susceptibility genes within this pathway and to characterize the biological factors that regulate it. They explore the genetic/epigenetic hallmarks of affected individuals using high-throughput genotyping and sequencing-based methods, in combination with clinical, neurobiological and neuro-imaging data collected from patients or using cell and animal models. Professor Bourgeron is the recipient of several prestigious awards and honours, including the 2005 Young Investigator Award from the European Neuroscience Institute, the French Academy of Sciences' award for Biological Discoveries of 2007, and election in 2008 to membership in the European Molecular Biology Organization.

Petrus J. de Vries

Petrus de Vries is the Sue Struengmann Professor of Child & Adolescent Psychiatry at the University of Cape Town, a post he took up in 2012. He trained in Medicine at Stellenbosch University in South Africa before moving to the UK where he completed his clinical training in Psychiatry and Child & Adolescent Psychiatry, and a PhD in Developmental Neuropsychiatry at the University of Cambridge.

Until 2011, Prof de Vries was the clinical lead for a multi-agency, multi-disciplinary service for school-aged children with neurodevelopmental disorders in the Cambridgeshire & Peterborough NHS Foundation Trust, UK. He has a clinical interest in assessment and intervention for young people with very complex neurodevelopmental and mental health needs.

His research interests include autism spectrum disorders, tuberous sclerosis complex and the application of neuropsychological assessments in the clinical and educational setting. Prof de Vries has a particular interest in the molecular mechanisms underlying neurocognitive and neurodevelopmental deficits associated with the TSC1/2-mTOR signalling pathway.

Prof de Vries is a Medical Advisor to the Tuberous Sclerosis Association (UK), a member of the Professional Advisory Board and International Scientific Advisory Panel of the Tuberous Sclerosis Alliance (USA), and a Specialist Advisor to TSDeutschland. He has been a member of the SSBP since 1998, has been on the executive committee since 2003, was Treasurer in 2007-2008, and has been Chairman since 2008.

Jonathan Green

Professor of Child & Adolescent Psychiatry at the University of Manchester and Honorary Consultant Psychiatrist at the Royal Manchester Children's Hospital

Jonathan Green did general medical training in Cambridge University and University College London; Paediatrics and Developmental Paediatrics at Queen Elizabeth Hospital for Children, Nuffield Hearing and Speech Centre and the Thomas Coram Research Centre in London; before specialising in Child Psychiatry in Oxford and then Manchester.

He has a long standing clinical and research interests in autism and other aspects of social development in children. Clinically, he runs a regional specialist Social Development Clinic at the Royal Manchester Children's Hospital, which undertakes assessment and treatment innovation with ASD and other impairments of social development in children. He co-led the UK's first study into ICD Asperger Syndrome and has published on social and language development in ASD, co-morbidity and treatment intervention, as well as on the social development consequences of early attachment failure. Professor Green leads a number of clinical trials into child and adolescent mental health interventions; including the MRC Preschool Autism Communication Trial (PACT), currently the largest early intervention RCT for autism internationally; the i-BASIS prodromal intervention trial for autism, which is the first of its kind to target high risk infants under one year; the Care Placement Evaluation Trial, looking at the effectiveness of therapeutic foster care for adolescents in care after early maltreatment; and trials of adolescent self harm. Other interests are in the process of treatment and the methodology of treatment trials. He is part of a MRC methodology research group developing better methods of process and causal analysis in trials and works on studies of therapeutic alliance and mediation processes.

He serves on the Editorial/Advisory Boards of the Journal of Child Psychology and Psychiatry, Advances in Psychiatric Treatment and European Journal of Child & Adolescent Psychiatry, and is a member of the Commissioning Board for the NIHR Health Technology Assessment programme and is on the current NICE guideline development group for interventions in autism.

The 15th SSBP International Meeting

"Social Phenotypes in Genetic Disorders"

Educational Day: Thursday 11th October 2012

08.30-09.20	Registration and coffee/tea in the Jubileum Hall, De Hallen
09.20-09.30	Welcome: *Petrus de Vries, Thomy de Ravel, Ann Swillen*
09.30-13.00	**Chairs: Eric Legius and Annick Vogels**
09.30-10.15	**Genetics of speech/language disorders** *Eric Legius, Leuven, Belgium*
10.15-11.15	**From mouse models to clinical trials; opportunities and challenges** *Ype Elgersma, Rotterdam, The Netherlands*
11.15-11.45	Coffee/ tea
11.45-12.20	**Microdeletions and microduplications in adults with intellectual disability and a psychiatric disorder** *Annick Vogels, Leuven, Belgium*
12.20-13.00	**Ethical considerations in the application of personalized medicine** *Kris Dierickx, Leuven, Belgium*
13.00-13.45	Lunch
13.45-15.50	**Chairs: Ann Swillen and Ilse Noens**
13.45-14.30	**Building causal models of challenging behaviour in people with intellectual disability** *Chris Oliver, Birmingham, UK*
14.30-15.15	**Psychiatric disorders in individuals with intellectual disabilities, and possible interventions** *Anthony Holland, Cambridge, UK*
15.15-15.50	**Educational strategies in individuals with developmental disabilities** *Ilse Noens, Leuven, Belgium*
15.50-16.00	Closure *Chairpersons*

Research Symposium: Thursday 11th October 2012

18.30-	Registration for Research Symposium at the University Library
19.00-22.00	Guided tour and Welcome Reception in the University Library

Research Symposium: Friday 12th October 2012

08:30-	Registration and coffee/ tea in the Jubileum Hall, De Halle Poster hanging by 09:00
09:00-09:15	Welcome: *Petrus de Vries, Thomy de Ravel, Ann Swillen*
09.15-12.30	**Chairs: Patricia Howlin and Herbert Roeyers**
09:15-10:00	**Autism: What is the social phenotype of a developmental disorder?** *Peter Mundy, Sacramento, CA, USA*
10:00-10:45	**The Social Brain** *Kevin Pelphrey, New Haven, CT, USA*
10:45-11:15	Coffee/ tea in the Jubileum Hall
11:15-12:30	**Free session A** A1: **Joint attention and social-communicative development of 12 to 18 month old siblings of children with ASD** ***P. Warreyn**, I. Schietecatte, M. Dereu and H. Roeyers* A2: **Can social communicative abilities in toddlers screening positive for autism spectrum disorder predict outcome at age 7-8?** ***M. Dereu**, R. Raymaekers, P. Warreyn and H. Roeyers* A3: **Vulnerability for autism traits and theory of mind skills in boys and girls with an extra X chromosome (XXY, XXX)** ***S. van Rijn** and H. Swaab* A4: **A comparison of social deficits in XXY, XYY and XXYY syndromes** ***N. Tartaglia**, L. Cordeiro, D. Roeltgen and J. Ross* A5: **Interpreting faces and eyes in individuals with autism spectrum disorder, fragile X syndrome and Rubinstein Taybi syndrome** ***H. Mace**, J. Moss, G. Anderson, C. Oliver and J. McCleery* A6: **Social cognition and broad autism phenotype in men with the fragile X premutation** *A. Schneider, C. Johnston, F. Tassone, S. Sansone, F. Abucayan, V. Narcisa, P.J. Hagerman, R.J. Hagerman, S. Rivera and **D. Hessl***
12:30-13:30	Lunch and Poster-viewing in the Jubileum Hall

13.30-15.30	**Chairs: Randi Hagerman and Hilde Van Esch**
13:30-14:15	**Genetics in Autism** *Thomas Bourgeron, Paris, France*
14:15-15:30	**Free session B** B1: **Autism symptoms and behavioural disturbances in 500 children with Down syndrome in England and Wales** ***G. Warner*** *and P. Howlin* B2: **Genetic markers for autism profiles** ***H. Bruining****, M.J.C. Eijkemans, M.J.H. Kas, S.R. Curran, P.F. Bolton and J.A.S. Vorstman* B3: **Fragile X newborn screening, cascade testing, prevalence data** ***L.W. Gane****, P. Sorenson, J. Famula, J. Lo, S. Rivera, R.J. Hagerman and F. Tassone* B4: **Immune mediated disorders among female carriers of fragile X premutation alleles** *T.I. Winarni, W. Chonchiaya, T.A. Sumekar, F. Tassone, D. Nguyen, S. Faradz, Y. Mu, P. Hagerman and* ***R. Hagerman*** B5: **The role of DGCR8 in FXTAS and 22Q deletion syndrome: overlapping pathogenic mechanisms involving altered miRNA biogenesis** ***F. Tassone****, R.J. Hagerman, T.J. Simon and P.J. Hagerman*
15:30-16:00	Coffee/ tea in the Jubileum Hall
16:00-17:30	**Chairs: Petrus de Vries and Thomy de Ravel**
16:00-16:15	**The Pat Howlin Prize Lecture** **Parental social support, coping strategies, resilience factors, stress, anxiety and depression levels in parents of children with mucopolysaccharidosis type III (MPS III, Sanfilippo syndrome) and parents of children with intellectual disabilities (ID)** ***Sheena G. Grant****, E.C. Cross, E.W. Wraith, S.J. Jones and D.H. Hare*
16:15-17:00	**SSBP 25th Anniversary Talks**
17:00-17:20	**Tribute to Emeritus Professor dr Jean-Pierre Frijns** *Hilde Van Esch, Leuven, Belgium*
19:30-23:00	Dinner at The Infirmary Dining Room, Faculty Club, The Beguinage/Begijnhof

Research Symposium: Saturday 13th October 2012

08:30-	Registration and coffee/ tea in the Jubileum Hall
09:00-12:00	**Chairs: Jeremy Turk and Anna Janssen**
09:00-09:45	**Neurofibromatosis (NF1) Targeted Therapy** *Eric Legius, Leuven, Belgium*
09:45-10:30	**Targeted Therapies in Tuberous Sclerosis Complex** *Petrus de Vries, Cape Town, South Africa*
10:30-11:00	Coffee/tea in the Jubileum Hall
11:00-12:00	**Free session C** C1: **The role of Spred1 in a mouse model for Legius syndrome** ***H. Brems**, Y. Elgersma, E. Plasschaert, S.A. Kushner, W. Van Den Berg, C.I. De Zeeuw and E. Legius* C2: **Relative importance of autistic traits and hyperactivity-inattention for social functioning in neurofibromatosis type 1** ***S.C.J. Huijbregts**, R Jahja and H. Swaab-Barneveld* C3: **Language, cognition and behavior over time in young children with NF1 - A retrospective longitudinal study** ***A.B. Rietman**, P.F.A. De Nijs, K. Van Noort, S. Van Abeelen, J. Hendriksen, A. Weber and Y. Elgersma* C4: **Is there a link between neurofibromatosis type 1 and autism spectrum disorder?** ***E. Plasschaert**, M.-J. Descheemaeker, M. Borghgraef, D. Willekens, W. de la Marche, L. Van Eylen, J. Steyaert, I. Noens and E. Legius* C5: **Investigating neurocognitive endophenotypes of autism spectrum disorders (ASD) by including an ASD sample with co-occuring neurofibromatosis type 1** ***L. Van Eylen**, I. Noens, M.-J. Descheemaeker, D. Willekens, M. Borghgraef, E. Legius and J. Steyaert*
12:00-13:00	Lunch and Poster viewing in the Jubileum Hall
13:00-13:45	SSBP AGM

13:45-15:45	**Chairs: Honey Heussler and Raja Mukherjee**
13:45-14:30	**The Tom Oppé Distinguished Lecture** **Refining the social phenotypes of genetic disorders** *Chris Oliver, Birmingham, UK*
14:30-15:45	**Free session D** D1: **Cognitive-social development in microdeletion disorders: Wolf-Hirschhorn, Williams-Beuren, and Jacobsen syndromes** ***G.S. Fisch**, A. Battaglia and J. Carey* D2: **Expanding the phenotypic profile of boys with XXY - Is it all about the X?** ***C.A. Samango-Sprouse**, E.J. Stapleton, F.L. Mitchell, T. Sadeghin and A.L. Gropman* D3: **Characterising the behavioural phenotype of Rett syndrome** ***R. Cianfaglione**, D. Felce, A. Clarke, M. Kerr and R.P. Hastings* D4: **Effect of adult familiarity and level of attention on social behaviour in Smith Magenis syndrome** ***L. Wilde**, J. Moss, J. Tanner, A. Mitchell, C. Jackson and C. Oliver* D5: **22q11 Deletion syndrome in moderate and severe learning disabled adults. Relation between psychosis and cognitive deterioration** ***L.J.M. Evers**, T.A.M.J. Van Amelsvoort, M.J.J.M. Candel, H. Boer, J.J.M. Engelen and L.M.G. Curfs*
15:45-16:15	Coffee/ tea break in the Jubileum Hall
16:15-17:00	**Chairs: Petrus de Vries, Thomy de Ravel, Ann Swillen**
16:15-16:20	**Presentation of SSBP Symposium 2013, Cape, South Africa** *Petrus de Vries, Cape Town, South Africa*
16:20-17:00	**Developmental intervention within the social phenotype** *Jonathan Green, Manchester, UK*
17:00	Closure *Chairpersons*

Abstracts for Oral Presentations

(in order of presentation)

Educational Day

Genetics of speech/language disorders

Eric Legius
Department of Human Genetics, KU Leuven, Belgium

Several genes have been identified that code for proteins important for speech/language disorders. The first gene to be identified was *FOXP2*. This gene was mutated in a family with verbal dyspraxia. The protein is a forkhead domain transcription factor and is important for vocalization in both human and mice and for the development of the cerebellum and the proper functioning of the frontocerebellar circuit of the motor system. FOXP2 binds to FOXP1. The *FOXP1* gene is mutated in some cases of intellectual disability and autism. *CNTNAP2* is a target gene regulated by FOXP2. Variants in *CNTNAP2* are associated with specific language impairment and with autism. Homozygous mutations in *CNTNAP2* are found in the cortical dysplasia-focal epilepsy syndrome and Pitt-Hopkins-like syndrome (intellectual disability, seizures and hyperbreathing). Specific language impairment was also linked to markers in the *CMIP* and *ATP2C2* genes in families with SLI. Markers in the same genes were also associated with short-term memory.

Genome-wide linkage analysis in consanguineous families showed linkage on chromosome 12q23.3 with stuttering. *GNPTAB* is localized in this region and a missense mutation in this gene was responsible for the linkage signal. Mutations in *GNPTG* and *NAGPA* were subsequently found to be associated with stuttering in other families. These three genes code for proteins of the lysosomal enzyme-targeting pathway linking a deficit of intracellular lysosomal function to susceptibility for stuttering.

Genetic studies of dyslexia pointed towards *ROBO1*, *DCDC2* and *KIAA0319* as candidate genes for this disorder. Functional studies in animal models will help elucidating the basic function of these genes for brain function.

From mouse models to clinical trials; opportunities and challenges

Ype Elgersma
Erasmus University Medical Center, ENCORE expertise center for neurodevelopmental disorders, Rotterdam, The Netherlands

Genetic disorders present us with the unique knowledge of knowing the causal gene and study the impact of the genetic mutation in mouse models of disease. Because of these mouse models, insight in the molecular and cellular basis of the neurological deficits associated with childhood developmental disorders gains rapid progress. This insight can then be used to guide drug discovery and clinical trials. In this symposium, I will describe basal and clinical research performed at the Dutch ENCORE center for neurodevelopmental disorders. I will specifically describe progress made in understanding the molecular mechanisms underlying Neurofibromatosis (NF1), Tuberous Sclerosis Complex (TSC) and Angelman Syndrome. I will also outline how these pre-clinical finding are currently translated to the clinic, and what kind of trials we are currently performing for NF1 and TSC.

Microdeletions and microduplications in adults with intellectual disability and a psychiatric disorder

Vogels Annick M.L.[1], Van Buggenhout G.J.C.M.[1], Weyts E.[2], Vermeesch J.[1], Fryns J.P.[1] and Caeyenberghs R.[2]

[1]Centre for Human Genetics, University Hospitals of Leuven, Belgium. [2]Psychiatric Hospital Sint-Kamillus of Bierbeek, Belgium

Background: Comparative genomic hybridization (array-CGH) studies have suggested that rare copy number variations (CNVs) at numerous loci are involved in the etiology of intellectual disability and psychotic disorder. It is hypothesized that weakly to moderately recurrent CNVs are causing or contributory factors for these diseases. Most of these CNVs contain genes involved in neurotransmission or synapse formation and maintenance. These CNVs are present in both, supporting the existence of shared biological pathways between these neurodevelopmental disorders. We hypothesized that in patients with a dual diagnosis of intellectual disability and psychotic disorder, even more CNVs will be detected. **Methods:** A 180k resolution array (Cytosure ISCA v2 array by Oxford Gene Technology) was performed in 120 adults with a dual diagnosis of intellectual disability and psychotic disorder. All subjects were admitted to the inpatient unit of the psychiatric hospital of Sint-Camillus. An extensive cognitive and psychiatric examination as well as a clinical genetic examination was performed in all patients. **Results:** The results will be presented at the meeting. CNV previously described in the literature as well as new CNVs were detected. **Conclusion:** A large number of causal CNVs were found in this well described population of adults with a dual diagnosis of intellectual disability and psychotic disorder. Some of these microdeletions/microduplications contain genes that play a crucial role in the subtle regulation of synaptic activity. This study confirms the previous hypothesis that CNVs, and thus hypothetically genetic risk factors, are shared between psychotic disorder and intellectual disability.

Ethical considerations in the application of personalized medicine

Kris Dierickx
Centre for Biomedical Ethics and Law, Faculty of Medicine, KU Leuven, Leuven, Belgium

The paradigm shift in genome-wide testing, moving from a focused search for one particular genetic mutation to a full examination in the hope of finding that which is relevant to a certain clinical question, puts such pressure on these carefully outlined frameworks that familiar distinctions seem to disappear Just think of the distinction between diagnosis and screening, between monogenic and multifactorial disorders, between the implications for one's personal health and reproductive health, Moreover, all of this not only has implications for the patient himself or herself, but for the patient's relatives as well since they share the patient's DNA to a large extent. The present day's normative frameworks are being placed under pressure. Therefore we focus in this contribution on the major ethical challenges in this evolution: how shall we deal with the massive amount of test results that can become available? And what are the implications hereof for the practice of free and informed consent? What happens if genetic abnormalities are found in a patient that have no relation to the specific disease or the particular request for information, but that can have consequences for that patient and possibly for his or her relatives? It becomes even more complicated when there are preventive or therapeutic options for some abnormalities and not for others; or when the abnormality can only be expressed as a heightened risk of which the clinical relevance is as yet inconclusive. What are ethical criteria in order to cope with incidental findings? Finally we will conclude with the implications of this new genomic technology for the concepts of privacy and confidentiality, especially in the communication with family members.

Building causal models of challenging behaviour in people with intellectual disability

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

Between 5% and 15% of people with severe intellectual disability will show challenging behaviour at a level that warrants intervention. The dominant causal model draws on operant learning theory to explain the maintenance and increasing severity of these behaviours with a robust empirical literature demonstrating the utility of an applied behaviour analytic approach. However, this literature is not well integrated with the results of prevalence and cohort studies and the rapidly developing field of behavioural phenotypes. In this presentation these diverse strands of research are combined to extend existing causal models. A broader, integrated model is proposed and implications for assessment and intervention are explored. Emphasis is placed on an early intervention strategy that draws on this broad model and an empirical approach to risk for developing severe challenging behaviour.

Psychiatric disorders in individuals with Intellectual Disabilities, and possible interventions

Anthony J. Holland
Cambridge, UK

No abstract received

Educational strategies in individuals with developmental disabilities

Ilse Noens
Parenting and Special Education Unit, KU Leuven, Belgium

Parents (and other caregivers) of children with developmental disabilities often face specific challenges in parenting. Apart from the parenting skills that every parent has to demonstrate, more intensive and specific interventions are needed, especially if their child also shows challenging behaviours. Two aspects turn out to be crucial: on the one hand it is necessary to tune the environment to the needs of the child; on the other the atypical development of the child asks for specific developmental stimulation (Lambrechts et al., 2011).

Contrary to the extensive amount of empirical findings about parental perceptions, cognitions and coping strategies, research about parenting behaviour itself is very scarce. In this presentation the first results of our research line comparing parenting behaviour among parents of children with intellectual disabilities and/or autism spectrum disorders with parenting behaviour among parents of typically developing children will be presented. Also, the relationship between parenting behaviour of parents and specific characteristics of their children such as the degree of communication problems and challenging behaviour will be discussed.

Given that parenting behaviour can be considered both as a risk and a protective factor for the development of challenging behaviours, this research can offer clues for prevention and intervention programmes aiming at the reduction of challenging behaviours via the stimulation of parenting skills. It will also yield instruments that can be applied in clinical assessment and for the evaluation of prevention and intervention programmes including parenting skills training.

Abstracts for Oral Presentations

Research Symposium

Autism: What Is the social phenotype of a developmental disorder?

Peter Mundy[1,2]
[1]*University of California at Davis M.I.N.D. Institute.*
[2]*University of California at Davis School of Education*

Background: The definitive description of the social phenotype of Autism Spectrum Disorders (ASD) remains a goal, rather than an accomplishment of science. Nevertheless, a significant attenuation of the human tendency to engage in joint attention has been recognized as one central element of the early expression of the phenotype of autism. Joint attention involves the capacity, and motivation to adopt the same visual-spatial frame of reference with other people. Theoretically, its development provides a foundation for the subsequent emergence of the capacity, and motivation to adopt the same mental frame of reference with other people (i.e. social cognition). Understanding the role of joint in human social development may be critical to a more precise understanding of the social phenotype of autism. **Methods:** Thirty years of research on joint attention will be reviewed. This will include research on the role of joint attention in human learning and social cognitive development, as well as neurocognitive, genetic, diagnostic and intervention studies on joint attention in Autism Spectrum Disorders. **Results:** The results of a large accumulation of quasi-experimental and experimental (e.g. intervention) studies supports the thesis that joint attention is central to human learning and social cognition. This literature also supports the dual hypotheses that the developmental impairment of joint attention is a symptom that is central to the phenotype of autism, as well as part of the etiology of autism. **Conclusion:** A deeper understanding of the role of joint attention impairments in the phenotype and course of autism may be vital to advances in translational, genetic, comparative and neurodevelopmental research on this disorder.

The Social Brain

Kevin Pelphrey
New Haven, CT, USA

Humans are intensely social beings that have evolved and developed within highly social environments in which each individual is dependent upon others. We constantly engage in social perception, using cues from facial expressions, gaze shifts, and body movements, to infer the intentions of others and plan our own actions accordingly. My laboratory has been investigating the properties of specialized brain systems that are important for social perception using functional magnetic resonance imaging (fMRI), eye tracking, and molecular genetics in typicallydeveloping adults and children, as well as in children and adults with autism, a neurodevelopmental disorder marked by severe dysfunction in aspects of social perception. In this talk, I will describe these studies in two parts: First, I will describe our basic research using fMRI to identify the basic brain mechanisms for social perception in typically developing children and adults. Second, I will describe our most recent efforts to chart the typical and atypical development of brain mechanisms for social perception in children with and without autism, as well as in unaffected siblings of children with autism.

A1: Joint attention and social-communicative development of 12- to 18-month old siblings of children with ASD

Warreyn P., Schietecatte I., Dereu M. and Roeyers H.
Research Group Developmental Disorders, Ghent University, Dunantlaan 2, 9000 Ghent, Belgium.

Background: Siblings of children with an autism spectrum disorder (ASD) have an elevated risk of developing the disorder themselves or showing mild social-communicative impairments. Therefore, following up these children in their first years of life is of clinical as well as scientific importance. In both typical and atypical development, joint attention seems to be an important skill in infancy, facilitating exchanges between social partners as well as later social-communicative development. **Methods:** We tested 18 infant siblings of children with ASD (without ASD diagnosis at the age of 3) and 32 typically developing children (TD) at 12 and 18 months of age. At 12 months, we measured initiating joint attention (IJA) and responding to joint attention (RJA) and we administered the Mullen Scales of Early Learning. At the age of 18 months, the joint attention measures were repeated, parents filled in the Modified Checklist for Autism in Toddlers (M-CHAT) and the Dutch version of the Communicative Development Inventory NCDI, and the ADOS was administered. **Results:** As a group, the siblings showed as much IJA and RJA as the TD group at both 12 and 18 months. At 18 months, four of the siblings showed social-communicative problems on ADOS, M-CHAT and/or NCDI. Especially RJA and Developmental Index at 12 months were predictive of ADOS and NCDI scores at 18 months. **Conclusion:** Siblings of children with ASD have no generalised joint attention deficits at the ages of 12 and 18 months, but a minority of them show social-communicative problems at 18 months, possibly pointing to the Broader Autism Phenotype. These problems were strongly predicted by earlier RJA and Developmental Index, making the latter two measures especially important in the follow-up of infants at risk.

Keywords: siblings, broader autism phenotype, autism spectrum disorder, joint attention, social impairment, longitudinal study

A2: Can social communicative abilities in toddlers screening positive for autism spectrum disorder predict outcome at age 7-8?

Dereu M., Raymaekers R., Warreyn P. and Roeyers H.
Ghent University, Department of Experimental Clinical and Health Psychology, Henri Dunantlaan 2, 9000 Ghent, Belgium.

Background: In recent years, more attention has been given to the early detection of autism spectrum disorder (ASD) to enable early intervention. This might benefit the outcome of children with ASD. Diagnosis of ASD in toddlers is largely based on social communicative impairments. More research is needed to determine the predictive validity of these social communicative impairments in children at risk for ASD. **Methods:** Out of a larger population screening in 7,092 children attending Flemish day-care centres, 79 children were identified as high-risk for ASD and were seen at the university lab between the ages of 2 and 4 years. Initial assessment consisted of measures of language and general development, ASD symptomatology, and social communicative skills. Currently, all children are asked to participate in a follow-up study when they are 7 to 8 years to measure their language, intelligence, and theory of mind. In addition, parents are asked to complete some questionnaires regarding overall wellbeing, ASD symptomatology, temperament and personality of their child. **Results:** Preliminary results suggest that social communicative abilities measured in toddlerhood (e.g., pointing or showing behaviours) are predictive of later language, intelligence, and theory of mind. True positive screens between ages 2 and 4 years especially have lower scores for receptive language at age 7 to 8 years compared to false positive screens. More conclusive results will be presented at the research symposium, including results on temperament/personality and diagnoses. **Conclusion:** Results suggest that outcome at 7 to 8 years for children who screened positive for ASD during toddlerhood, can be predicted by their social communicative development between the ages of 2 and 4 years.

Keywords: autism spectrum disorder, screening, longitudinal study, early intervention, language, social-communicative impairment

A3: Vulnerability for autism traits and theory of mind skills in boys and girls with an extra X chromosome (XXY, XXX)

van Rijn S., Swaab, H.
Clinical Child and Adolescent Studies, Leiden University, The Netherlands

Background: Earlier studies have shown that boys and men with an extra X chromosome (Klinefelter syndrome) may be at increased risk for autism traits. It has remained unclear however, 1) to what extent girls with an extra X chromosome have an increased vulnerability for autism traits, 2) what the profile and severity is of autism traits as compared to children with autism spectrum disorders (ASD) and 3) to what degree children with an extra X chromosome show cognitive deficits similar to children with ASD.

Method: We studied 54 boys and girls with an extra X chromosome (mean age 12.2 years). Half of this group was recruited with help of clinical genetics departments in the Netherlands and Belgium, the other half with help of support groups. Comparison groups included 56 boys and girls with ASD (mean age 12.8 years) and 77 typically developing boys and girls (mean age 12.4 years). Measures included the Autism Diagnostic Interview-R (ADI-R), the Autism-spectrum Quotient (AQ) and a Theory of Mind Test (Social Cognitive Skills Test, SCVT).

Results: Results showed that 28.8 % of the children with an extra X scored above cut-off on all three domains of the ADI-R. In line with this, the level of autism traits was significantly increased in both girls and boys with an extra X, their scores were in between those of controls and children with ASD. Furthermore, both girls and boys with an extra X showed significant impairments in Theory of Mind, their scores could not be distinguished from the ASD group. None of the measures showed group by gender interactions. Also, none of the measures showed differences between those recruited through clinical genetics departments versus support groups.

Conclusion: This study has shown an increased vulnerability for autism traits in both boys and girls with an extra X chromosome. Similar to children with ASD, both boys and girls with an extra X showed impairments in Theory of Mind skills. These findings may help in diagnosis and treatment of children with an extra X. The absence of gender effects is not only relevant for clinical practice, but may also provide important clues with regard to role of the extra X chromosome in social development.

Keywords: XXY syndrome, XXX syndrome, Klinefelter syndrome, autism spectrum disorder, theory of mind, behavioural phenotype.

A4: A comparison of social deficits in XXY, XYY and XXYY syndromes

Tartaglia N.[1], Cordeiro L.[1], Roeltgen D.[2] and Ross J.[2]

[1]Univ of Colorado School of Medicine, Children's Hospital Colorado, USA. [2]Thomas Jefferson Univ, Dept of Pediatrics, Philadelphia, USA.

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. In this study, we compare profiles of social skills in three SCA syndromes (XXY, XYY and XXYY) across different domains of social responsiveness. We also investigate how age, verbal and nonverbal IQ, previous clinical ASD diagnosis, and socioeconomic status affect social skills. **Methods:** Participants include 174 males age 4-18 with XXY (N=102), XYY (N=40), and XXYY (N=32). Study protocol included cognitive testing, a developmental history and the Social Responsiveness Scale (SRS), which includes subscales of social communication, social cognition, social awareness, social motivation, and autistic mannerisms. Statistical analyses included ANOVA with post-hoc Tukey and proportion z-tests. **Results:** The XXY group had lower (better) SRS scores compared to XYY and XXYY in all subscales of the SRS, with the exception of the social motivation domain which was relatively preserved in all groups. XXYY participants had significantly lower cognitive scores compared to participants with XXY and XYY. However, mean total SRS scores in the XYY and XXYY groups were significantly higher (worse) than the XXY group (XYY 72.8, XXYY 72.2, XXY 62.0, $p<0.0001$). In all groups, there were significantly more participants with SRS scores in the severe range compared to the SRS normative sample. Relationships between SRS scores and demographic and clinical variables were examined. **Conclusions:** Social deficits are present in males with SCA at a higher rate than the general population, with participants XYY and XXYY showing more difficulties than those with XXY. Social motivation is an area of strength in the social profile of SCA. An additional Y chromosome may contribute to increased risk of social deficits and autistic behaviours.

Keywords: sex chromosome aneuploidy, XXY syndrome, XYY syndrome, XXYY syndrome, behavioural phenotype, autism spectrum disorder, social impairment

A5: Interpreting faces and eyes in individuals with autism spectrum disorder, fragile X syndrome and Rubinstein Taybi syndrome

Mace H.[1], Moss J.[1], Anderson G.[2], Oliver C.[1] and McCleery J.[2]

[1]The Cerebra Centre for Neurodevelopmental Disorders, School of Psychology, University of Birmingham, Birmingham, UK. [2]School of Psychology, University of Birmingham, Birmingham, UK.

Background: Different viewing patterns of faces have been reported in individuals with different social phenotypes e.g. Williams syndrome vs. autism spectrum disorder (ASD). In this study, viewing patterns were investigated in ASD, Fragile X (FXS) and Rubinstein Taybi (RTS) syndromes, in which contrasting profiles of social impairments and skills are evident. The impact of atypical looking patterns on spontaneous emotion discrimination was also investigated. **Methods:** Individuals with ASD (N=15; M_{age}=11.01, SD=3.48), FXS (N=13; M_{age}=19.70, SD=9.00), RTS (N=17; M_{age}=17.33, SD=10.14) and contrast groups of typically developing (TD) children (N=14;M_{age}=6.99, SD=1.67) and adults (N=12; M_{age}=21.42, SD=2.91) were assessed using eye tracking methodology. During baseline trials, two neutral faces were presented side-by-side. During critical trials, one neutral face was presented alongside a disgusted or happy face. Baseline trials were examined for dwell time to the eyes and mouth. Critical trials were examined for preferential looking to the emotional expressions. **Results:** Individuals with FXS looked significantly less at the eye region than ASD and TD groups (p<.001). Individuals with RTS looked significantly less at the eye region than TD adults (p=.002). No differences in looking to the mouth region were revealed. During critical trials, ASD, FXS, RTS and TD groups looked more at disgusted than neutral faces (p≤.008). There were no significant differences in looking time for happy vs. neutral faces. **Conclusion:** Results indicate decreased looking to the eye region in FXS. Results also indicate typical looking to the eye region in RTS when compared to those with similar ability levels but different looking patterns when compared to TD adults. These differences may be important for understanding the contrasting social phenotypes in these syndromes. Atypical looking patterns in FXS and RTS do not appear to affect spontaneous emotion discrimination.

Keywords: Fragile X syndrome, emotion recognition, eye gaze, Rubinstein Taybi syndrome, behavioural phenotype, social phenotype

A6: Social cognition and broad autism phenotype in men with the fragile X premutation

Schneider A.[1, 3], Johnston C.[1, 2], Tassone F.[1, 6], Sansone S.[1, 7], Abucayan F.[1, 2], Narcisa V.[1], Hagerman P.J.[1, 6], Hagerman R.J.[1, 3], Rivera S.[1, 5] and Hessl D.[1, 2]

[1]MIND Institute, UC Davis Medical Center, Sacramento, California, USA. [2]Department of Psychiatry and Behavioral Sciences, UC Davis School of Medicine, Sacramento, California, USA. [3]Department of Pediatrics, UC Davis School of Medicine, Sacramento, California, USA. [4]Department of Psychology, UC Davis, Davis, California, USA. [5]Center for Mind and Brain, UC Davis, Davis, California, USA. [6]Department of Biochemistry and Molecular Medicine, UC Davis, Davis, California, USA. [7]Department of Human Development, UC Davis, Davis, California, USA.

Background: A substantial number of individuals with the fragile X premutation, especially males, present clinically with symptoms of autism spectrum disorder (ASD). Given the high rate of ASD in the general population and referral patterns, it is often difficult to determine whether the symptoms are caused by fragile X or another aetiology. Recent evidence from our centre indicates that abnormal elevation of *FMR1* mRNA and/or reduced FMRP is associated with functional alternations in brain regions that mediate social cognition in adult premutation carriers. Here we sought to extend this research by examining several aspects of social cognition and the broad autism phenotype and molecular correlates in a non-clinic referred sample of men with the premutation (obtained primarily through cascade testing or randomly selected from pedigrees without regard to clinical status) and matched controls in the context of a larger NIH-funded neuroimaging and neuropsychological study. **Methods:** Thus far, the sample includes 36 men with the *FMR1* premutation (mean age = 32.0 ± 8.8 years) with normal neurological exam and 47 male controls (mean age = 29.5 ± 7.2 years). Individuals completed the Reading the Mind Through the Eyes task (Baron-Cohen et al. 2001), the Movie for the Assessment of Social Cognition (MASC; Dziobek et al., 2006), and the self-report Autism Quotient (Baron-Cohen et al., 2001). A spouse, relative or close friend completed the Social Responsiveness Scale (Constantino et al., 2005), as a measure of the broad autism phenotype of each participant. **Results:** The groups significantly differed by Full Scale IQ (premutation, 114.9 ± 16.3; control, 123.4 ± 16.8) and therefore IQ was used as a covariate in subsequent analyses. No significant group differences were observed on measures of social cognition or the broad autism phenotype (all $p > 0.15$), and premutation carrier results did not differ from male controls in previously published studies focused on these instruments. *FMR1* mRNA and CGG repeat length were associated with lower performance on the Reading the Mind in the Eyes task ($r = -.46$, $p = .01$ and $r = -.38$, $p < .05$, respectively). No other significant molecular-clinical correlations were observed. FMRP ELISA assays and correlates with the measures are in progress and will be reported. **Conclusion:** As a group, men with the premutation do not demonstrate social cognition deficits or prominent broad autism phenotype features, although there may be subtler effects in carriers with longer CGG repeat alleles, or among clinically-referred subgroups.

Keywords: Fragile X syndrome, autism spectrum disorder, premutation, social cognition, theory of mind, behavioural phenotype

Genetics in Autism

Thomas Bourgeron
Paris, France

No abstract received

B1: Autism symptoms and behavioural disturbances in 500 children with Down syndrome in England and Wales

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Background: Recent research shows that a significant minority of children with Down syndrome (DS) also meet diagnostic criteria for an autism spectrum disorder (ASD). The present study explored rates of autism symptoms and associated behaviour problems in children aged 6-15 years with DS in England and Wales. **Methods:** Potential participants (*n*=1382) were recruited via the UK Down's Syndrome Association. The Social Communication Questionnaire (SCQ) was used to screen for autistic symptoms and the Strengths and Difficulties Questionnaire to explore behavioural difficulties. The survey also considered possible developmental regression. **Results:** Questionnaires were completed by 473 families (34% of the cohort). The proportion of children meeting cut-off scores on the SCQ for ASD was 38.3% (95% confidence interval [CI]: 33.9% - 42.7%) and for autism 16.5% (95% CI: 13.2% - 19.8%). Children scoring above cut-off for ASD/autism displayed higher levels of emotional symptoms, conduct problems, peer problems and hyperactivity than those who did not. Developmental regression, in both general and language skills, was also higher. However, the profile of autism symptoms on the SCQ in children with DS was atypical compared to children with idiopathic ASD. **Conclusion:** The pervasiveness of ASD in children with DS in England and Wales is substantially higher than in the general population. These children experience significantly greater behavioural problems than DS children who show no significant autism symptoms. Early detection of autistic symptoms is essential for the provision of appropriate intervention. However, the atypical ASD profile may affect the recognition of the disorder and inhibit the implementation of standard autism interventions.

Keywords: Down syndrome, autism spectrum disorder, prevalence, behavioural phenotype, developmental regression, hyperactivity

B2: Genetic markers for autism profiles

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Background: A significant proportion of autism spectrum disorders (ASD) are the result of rare, aetiological genetic variants. One evident question is whether these variants make specific contributions to the clinical phenotype of ASD and related disorders. In this context, we investigated the feasibility of behavioural stratification on the basis of genotype information. **Methods:** We analysed autism symptom profiles in a sample of six different genetic conditions: 22q11.2 deletion syndrome, Down syndrome, Prader-Willi, Supernumerary Marker chromosome 15, Tuberous Sclerosis Complex and Klinefelter syndrome (n = 347, groups ranging 26-90). ADI-R symptom scores were entered in Support Vector Learning Machine Analysis (SVM), Principal component analysis (PCA) and clustering analysis. **Results:** The conjoint SVM analysis of all groups together showed that the genotype of 71.7 % of participants was predicted accurately by the SVM on the basis of ADI-R symptom profiles, where random allocation would have resulted in 21.1 % accuracy. The accuracy of genotype prediction by SVM varied across the different genetic groups, which was due to different overlap in symptoms profiles which we confirmed by PCA. K-means clustering on the ADI-R data showed that only two clusters appeared to stand out; more clusters were not clearly separated. Thus, in contrast with the SVM no genotype effect was detected. **Conclusion:** Together, these results showed that a supervised (with knowledge of genotype) analysis such as SVM could detect genetic markers for ASD behavioural phenotypes, where unsupervised (without knowledge of genotype) analyses such as clustering analysis did not deliver behavioural contrasts by genotype. This implies that ASD behavioural profiles will not deliver a sufficiently discriminative signal to identify genetic subgroups, but the reverse, i.e. using genotype information to stratify groups seems meaningful. This study supports the growing incentive to stratify-by-genotype as a first step to translate genomic information into the clinical setting for ASD.

Keywords: autism spectrum disorder, Down syndrome, Prader-Willi syndrome, Autism Diagnostic Interview, behavioural phenotype, Tuberous Sclerosis Complex, 22q11.2 deletion syndrome

B3: Fragile X newborn screening, cascade testing, prevalence data

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Background: A fragile X newborn screening (NBS) pilot study is being conducted at UC Davis MIND Institute, Rush Memorial Hospital and University of North Carolina. We report clinical findings from the MIND Institute and FMR1 mutation frequencies across all sites. **Methods**: The family of a newborn diagnosed by bloodspot with the FMR1mutation is seen in clinic. Follow up evaluations, cascade testing, blood spot and confirmatory testing are done. **Results**: The MIND Institute has screened 3042 newborns and 44 extended family members. 14 newborns (7 males, 7 females), 27 extended family members (5 males, 22 females) have been identified with the FMR1 mutation including a male full mutation. Three families had significant clinical and/or molecular findings by cascade testing. 3 premutation infants preliminarily show visual processing disorders. 11,217 (5766 males, 5451 females) newborns across 3 sites have been screened. 30 newborns (11 males, 19 females) have the FMR1 mutation including one full mutation. 132 newborns (54 males, 75 females) had grey zone (45-54 CGG repeats). 474 newborns (177 males, 297 females) had grey zone (40-54 CGG repeats). **Conclusion**: This FXS newborn screening project demonstrates the importance of identifying the FMR1 mutation. Monitoring of development, intervention and access to treatments can be offered if needed. Cascade testing provides family members with the opportunity to receive accurate diagnosis for FMR1 mutation problems and to make informed reproductive decisions. This ongoing project is providing a unique opportunity for large population screening within the US providing gene frequencies for the FMR1 grey zone, premutation and full mutation.

Keywords: Fragile X syndrome, screening, FMR1, premutation, newborn, early intervention

B4: Immune mediated disorders among female carriers of fragile X premutation alleles

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Background The fragile X premutation (55 to 200 CGG repeats) occurs in approximately 0.5% of women in the general population.

Methods The relative risk of immune-mediated disorders (IMDs) among female carriers of premutation alleles is estimated by survey of IMDs among 344 carrier females (age 19 to 81 years; mean 46.35 and SD 12.60) and 72 controls (age 18 to 87 years; mean 52.40 and SD 15.40). All patients and controls underwent a detailed medical history and examination including review of medical records.

Results 154 (44.77%) female carriers had at least one IMD, as did 20 controls (27.78%). Among female carriers, autoimmune thyroid disorder was the most common (24.4%), then fibromyalgia (10.2%), irritable bowel syndrome (IBS; 9.9%), Raynaud's phenomenon (7.6%), rheumatoid arthritis (RA; 3.8%), Sjogren syndrome (2.6%), systemic lupus erythematosus (SLE; 2.03%), multiple sclerosis (1.74%). Of 55 carriers age 40 or older with FXTAS, 72.73% had at least one IMD, compared to 46.54% of those without FXTAS (n=159), and 31.58% of controls (n=57). The estimated odds ratio (OR) for IMD is 2.6 (95% CI 1.2-5.6, p = 0.015) for females with FXTAS relative to those without FXTAS; the likelihood of IMD in carriers without or with FXTAS was also significantly higher than for controls (OR 2.1, 95% CI 1.1-4.2, p = 0.034; OR 5.5, 95% CI 2.4-12.5, p < 0.001 respectively). Similarly, the odds of having an IMD among carriers with FXPOI is about 2.4 times higher when compared to carriers without FXPOI (95% CI 1.1-5.0; p = 0.021). The likelihood of IMD in carriers with or without FXPOI is greater (OR 2.4, 95% CI 1.1-5.0; p = 0.021) compared to controls.

Conclusions IMD are common among women with the premutation and FXTAS and their pathogenesis may be linked molecularly through DGCR8/DROSHA sequestration and miRNA dysregulation CA.

Keywords: Fragile X syndrome, FXTAS, premutation, immune system disorders, carriers, females

B5: The role of DGCR8 in FXTAS and 22Q deletion syndrome: overlapping pathogenic mechanisms involving altered miRNA biogenesis

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Background: It is estimated that micro (mi)RNAs regulate the expression of at least one-third of the genes within the human genome, and that global miRNA expression is, itself regulated by the "Di George Critical Region8" (DGCR8) gene located within the deleted region of chromosome 22q11. **Methods:** Total RNA was isolated from peripheral blood leukocytes and quantification of miRNAs was performed using qPCR; miRNA expression levels were determined using the Global Pattern Recognition™ software. **Results:** Participants with either 22q11DS or FXTAS show decreased expression of a number of miRNAs targeting several pathways, whereas mirtron (miRNAs produced by the splicing machinery; i.e., independent of DGCR8/DROSHA) levels remain unchanged. Thus, impaired miRNA processing in these two disorders is due to decreased free DROSHA/DGCR8 "microprocessor" complex. In FXTAS, the expanded CGG repeat, as an RNA hairpin, binds and sequesters DGCR8, and hence Drosha; whereas in 22q11DS, DGCR8 haploinsufficiency effectively reduces microprocessor activity, resulting in reduced miRNA biogenesis. **Conclusion:** We observed an altered miRNA biogenesis, with reduced mature miRNA in both FXTAS and 22q11DS. In the latter, the reduction of mature miRNA is due to decreased DGCR8 protein production, whereas in FXTAS, reduction in effective DGCR8 protein is due to its sequestration. Understanding the role of miRNA in 22q11DS and FXTAS will provide an understanding of the mechanisms leading to the psychiatric and cognitive phenotypes associated with the two disorders and to their phenotypic variability, and may also yield therapeutic opportunities for both disorders.

Keywords: Fragile X syndrome, 22q11 deletion syndrome, FXTAS, micro RNA, DGCR8, DROSHA

Pat Howlin Lecture

Parental social support, coping strategies, resilience factors, stress, anxiety and depression levels in parents of children with mucopolysaccharidosis type III (MPS III, Sanfilippo syndrome) and parents of children with intellectual disabilities (ID)

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Objective: As part of a large research project on the presentation and impact of MPS III, the current study examined social support levels, coping, resilience, stress, anxiety and depression levels among parents of children with MPS III and parents of children with intellectual disabilities, and examined the differential effects on family functioning of having a child with MPS III.

Methods: Twenty three parents of children with MPS III and a control group of twenty three parents of children with intellectual disabilities completed postal questionnaires about their child's behaviour and level of intellectual disability, how they cope with these behaviours, their level of perceived social support, and the impact on parental stress, anxiety, depression and resilience levels.

Results: Results indicated that parents of children with MPS III reported fewer behavioural difficulties, more severe level of intellectual disability in their children, and similar levels of perceived social support, coping techniques, stress, anxiety and depression levels as parents of children with ID. Both groups of parents were in the clinical range for possible anxiety and depression. Parents with children with MPS III rated themselves as significantly less future-orientated and goal directed than parents of children with ID.

Conclusion: Services should pro-actively develop support packages for parents of children with MPS III that incorporate an understanding of the unique stressors and present-orientated approach of this population. Future research should examine gender differences between parental psychological functioning and impact on siblings, using mixed qualitative and quantitative approaches.

Neurofibromatosis (NF1) Targeted Therapy

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Neurofibromatosis type 1 (Von Recklinghausen's disease) is an autosomal dominant disorder characterized by multiple café-au-lait spots, benign tumors of the peripheral nerves and learning and behavioral problems.
The *NF1* gene codes for neurofibromin, a protein responsible for the downregulation of activated RAS proteins. RAS signalling is highly increased in many malignancies. More recently it has been shown that the RAS-pathway is also very important for learning and memory. There are now a number of inherited conditions known that are caused by mutations in genes coding for key components of the RAS-pathway such as neurofibromatosis type 1, Noonan syndrome, LEOPARD syndrome, CFC syndrome, Costello syndrome, and Legius syndrome. All these conditions are characterized by an increased activity of the RAS-pathway and they are grouped under the term Ras-o-pathies. These disorders are all associated with learning and behavioral problems.
A mouse model for neurofibromatosis type 1 revealed that reversing of the hyperactive RAS pathway was able to acutely correct the learning problems in adult mice. One of the drugs successfully used in mice was lovastatin. This opened the door to clinical trials in humans with neurofibromatosis type 1. At this moment three different trials are being conducted. Results will be available mid 2013.

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Targeted Therapies in Tuberous Sclerosis Complex

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Tuberous Sclerosis Complex (TSC) is a multi-system genetic disorder associated with mutations in the *TSC1* or *TSC2* gene. The TSC1-TSC2 proteins form an intracellular complex that acts as a global regulator and integrator of a range of physiological processes (GRIPP) in peripheral organ systems and the central nervous system. Loss of either TSC1 or TSC2 leads to overactivation of mTOR (mammalian Target of Rapamycin). Understanding this pathophysiological consequence has led to significant research activity including pre-clinical and clinical trials of mTOR inhibitors (mTORi) as targeted therapies for TSC. Results to date have shown mTORi to be real medical treatment options for SEGA (subependymal giant cell astrocytomas), and for renal AML (angiomyolipomas), and are showing promise in the treatment of facial angiofibromas, seizure disorders and some of the neuropsychiatric manifestations associated with TSC. In this talk we will discuss some of the progress to date, and consider the potential risks and benefits of next steps in targeted therapies for TSC.

C1: The role of Spred1 in a mouse model for Legius syndrome

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Background: Legius syndrome is an autosomal dominant disorder caused by inactivating mutations in the *SPRED1* gene. SPRED1 is a negative regulator of the RAS-MAPK pathway. This syndrome belongs to the group of the RASopathies and presents clinically as a mild neurofibromatosis type 1 phenotype. The disease is clinically characterised by the presence of multiple cafe-au-lait spots with/without axillary and inguinal freckling. Specific NF1-associated tumours are systematically absent. Learning and attention problems are regularly reported in children with Legius syndrome. **Methods:** To better understand the underlying mechanisms, a Spred1 knockout mouse model was investigated. **Results:** Spred1 knockout mice have a lower weight and typically show dysmorphic features. Hippocampus-dependent learning and memory deficits were noticed in Spred1 knockout mice. Preliminary data showed abnormalities in social behaviour in Spred1 knockout mice. Therefore, the tube test was used as a paradigm to measure the social hierarchy between mice. Motor performance and motor learning were investigated using the Erasmusladder. Preliminary results demonstrated deficits in associative motor learning. **Conclusion:** This Spred1 mouse model showed several interesting phenotypes and will allow us to test possible therapeutic strategies.

Keywords: Neurofibromatosis type 1, knockout mouse, Legius syndrome, learning, attention, behavioural phenotype

C2: Relative importance of autistic traits and hyperactivity-inattention for social functioning in neurofibromatosis type 1

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Background: Attention and social problems have been well documented in Neurofibromatosis Type 1. Autistic traits have received less attention, although they may also impact strongly upon the social functioning of people with NF1. **Methods:** In study 1, 30 NF1 participants (mean age 11.7 yrs; SD = 3.3) were compared with 30 controls (mean age 12.5 yrs; SD= 3.1) on social skills and peer problems. In study 2, 21 NF1 participants (mean age =12.5 yrs; SD = 2.7) were compared with 18 controls (mean age 13.8 yrs; SD 3.6) on social skills and social problems. In both studies autistic traits and hyperactivity-inattention were assessed. Analyses of (co-)variance and regression analyses were performed to investigate 1) whether autistic traits and/or hyperactivity-inattention could account for potential group differences regarding social functioning, and 2) what their relative contributions were to social functioning. **Results:** In both studies group differences were evident for all social outcome measures, autistic traits and hyperactivity-inattention. Group differences, which were largest for autistic traits, were not influenced by age or gender. Analyses of covariance showed that autistic traits could account for all group differences regarding social functioning, whereas hyperactivity-inattention could not. Regression analyses confirmed a much larger contribution of autistic traits to social functioning than for hyperactivity-inattention. **Conclusion:** Treatment and training programs aimed at improving social functioning of people with NF1 should be aimed more at autistic traits.

Keywords: Neurofibromatosis Type 1, autism spectrum disorder, hyperactivity, attention, social impairment, behavioural phenotype

C3: Language, cognition and behavior over time in young children with NF1 - A retrospective longitudinal study

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Background: Scores on intelligence scales, tests for language abilities and on questionnaires for behavioural and emotional problems are often lower in children with Neurofibromatosis type 1 (NF1) compared to controls. In the Netherlands, a large part of the children with NF1 (50%) attends special education. Because almost no longitudinal research has been done, it is yet unclear which factors contribute to the placement in regular or special education. It is also not known how these problems develop over time and how these problems influence each other. **Methods:** 70 children (mean age 4.5; 1.2 SD) with NF1 had their language development (comprehension and production) assessed, together with a neuropsychological assessment of nonverbal intelligence and behavioral and emotional problems (T1). Thirty of these children were seen on a later age (mean age 8;8, 2.3 SD) for a neuropsychological evaluation, comprising the assessment of verbal and performance intelligence and of behavioral and emotional problems (T2). Multiple regression analysis was performed to find the factors that influence behavioural problems and school placement. **Results:** A growing number of children show internalizing behavioral and emotional problems over time (22% on T1 and 52 on T2). Scores on receptive and expressive language tests are in the same range. Scores of 19 % of the children are below average for receptive language and 20-25% show below average expressive language abilities. Especially expressive language abilities on a young age could predict later internalizing behavioral and emotional problems. The placement in special education seems to be influenced by a combination of factors. **Conclusion:** Internalising behavioral and emotional problems increase with age. These problems (on T2) can be the result of problems in expressive language on an earlier age (T1). Behavioral problems on T1 (especially externalizing) predict school success on T2.

C4: Is there a link between neurofibromatosis type 1 and autism spectrum disorder?

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Background: Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder with an incidence of approximately 1 in 3000. Next to the clinical manifestations, cognitive deficits are reported in NF1 children. In general, an average IQ of about 90 is found and additional specific impairments in attention, memory, language and visuo-perceptual skills are described. However, concerning social development and functioning, limited data are described in literature. Nonetheless, clinical experience shows particularly persistent social complaints from parents and schoolteachers.

Method: A study was conducted in the University Hospital of Leuven (Human Genetics) to estimate the prevalence of social impairments and autistic symptoms in NF1 children (5-18 y), attending the clinic for annual medical follow-up. Information on social functioning and social behavior problems was collected from parents two questionnaires (SRS, CSBQ). Meanwhile, based on clinical need, in 27 NF1 children a comprehensive diagnostic examination (ADOS) on autism spectrum disorder (ASD) was performed.

Results: Results will be presented 1) on the prevalence of social deficits and autistic symptoms in NF1 children and 2) on the presence of ASD comorbidity, including the social phenotype, in NF1 children.

Conclusions: The prevalence of social impairments, autistic symptoms and ASD comorbidity is remarkably high in NF1 children. NF1 is an additional syndrome with a known genetic mutation associated with ASD affecting the Ras-MAPK pathway. This finding has consequences on the insight of behavioral, cognitive and neurobiological aspects of both NF1 and ASD.

C5: Investigating neurocognitive endophenotypes of autism spectrum disorders (ASD) by including an ASD sample with co-occuring neurofibromatosis type 1

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Background: Insight in the aetiology of autism spectrum disorder (ASD) is still limited, mainly due to considerable heterogeneity characterising the ASD population. This large heterogeneity stimulates the search for more 'genetically informative phenotypes' or 'endophenotypes' that allow us to delineate more genetically homogeneous subgroups. Endophenotypes are phenotypes that mediate the relationship between genotype and phenotype. The endophenotype hypothesis predicts that genetically distinct, more homogeneous ASD subgroups should be characterised by a distinct, more homogeneous endophenotypic profile. Our study aimed to test this hypothesis in an ASD subgroup of individuals with co-occuring neurofibromatosis type 1 (ASD+NF1). NF1 is an autosomal dominant single gene disorder. The ASD endophenotypes under study are neurocognitive measures of executive functioning (EF). **Method:** A battery of EF tasks was administered to children with ASD, children with ASD+NF1 and typically developing (TD) children and we investigated whether the groups demonstrated a distinct EF profile and whether particular EF measures showed less variance in the ASD +NF1 compared to the ASD sample. **Results:** The three groups were characterised by distinct EF-profiles, but no EF measure showed significantly less variance in the ASD +NF1 compared to the ASD sample. On the contrary, some of the measures had a significantly larger variance in the ASD+NF1 group. **Conclusions:** The three samples included in this study have a different genetic background and as predicted they all have a distinct endophenotypic profile. However, contrary to predictions, we found more variance in the EF performance of this group for some of the measures. This makes us question whether the ASD+NF1 group is indeed more homogeneous then the ASD sample and might indicate that the reduced variance hypothesis is too simplistic.

Keywords: neurofibromatosis type 1, autism spectrum disorder, executive function, behavioural phenotype, cognitive performance

Tom Oppé Distinguished Lecture

Refining the social phenotypes of genetic disorders

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Early descriptions of behavioural phenotypes invariably made reference to the social behaviour of children and adults with genetic disorders. These descriptions were crude but clearly indicated gross differences between syndromes, of a similar magnitude to those observed for more overt behaviour and psychiatric disorder for example. However, whilst the assessment of behaviours of clinical significance has become more refined, both conceptually and methodologically, the routine assessment and description of the dimensions of social behaviour has lagged behind. This may in part be due to an assumption that the broad appraisal of social impairments diagnostic of autism spectrum disorder (ASD) across syndromes would suffice to capture differences in social behaviour. However, it is becoming clear that: 1) there are differences between syndromes in ASD characteristics even when scores on ASD are comparable at item and\or subscale level 2) the assessment of ASD does not address important social behaviours such as social anxiety or selective mutism 3) there may be different cognitive endophenotypes that might underlie similar presentation of ASD social impiarments 4) other dimensions of social behaviour, such as motivation for social interaction, also differ across syndromes 5) motivation for social interaction can be unusually high and also very focused and 6) different trajectories for these dimensions might be evident across syndromes. Differences along these dimensions are evident in the broad social presentation of children and adults with Cornelia de Lange, Smith-Magenis, Rubinstein-Taybi, Angelman, fragile X and Cri du Chat syndromes. Description of these syndromes can be used as a vehicle for developing a broader social assessment that goes beyond the social impairments definitive of ASD.

D1: Cognitive-social development in microdeletion disorders: Wolf-Hirschhorn, Williams-Beuren, and Jacobsen syndromes

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Background: Cognitive-behavioural profiles in children with intellectual disability (ID) can be used to identify strengths and weaknesses to target skills for training. Developmental trajectories reveal other limitations as these individuals age. For research, profiles and trajectories generate hypotheses for gene-brain-behaviour pathways. We compared cognitive-behavioural profiles and developmental trajectories in children with microdeletion disorders: Wolf –Hirschhorn [WHS], Williams-Beuren [WBS], and Jacobsen syndrome [JBS]. **Methods:** Sixty-four children diagnosed with WHS [n=20], WBS [n=34], or JBS [n=10] were recruited. Ages at initial testing [T1] ranged from 4 to 20 years. Male-female ratio was 1:1. Children were assessed for cognitive ability using the Stanford Binet: Fourth Edition and adaptive behaviour using the Vineland Adaptive Behavior Scale [VABS]. Forty-one participants were available for retesting two years later [T2]. **Results:** At T1, mean IQs were significantly different from each other. Children with JBS were least cognitively affected [Mean IQ=59.2±16.2]; those with WHS the most severely affected [42.1±11.2]. Cognitive profiles in WHS and WBS show similar relative strengths in Verbal [VR] and Quantitative Reasoning [QR]; in JBS, relative strength is in QR only. In WHS and WBS, there are similar relative weaknesses in Abstract/ Visual Reasoning [AVR] and Short-term Memory [STM]; in JBS, there is weakness in STM only. Mean Developmental Quotients (DQ) were also significantly different. Interestingly, children with WBS were least affected [Mean DQ=56.6±16.2]; those with WHS were more severely affected [Mean DQ=35.6±13]. On the VABS children with WBS or WHS show significant strengths in Socialization and weakness in Daily Living Skills; children with JBS exhibit a flat adaptive behaviour profile. At T2, profiles from all three syndromes show no significant changes from T1, which is different from the developmental trajectories observed in fragile X syndrome. **Conclusion:** Different cognitive-behavioural profiles suggest distinctive gene-brain-behaviour pathways in these disorders.

D2: Expanding the phenotypic profile of boys with XXY - Is it all about the X?

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Background: The neurodevelopmental profile of males with XXY (Klinefelter Syndrome) has been characterized by developmental dyspraxia, language based learning disorders, executive dysfunction and attentional deficits. Research studies have been confounded by ascertainment bias and insufficient numbers of study participants. **Objective:** To assess the impact of learning disorders in family members on the phenotypic profile of the child with XXY. **Methods:** 65 boys with XXY diagnosed prenatally who did not receive hormonal replacement had comprehensive neurodevelopmental evaluations between 36 and 108 months. The assessments included intelligence (nonverbal and verbal), neuromotor (fine and gross), speech and language. **Results:** There was significant difference between the group with learning disabilities and those without in the multiple neurodevelopmental domains on the Wechsler the VIQ p=0.0063, FSIQ p=0.0002, on the Leiter the Brief IQ p=0.0793, in Auditory Comprehension p=0.0505, Expressive Communication p=0.0055 and on multiple neuromotor domains on Manual Coordination p=0.0669, Fine Motor Control p=0.0788 and the Beery Motor Coordination p=0.0144. **Conclusion:** Our study demonstrates the significant influence of family learning disorders on multiple domains of development in a large and homogenous group of boys with XXY. It further expands our understanding of the phenotypic profile of this chromosomal disorder. Our findings suggest that some of the variability in neurodevelopmental performance is attributable to factors other than the presence of an additional X. Family history of learning disorders may increase the vulnerability of the child with XXY and anticipatory guidance should be provided.

Keywords: XXY syndrome, Klinefelter syndrome, learning disability, behavioural phenotype, family study, motor development

D3: Characterising the behavioural phenotype of Rett syndrome

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Background: Rett Syndrome (RTT) is a neurodevelopmental disorder mainly affecting females and usually associated with a mutation of the *MECP2* gene. Genetic and neurobiological understanding of RTT has advanced but there is still insufficient understanding of behavioural development. The aim here was to explore behavioural variation amongst females with RTT across age, severity of clinical phenotype, mutation and age of regression. **Methods:** The 91 participants have a clinical diagnosis of Classic RTT, Atypical RTT or *MECP2* related disorder. Clinical symptoms were assessed using a simplified Severity Score, RTT behavioural features using the Rett Syndrome Behavioural Questionnaire (RSBQ), mood using the Mood, Interest and Pleasure Questionnaire (MIPQ), impulsivity and overactivity using The Activity Questionnaire (TAQ) and self-injurious behaviour using the Challenging Behaviour Questionnaire (CBQ). **Results:** Severity of clinical presentation, activity level (TAQ total score, overactivity and impulsivity subscale) and mood varied across age groups. Mutation and age of regression were associated with the severity score. No significant differences were found in RSBQ score between groups, either based on age, type of mutation or age of regression. Self-injury was reported in 23.7% of the sample and was more frequent in girls with a more severe phenotype. **Conclusion:** This study attempted to describe the behavioural phenotype of a group of females with RTT. Although analysis did not reveal differences across subgroups in the RSBQ, interesting findings were highlighted with other measures. Depression and impulsivity and overactivity have never been reported in RTT, thus these findings add to the literature on RTT.

Key-words: Rett syndrome, behavioural phenotype, self-injurious behaviour, hyperactivity, depression, MECP2

D4: Effect of adult familiarity and level of attention on social behaviour in Smith Magenis syndrome

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Background: Reports suggest that there is an unusually strong drive for adult attention shown by individuals with Smith Magenis syndrome (SMS). Limited experimental investigation of this behaviour has been carried out to date. **Methods:** Twenty one children with SMS and a contrast group of chronological and mental age matched children (n=21) with Down syndrome (DS) were exposed to structured social situations, in which familiarity of adults present and level of available attention were manipulated. Children's mothers and an unfamiliar adult alternated roles as an interacting adult who provided high and low levels of attention. An unresponsive adult was also present but provided no attention in order to assess behaviour in the presence of competing sources of attention. **Results:** No group differences were found for enjoyment of social interactions but children with SMS demonstrated stronger motivation to interact with their mother than the unfamiliar researcher whereas children with DS showed stronger preference towards the unfamiliar researcher. Children with SMS also accessed the attention of the unfamiliar researcher as an alternative source of attention when their mother was unavailable less than children with DS. No differences were found for these behaviours towards the interacting adult. **Conclusion:** Results support suggestions of unusual social behaviour in SMS, characterised by strong drive for the attention of familiar adults and relative lack of interest in strangers. Results are considered in the context of factors underpinning motivation for attention and potential impact of this behaviour on caregivers and implications for socially motivated challenging behaviour.

Keywords: Smith-Magenis syndrome, behavioural phenotype, social motivation, challenging behaviour, social interaction, attention seeking

D5: 22q11 Deletion syndrome in moderate and severe learning disabled adults. Relation between psychosis and cognitive deterioration

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Background: 22q11 deletion syndrome (22q11DS) is the most common recurrent copy-number variant disorder, which is caused by a microdeletion in chromosome band 22q11.2 occurring with an incidence of 1 in 4000. Most studies report that 22q11DS is associated with mild or borderline intellectual disability. There are hardly any reports on 22q11DS participants with moderate or severe intellectual disability. Behavioural and psychiatric characteristics of this group have been poorly described. **Methods:** In this study we described adult participants with 22q11DS (n= 33) and a Full Scale IQ (FSIQ) below 55. Participants were divided into two groups: one group who had previously been measured to have a higher FSIQ, but now have a FSIQ ≤ 55 caused by cognitive deterioration, the deterioration group (n=21) and one group with a FSIQ ≤ 55 who had always functioned at this level, the stable low IQ group (n=12). We describe and compare behavioural and psychiatric characteristics in those two subgroups. The Adult Behavior Check List (ABCL) and the Mini Psychiatric Assessment Schedule for Adults with a Developmental Disability (Mini PAS-ADD) were administered to assess for psychopathology. The Vineland Screener was used to assess present level of intellectual functioning. **Results:** Strikingly high scores on psychopathology subscales were found for both subgroups. 22q11DS patients with cognitive deterioration (the level of IQ drop) in adulthood showed higher rates of comorbid psychopathology, particularly psychosis, compared to adult 22q11DS patients with premorbid moderate to severe intellectual disability. Furthermore, a positive correlation between psychosis and cognitive deterioration was found **Conclusion:** In conclusion, we found that in the participants with 22q11DS and a low IQ, psychosis during life is associated with significant cognitive decline. Longitudinal studies are needed to provide more insight in the behavioural, cognitive and psychiatric problems of this specific group.

Keywords: 22q11DS, psychosis, cognitive decline, psychopathology, behavioural phenotype, aging

Developmental intervention within the social phenotype

Jonathan Green

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Modern intervention to improve social interaction and communication can and should be based on current and emerging developmental theory and subject to rigorous testing. Appropriately designed trials not only test effectiveness but can be used as 'developmental experiments' with which to better understanding in turn developmental theory.

My main focus will be on the emerging social impairments in autism spectrum disorder, but I will also touch on convergent thinking in relation to other developmental and familial risk.

Building on recent developmental research in the infancy prodrome of autism, I discuss theory and evidence behind the Intervention within the British Study of Infant Siblings (iBASIS) trial, currently ongoing, which tests a prodromal intervention targeted at infants aged 9 months at risk of autism. I will compare this with related approaches to other forms of developmental social risk.

In later development following diagnosis I discuss the Preschool Autism Communication Trial (Green et al 2010), which tested a parent mediated video-aided intervention in a large RCT. Discussing its results I illustrate how we used this trial also as a developmental experiment and what we have learned from it about prospects for autism intervention and about autism development.

These findings are set in context of increasing numbers of better quality trials in autism in recent years with some convergent findings on treatment sensitive and treatment resistant areas of the disorder. Progress will come from an accumulation of increasingly large trials of good quality which iteratively build on analysis of previous ones as well as testing new concepts.

I touch on tasks for the future, including:

- Integrating emerging neurodevelopmental research into new treatment models
- Conceptualising social impairments and strengths to develop common measures that are change sensitive
- Learning from cross–syndrome studies

Jonathan Green May 2012

Abstracts for Poster Presentations

Poster 1: Predictors of higher-level language skills in XXY (Klinefelter syndrome)

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Background: Children with 47,XXY are at increased risk for higher-level language deficits; however, our understanding of contributing cognitive factors is limited. This study explored the relationship between higher-level language skills (i.e., figurative and abstract language) and receptive/expressive language skills, cognitive ability, and executive functioning skills in children with XXY. **Methods:** 35 boys (age 6-21) underwent speech-language and neuropsychological assessment. The battery included standardized measures of expressive and receptive semantics and syntax, higher-level language skills, cognitive ability, and executive functioning (EF). Single sample t-tests evaluated differences in these domains relative to normative expectations. Hierarchical multiple regression analyses tested the extent to which cognitive and EF skills predicted higher level language, while accounting for semantic and syntactic skills. **Results:** Single sample t-tests showed deficits in expressive naming, figurative and abstract language, behavioral regulation, and metacognitive skills compared to normative expectations ($p<.05$). Multiple regression analyses showed that 87% of variance in higher level language skills could be explained ($p<.01$). Language and cognitive ability accounted for 57% of the variance. The addition of EF variables accounted for an additional 30% of the variance, and is a significant, unique predictor ($p<.05$). **Conclusion:** Results provide a better understanding of the cognitive factors contributing to higher-level language weaknesses, with EF having a unique contribution above basic language skills and cognitive ability. Clinicians working with this population should routinely assess both basic language and EF skills, and determine the impact of each on higher-level language deficits. Interventions targeting both language skills and EF may be needed in order to improve higher-level language function.

Poster 2: Behavioural problems, social development, executive functioning and sensory stimuli processing in girls with 47,XXX syndrome

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47,XXX is a chromosomal anomaly (SCA), characterized by the presence of an extra female sex chromosome and has an incidence of 1 out of 1000 females. In literature, descriptions of the phenotype of the Triple X syndrome are limited and results are highly variable because of the cognitive heterogeneity of the studied groups. This study aims to construct a descriptive picture of the behavioural problems, social development, executive functioning and sensory processing in these girls with normal IQ (> IQ 70). Families of seven girls with 47,XXX agreed to participate in this research project. The ages ranged from 3 to 14 years. The test battery contains different diagnostic tests, interviews and questionnaires. Analysis of the data showed that girls with 47,XXX and normal IQ had significantly higher scores on internalizing and externalizing behavioral problems in comparison with normal peers. They presented more somatic problems, social problems, attention problems and anxiety/depressive behavior. Results on the executive functioning showed no significant differences from norm scores except for cognitive flexibility. More than half of the study-group experienced problems in sensory processing, particularly sensorial oversensitivity and emotionally overreactivity are observed. These results and observations will be discussed. This study has some important restrictions (small number, selection bias and range in ages) but was part of a larger research project on behavioral phenotype and sex chromosomal abnormalities. Insight in the underlying mechanism of impaired development in these children is crucial to gain insight into the biological factors explaining the sex differences in disorders of social brain development and to select particular aspects of development requiring specific guidance and education.

Poster 3: Temperamental phenotypes in autism spectrum disorder and in Down syndrome: a meta-analytical evaluation

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Background: Temperamental variables become increasingly popular in the study of behavioral phenotypes in developmental disorders. To date, most of these studies have focused on autism spectrum disorders (ASD) or Down syndrome (DS). The wide diversity of trait frameworks, models and measures, however, substantially hinders the integration of this expanding research, hampering a critical evaluation of adopting such trait approaches. Applying an empirically-rooted, overarching trait taxonomy, this study presents two meta-analyses on how individuals with ASD and subjects with DS differ from controls in their temperamental characteristics. **Methods:** Extensive literature searches yielded 58 (ASD-meta-analysis) and 27 unique samples (DS-meta-analysis), providing temperamental information on 2100 subjects with ASD and 972 individuals with DS. From these studies, 278 (ASD-meta-analysis) and 135 (DS-meta-analysis) Hedges' *g* effect sizes were compiled and classified into six higher-order domains: Activity, Sociability, Emotionality, Agreeableness, Conscientiousness, and Sensitivity. Meta-analyses were performed for each of these six domains, applying random-effects modeling. **Results:** Compared to controls, persons with ASD present with a clearly distinct trait profile, showing substantially lower Sociability, Agreeableness, and Conscientiousness, moderately lower Sensitivity and higher Emotionality, but no deviation on Activity. The temperamental profile of persons with DS is less differentiated from controls: no differences are found for Activity, Sociability, and Agreeableness. Modest effects elucidate that persons with Down syndrome express slightly lower Conscientiousness, Emotionality, and Sensitivity than controls. In both meta-analyses, the between-studies variance did not depend on sample features but was moderated by type of trait assessment. **Conclusion:** The differential trait profiles associated with ASD and DS substantiate that temperament is a promising focus of inquiry in the study of behavioral phenotypes in developmental disabilities.

Poster 4: How stereotypical is the personality of children with Down syndrome? A three-group comparison

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Background: In popular media, persons with Down syndrome (DS) are often attributed personality traits such as 'pleasant', 'affectionate', 'predictable', 'stubborn', or 'passive'. Empirical research on this personality stereotype, however, has led to few conclusive answers. Up till now, studies often focused on young children or did not include controls also showing intellectual disabilities (ID). **Methods:** This study compares maternal ratings on the Hierarchical Personality Inventory for Children across three groups of 5-to-15 years old children: 23 children with DS, 23 typically developing (TD) matched controls, and 19 children with autism spectrum disorders (ASD) having co-occurring ID. **Results:** Compared to TD-controls, both the DS and ASD+ID-group show dramatically lower means on Imagination and Conscientiousness, moderately lower means on Extraversion and Agreeableness, but no deviations on Energy and Emotional Stability. Contradicting the DS-personality stereotype, we found that children with DS are more shy and equally compliant, dominant, irritable, persistent, and optimistic than TD-children. The ASD+ID-personality profile is more maladaptive and extreme than the personality profile of DS-children, showing substantially lower levels of Imagination (creativity, curiosity), Conscientiousness (achievement motivation) and Extraversion (optimism). Variance analyses reveal that the ASD+ID and TD-groups display the same degree of trait variability for all traits, whereas DS-individuals express significantly less trait variance in Conscientiousness and Extraversion. **Conclusion:** The documented commonalities and differences between children with DS and controls contradict the lingering DS-personality stereotype. Moreover, the diverging trait profiles of DS and ASD+ID substantiate the potential of personality traits in expanding our knowledge of the broad phenomenology within developmental disabilities.

Poster 5: Neuropsychopathology in 7 patients with the 22q13 deletion syndrome: presence of bipolar disorder and progressive loss of skills

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Background: The 22q13 deletion syndrome is characterised by intellectual disability (ID), delayed or absent speech, autistic-like behaviour and minor, nonspecific dysmorphic features. The deletion of the SHANK3 gene is thought to be responsible for these features. **Methods:** In this study, the clinical data of 7 patients with the 22q13 deletion syndrome are presented, obtained by clinical genetic examination, direct behavioural observation and by interview of family members and/or caregivers, complemented by behavioural questionnaires. The specific focus was on behaviour, psychopathology and the level of functioning during life course in order to determine common features that might contribute to the delineation of the syndrome. **Results:** Major findings were a high incidence of psychiatric disorders, more in particular bipolar disorder (BPD) and attention deficit hyperactivity disorder (ADHD), and a sudden deterioration after acute events, in addition to a progressive loss of skills over years. **Conclusion:** Therefore, a deletion of SHANK3 may result in a dysfunctional nervous system, more susceptible to developmental problems and psychiatric disorders on the one hand, less able to recuperate after psychiatric and somatic events, and more vulnerable to degeneration at long term on the other hand. These results are exploratory and need to be confirmed in a larger sample.

Poster 6: The 15q11.2 deletion and autism spectrum disorders

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Background: Autism Spectrum Disorders are frequent genetic neurodevelopmental disorders. Several studies have shown the association of Copy Number Variations (CNVs), both *de novo* and rare inherited, with ASD. Deletions of chromosome 15q11.2 (BP1-BP2 region) including *CYFIP1, NIPA1, NIPA2* and *TUBGCP5*, are associated with intellectual disability, epilepsy, schizophrenia and autism. Of interest, *CYFIP1* is an important binding partner of FMRP. *FMR1* mutations cause Fragile X syndrome, often associated with autism (30%). Also, patients with the Prader-Willi phenotype caused by paternal deletions of the 15q11-13 BP1-BP3 region present a more severe behavioral phenotype (ADHD, autism and OCD) compared to those having the BP2-BP3 deletion. Together, this pinpoints the 15q11.2 deleted region as a risk variant for ASD.

Method: Quantitative Real-Time Polymerase Chain Reaction (q-RT-PCR) is used to test the occurrence of deletions of *CYFIP1* in ASD patients with intellectual disability (IQ<70), ASD patients with normal intelligence (IQ>70) and controls. We also performed exome sequencing on three ASD families with the proband carrying the del15q11.2, inherited from a normal parent.

Results: We present the results of an association study of *CYFIP1* deletions in ASD patients. Interestingly, the phenotype of del15q11.2 is very variable and this variant is often inherited from a normal parent. As a consequence, we hypothesize that additional variants in the other allele, in other genes of the FMRP network or known ASD genes can contribute to the phenotype of these patients (multi-hit model). We present the results of exome sequencing of three ASD families, searching for additional hits contributing to the phenotype.

Conclusion: The 15q11.2 deletion is likely to be a risk factor for ASD with/without mental retardation. A multi-hit model could explain the variability of the phenotype.

Poster 7: An 18 year cohort study of behaviour in Williams syndrome

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Background: The Australian Child to Adult Development (ACAD) longitudinal study has followed a cohort of young people with intellectual disability (ID) for 18 years aiming to identify patterns and predictors of psychopathology overtime. Participants were identified from an epidemiological register of people with all levels of ID, as well as from specialist genetic clinics and parent organisations. Included in the ACAD sample was a cohort with Williams syndrome (WS).

Method: Parents and/or professional carers completed the Developmental Behaviour Checklist (DBC) on five occasions. The DBC measures behavioural and emotional disturbance in people with ID and includes five subscales: disruptive/antisocial; self-absorbed; communication disturbance; anxiety; and social relating. A random effects regression was conducted to compare the WS cohort to the epidemiological cohort with ID of mixed aetiology on patterns of psychopathology.

Results: Emotional and behavioural problem scores were higher in the WS cohort ($p<.001$) but decreased overtime at a faster rate ($p=.021$) than in the epidemiological cohort, with gender and ID level controlled. A similar pattern was evident for the communication subscale of the DBC. On the disruptive, self-absorbed and anxiety subscales, scores were higher on average overtime in the WS cohort, but did not decline at a different rate from those of the epidemiological cohort. Social relating scores increased slightly across time in both groups, and did not differ significantly between them.

Conclusions: The WS behavioural phenotype persists in adulthood. While the level of emotional and behavioural disturbance, communication disturbance and anxiety decreases overtime, it remains higher than in people with ID of mixed aetiologies.

Poster 8: The stepping stones triple P parenting program and syndrome specific modules

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Background: Stepping Stones Triple P (SSTP) is a public health strategy delivered to parents of children aged 0-12 with developmental disabilities (DD). It has five levels of increasing intensity, including tip-sheets, seminars and self-directed teaching, individual and group practitioner delivered sessions, and enhanced parent-training program. 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.

Method: Syndrome specific modules and materials will be developed to complement the multilevel SSTP five-tiered program and will include tip-sheets, seminars, practitioner led individual and group sessions, and enhanced parent training. Current intervention literature and consultation with carers and consumers will inform this process. The modules will be trialled in focus group discussions with families, before being implemented into SSTP.

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: to be determined.

Conclusions: 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.

Supported by a Program Grant of $5.25 m from the National Health and Medical Research Council of Australia.

Poster 9: Expansion of the language phenotype in XXY (Klinefelter syndrome)

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BACKGROUND: Children with 47,XXY are at increased risk for many neurodevelopmental challenges, including global weaknesses in expressive and receptive language. This study more critically examines semantic and syntactic skills, as well as higher level language abilities (i.e. figurative and abstract language) in children with XXY. **METHODS:** 35 boys (age 6-21) underwent speech-language assessment. The battery measured receptive and expressive semantics (Peabody Picture Vocabulary Test- IV, Boston Naming Test), receptive and expressive syntax (Test of Reception of Grammar, Clinical Evaluation of Language Fundamentals-4– Formulating Sentences), and higher level language skills (CELF-4 Understanding Paragraphs, Test of Language Competence-Figurative Language). Mean scores were compared to normative expectations, and subdomain differences were evaluated to elucidate the language profile. **RESULTS:** Expressive semantics and higher level language skills were significantly lower than expected compared to normative expectations ($p<0.05$; BNT SS=85.4; TLC-FL SS= 85.3; CELF-4-UP SS=88.6).Expressive syntactic skills (CELF-FS SS= 103) and receptive skills (PPVT-4 SS= 101.8; TROG SS= 95.4) did not differ significantly from norms. Comparisons between expressive and receptive semantic subtests (BNT vs. PPVT-4) showed significant weakness in expressive naming ($p<0.001$); however, no significant differences were found between expressive and receptive syntactic skills ($p=0.14$). There were also no differences between the higher level language measures (TLC vs. CELF-UP, $p =0.43$). **CONCLUSIONS:** Results expand upon previous description of the XXY language phenotype by characterizing specific weaknesses in expressive semantic skills and higher level language abilities, with preservation of receptive vocabulary and syntactic abilities. Further studies are needed to understand better the effects of cognitive, executive, attention, and working memory skills on language outcome. Improved understanding of language development in boys with XXY is critical as language disorders influence academics, social interactions, adaptive functioning, and vocational aptitude.

Poster 10: The Hebb-Williams mazes (HWMS): a novel visual-spatial assay for assessing synaptic protein deficits and behavioural correlates in *FMR1* knockout mice

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Background: Fragile X syndrome (FXS) is the most common cause of inherited mental retardation and involves a loss of the fragile X mental retardation protein (FMRP). FMRP has many functions one of which is the dynamic regulation of mRNA translation in response to learning. *In vitro* examination in mice and post-mortem autopsies in humans have identified dendritic spine abnormalities in the absence of FMRP. PSD-95 is a dendritic morphological protein and a molecular target of FMRP. It is unknown whether this protein is increased in expression following behavioural learning or how the loss of FMRP may impact PSD-95 levels. **Methods:***Fmr1* knockout (KO) mice and FMRP-intact controls were run through the HWMs, a series of visual-spatial problems of increasing difficulty. PSD-95 protein levels relative to β-tubulin levels were analysed by ANOVA. Pearsons *r* was used to correlate relative protein levels with total errors recorded on the HWMs. **Results:**Contrasted with non-runners of both genotypes, there was a significant upregulation of PSD-95 protein levels in FMRP-intact mice. There was a significant negative correlation of PSD-95 protein levels with total number of errors when collapsing across trials. PSD-95 protein levels accounted for 22% of the variance in the total number of errors on the HWMs. Within groups, PSD-95 protein levels accounted for 28% of the variance in maze errors in KO mice and 18% in normal controls. **Conclusion:**These data suggest that the HWMs are a valid measure and may be a useful assay to examine the impact of pharmacological agents such as mGluR-5 antagonists in reversing protein deficits associated with FXS.

Poster 11: Behavioral phenotype of neurofibromatosis type 1 (NF1)

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Background: NF1 is a single-gene neurodevelopmental disorder for which the gene-phenotype neurobiological pathway is well elucidated. While NF1 is noted mainly for its physical manifestations, the main morbidity from the disorder is actually in cognitive impairment, social disability and behavioural difficulties. The characteristics of the NF1 behavioural phenotype have been uncertain till recently because of the lack of well-designed epidemiological studies on representative samples. **Methods:** Parents & teachers of children aged 4-16 years were sent postal questionnaires to screen for Attention Deficit Hyperactivity Disorders, (ADHD) Autistic Spectrum Disorders (ASD) and other Emotional disorders. The measures includes Conners questionnaire, Social Responsiveness Scale (SRS) & Strengths & Difficulty questionnaire (SDQ). **Results:** The response rate was 49% (108). 26% scored on the severe range for ASD on the SRS, 53% for ADHD on Conners questionnaire and 41% in the abnormal range for total difficulty score on the SDQ. **Conclusions:** The high levels of morbidity in this population has further clinical and research implications. It has been consensus that main morbidity lies in ADHD and learning problems. The finding of prevalence of ASD has not been documented before. These finding are internationally novel in the rigour of the research design that produced them, the size of the sample and its representativeness. This work is also relevant in establishing NF1 as a single-gene disorder model of autism.

Poster 12: Parents with schizotypal feature may be a high-risk group for offspring autism

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Background: Autism shows growing tendency of prevalence, from 2002 to 2008 the number of diagnosed cases grew by 95%. There is strong evidence that genetic predisposition being facilitated by epigenetic factors needs an environmental trigger. Investigation of parents of autistic patients may lead us to early determination of individuals at risk. **Methods:** We investigated 179 individuals (12-65 years old) with Schizotypical Personality Questionnaire (SPQ), 18 of them were diagnosed with F21, others never consulted a psychiatrist. 66 were college students, 85 professionals, 50 of them were immediate family of patients with different mental pathology (mostly parents of autistic children). EEG was recorded in 27 individuals. **Results:** Of 151 healthy individuals 27 (18%) showed SPQ score over 24, which allowed to suggest that they were schizotypal. Such high score was found in 17 relatives of mental patients (34%) and in 10 individuals without mental patients within immediate family (10%). Comparison of different groups showed that negative symptoms (according to Four-Factor Structure, Compton 2009) were more frequent in schizotypal patients (76%) and parents (82%) than in individuals with schizotypy in population (40%). Correlation analysis of SPQ data with spectral parameters of EEG revealed a joint mechanism of schizotypy symptom complex, reflected in lower power of theta-activity and higher level of beta-activity, most probably associated with disbalance of inhibitory and excitative processes of the central nervous system. **Conclusion:** Thus, parents of autistic children show schizotypal features three times more often than general population. This indirectly supports the hereditary theory of autism. Early identification of risk families could enable more cautious application of possibly triggering interventions.

Poster 13: The social phenotype of Lesch Nyhan syndrome

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Background: Lesch Nyhan Syndrome (LNS) is an x-linked recessive, inborn metabolic disorder characterized by hyperuricemia, cognitive deficits, infantile onset of dystonia, and stereotypical self-biting and impulsive aggressive behavior. Despite their aggression towards others affected individuals are socially engaging and are apologetic following their aggression toward others.They engage socially and may inhibit their self injury in the company of a trusted parent or staff member in whose presence it is safe to release their restraints. **Methods:**Ten subjects with classic Lesch Nyhan syndrome and their parents completed a battery of psychosocial ratings including personality inventories. **Results:**Subjects demonstrated prosocial attitudes on psychosocial testing. on the five-factor NEO Personality Inventory they scored in the clinical range on Neuroticism and Extraversion, in the average range for Openness and Agreeableness, with low scores for Conscientiousness. **Conclusion:** Individuals with Lesch-Nyhan Syndrome are sociable and seek social stimulation. On clinical testing these subjects were socially attached to parents and caregiver but prone to impulsive aggression towards others. On the NEO personality inventory they score as unstable extroverts with high scores on neuroticism and extroversion.

Poster 14: Developing stimulus control of the high-rate social approach behaviours of children with Angelman syndrome

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Background: The behavioural phenotype of Angelman syndrome (AS) is characterised by a strong drive for social attention as evidenced by laughing and smiling in response to interaction, high rates of social approach behaviours and socially maintained challenging behaviours. Although communication-based interventions have successfully manipulated the levels of challenging behaviours, they do not reduce approach behaviours at times of adult unavailability. This proof of principle study assessed an intervention devised to teach children to discriminate adult availability using an environmental cue. **Methods:** Discrimination training was conducted with four children with AS aged 5:11 to 10:0 within an alternating treatment and withdrawal design. Sessions comprised alternating conditions of social reinforcement and extinction signalled using a novel cue. 25-35 discrimination training sessions were conducted with each participant. Levels of approach behaviours and the focus of attention (object vs. people focussed) were measured. **Results:** All participants showed lower rates of approach behaviours and eye contact when extinction conditions were signalled. This change occurred in the final 5-10 sessions for all participants, indicating a long training period. Despite the change in approach behaviours, three participants showed no change in the focus of attention across conditions. **Conclusion:** The initial results from this study suggest that after a long training period, the use of a novel stimulus may serve as a cue for children with AS to discriminate between times of adult availability. The consistency in participants' focus of attention suggests a change in behaviour rather than motivation. The data indicate a potentially effective intervention but highlight the need for extended teaching procedures within this population.

Poster 15: The genetic basis of autism spectrum disorders: identification and analysis of rare structural variants

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Background: The genetic causes of autism spectrum disorders (ASDs) are heterogeneous and still unknown in the majority of cases. Structural chromosomal variants (or copy number variants (CNVs) were found in sufficiently high frequency to suggest that cytogenetic and microarray analyses are considered in routine clinical workup. An interesting paradigm for clinical practice is that each rare CNV may account for only a small proportion of variance in ASD at the population level but may have a large effect in a few families in which it segregates.

Method: CNV association studies are performed in a family based cohort. The sample contains 195 families ascertained through one or more autistic probands with normal intelligence or mild intellectual disability. The study cohort contains 680 individuals: 252 probands, 392 parents, 36 unaffected siblings belonging to 195 families. All probands, unaffected siblings and parents are genotyped with Illumina OMNI 2.5-8v1 SNP arrays. For all individuals, an extensive list of phenotypic information is collected including IQ, SRS scores, 3DI, clinical genetic examination and family history.

Results: We present the results of a family based study on the validity of CNV detection in ASD using a high resolution platform. We study the segregation of known and novel rare CNVs with qualitative and quantitative autism phenotypes. Additionally association studies are performed with respect to e.g. gene content, parental origin.

Conclusion: With this study we aim to contribute to the clinical validation of the current knowledge on ASD risk variants and to the identification of novel variants.

Poster 16: Describing the developmental trajectory of executive function in Cornelia de Lange syndrome

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Background: Executive function impairments, autism spectrum phenomenology and repetitive behaviour have been described in Cornelia de Lange syndrome (CdLS). In this study, we address the associations between these aspects of the behavioural and cognitive phenotype of CdLS and their relationship with age **Methods:** The parents/carers of 192 individuals with CdLS (N=51; mean CA= 24.7; SD= 10.2), fragile X syndrome (FXS) (N=89; mean CA= 24.6; SD= 9.6) and Rubinstein Taybi syndrome (RTS) (N= 52; mean CA= 21.53; SD10.86) completed questionnaires from the Behaviour Rating Inventory of Executive Function-Preschool Version (BRIEF-P), the Mood, Interest and Pleasure Questionnaire - Short Version (MIPQ), the Repetitive Behaviour Questionnaire (RBQ) and the Social Communication Questionnaire (SCQ) **Results:** Data collection is ongoing, but data will be analysed using regression models and age band comparisons to describe the developmental trajectory and profile of executive function in CdLS compared to other syndromes. Preliminary analysis of BRIEF-P data shows markedly lower raw scores in the CdLS group on the Global Executive Composite score, when compared to FXS and RTS groups. **Conclusion:** Data collection will be analysed to describe the developmental trajectory of executive function in CdLS, to assess the changes in mood and behaviours associated with autism spectrum phenomenology (SCQ, MIPQ, RBQ) and describe how these map onto the developmental trajectory. Findings will be discussed in relation to changes in the behavioural phenotype of CdLS with age in the context of the ASD symptomatology of the syndrome.

Poster 17: Executive function deficits in adults with tuberous sclerosis complex

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Background: Tuberous Sclerosis Complex (TSC) is a genetic disorder with multi-system involvement. The behavioural phenotype includes a range of neuropsychological manifestations. There are few studies that have investigated executive skills in the disorder, either by group-wise comparisons or by examining the profile of executive deficits. The aim of this study was to examine four components of executive skills in normally-intelligent adults with or without TSC. We hypothesized that the TSC group would perform significantly worse than the non-TSC control group. **Methods:** The sample consisted of 21 adults with TSC and a gender-, age- and performance IQ-matched control sample of 18 non-TSC adults. Four subtests of the Cambridge Neuropsychological Test Automated Battery (CANTAB) were used to assess simple spatial working memory, self-ordered spatial working memory, planning, and attentional set-shifting. Data were analysed for group differences. In addition, the individual profiles of the TSC group were examined to identify the rates and pattern of clinical executive deficits (performance <5th Percentile). **Results:** Results showed significant group-wise differences on the Spatial Span (SSP) task and the Between Error Score of Spatial Working Memory (SWM), but not on the other tasks. Overall 52% of TSC individuals scored in the impaired range on one or more executive function task. Ten percent (10%) were impaired on the SWM task, 20% on the planning (SoC) task, 30% on the extra-dimensional aspects of the set-shifting task, and none were impaired on the SSP task. **Conclusion:** We confirmed that adults with TSC, even with entirely normal intellectual ability, may present with a mixed range of clinically significant deficits in various executive functions. Interestingly, group-wise comparisons suggested a different impression of executive weaknesses in TSC. This study highlighted the importance not only of performing group-wise comparisons but also of investigating profiles of clinical deficits in those with TSC and other genetic disorders.

Poster 18: Agrammatism in Prader-Willi syndrome: a single case study of acquisition of prepositions and case in Polish

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Background: Language deficits constitute an important aspect of the social phenotype of Prader-Willi syndrome (PWS), a rare genetic condition with multisystemic manifestations, including psychomotor delay. Comprehensive reviews of language skills in individuals with PWS indicate widespread presence of grammatical impairments affecting morphosyntax, inflectional errors and omissions of function words in particular. However, in-depth research on this aspect of linguistic development in PWS has been scarce. Polish prepositions assign case to the following noun, which makes them particularly suited for studies on morphosyntactic development. **Methods:** A single case study of the acquisition of prepositions and case marking in an 8 year old Polish speaking girl with PWS. Spontaneous speech samples were recorded in 12 sessions held in everyday settings over a 2 month period. As the spontaneous speech was characterized by frequent omissions of even most basic spatial prepositions, a spatial relation understanding test was administered, followed by an elicitation of spatial prepositions task to assess possible spatial term deficit. **Results:** The analysis revealed a pattern of omission of prepositions in obligatory contexts in spontaneous speech that could not be explained in terms of language delay or deficits in understanding of spatial terms, suggesting involvement of a syntactic or post-syntactic processing level. Those prepositions that on elicitation tasks appeared to be best mastered were missed most frequently in spontaneous speech, while appropriate case endings on the following nouns were typically preserved. Parallels are drawn with Specific Language Impairment and a tentative information-theoretic explanation of this phenomenon is offered. **Conclusion:** So far morphosyntactic deficits in PWS tended to be explained in terms of global cognitive and/or language delay. These findings suggests that more specific processing difficulties may be responsible for agrammatic production in this syndrome.

Poster 19: Gender differences in autism spectrum disorders and hyperkinetic disorders. a cross-sectional item sheet study

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Background: We report our study into possible gender differences in symptomatology of young people with Autistic Spectrum Disorders (ASD) or Hyperkinetic Disorders (HKD). **Methods:** An exploratory cross-sectional study was undertaken. Clinical records of young people meeting International Classification of Diseases criteria for ASD or HKD were analysed. Data source was the 'Maudsley Hospital Children's and Adolescent's Department Item Sheets'. Core and coexisting symptomatology of 59 boys and 59 girls with ASD, and 55 boys and 55 girls with HKD, matched for age, intellectual level and socioeconomic status, were compared. **Results:** Results suggest similar patterns of core and co-existing symptomatology in girls and boys with ASD apart from 'articulation of speech' where boys were more impaired. In HKD, boys were more 'restless and fidgety'. In comorbid symptomatology a trend consistent with girls presenting more emotional features emerged. Girls had significantly higher scores on features of 'school refusal, school phobia, crying on arrival at school', 'abnormally elevated mood (including hypomania)' and 'conversion hysterical symptoms'. Conversely, hyperkinetic boys were found to 'fight, bully and be more aggressive'. Surprisingly, girls with HKD were more likely to commit 'violent assault'. Girls with HKD were more 'socially disinhibited' and more impaired in 'articulation of speech'. **Conclusion:** These findings, if replicated on larger, unbiased, independent samples will have clinical, diagnostic and therapeutic implications. The fact that proportionally more boys than girls with ASD and HKD present to clinics might reflect neglect of possible gender differences in presentation and may suggest that females with these disorders are being unascertained and hence unhelped.

Poster 20: Genetic abnormalities in children with ASD identified by array comparative genomic hybridization

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Background: Autism spectrum disorders (ASD) represent a complex, behaviorally defined neurodevelopmental disorders with risk deriving from genetic variations in multiple genes. The aim of our study was to determine genetic abnormalities in a group of children with ASD using array comparative genomic hybridization (a-CGH). **Methods:** 78 children with ASD, 66 boys and 11 girls, aged 3 to 15, were included in the study. The patients DNAs were extracted from peripheral blood leukocytes. The a-CGH analyses were performed using Agilent SurePrint G3 Human CGH Microarray Kit 8 × 60K and BlueGnome CytoChip 8X60K and 4X180K. The assays were performed according to the manufacturers' instructions with minor modifications. The obtained data were analysed using the Blue Fuse Multi software tool. **Results:** In 12 of 78 patients (15%) small deletion or duplication on different loci were detected: 2q37.3del, 3p26.3dupl, Xq23dupl+Xp22.33del, 22q11.21dupl, 1p36.13dupl, 6q26dupl, 19p13.2del, 22q13.33del, 9q34.13dupl, 8p23.1del, 16p12.2 + 22q11.21dupl, 22q11.21dupl. **Conclusion:** Result of our study support previous findings of genetic heterogeneity in children with ASD. Because of its much bigger power to detect genetic abnormalities compared with “classic” cytogenetic techniques, a-CGH is strongly advised as a genetic screening method in children with ASD.

Poster 21: Knowledge of fetal alcohol spectrum disorders in the UK general public and professionals

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Background:FASD is a preventable Disorder. In order to identify public health strategy needs it was considered important to first establish what was already known in the UK. **Methods:**Following ethical review subjects were recruited by self selection in response to advertising. Research sessions, linked to open education sessions held by RM, were held. A mixed method approach using focus groups and questionnaires was used. Thematic analysis of qualitative data and frequency data from questionnaires was conducted. **Results:**1031 people completed questionnaires (623 public and 408 Professionals) and Both the general public and professionals had heard about FASD but had little knowledge in depth beyond that. Both groups found the current health messages in the UK confusing and wanted clear guidelines as well as further education. The confusion led to cynicism in the professional group, The Public ignored the message until it was considered relevant. **Conclusion:** There is a lack of in depth knowledge about FASD. This has implications about how to deliver public health messages. Targeting a simple message seems to be most appropriate.

Poster 22: Experience of carers of individuals affected by FASD in the UK

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Background: Information from other countries suggest that carers of individuals with FASD struggle. The social and health care provision, alongside legislation for support for people adopting children means that there may well be better outcomes. We decided to explore if this was true. **Methods:**Subjects were recruited by self selection in response to advertising via FASD support agencies. Focus groups and the Parental Stress Index questionnaire were completed. Focus groups were analysed thematically. Frequency data and multivariate analysis of PSI data was made where possible **Results:**66 people attended Education sessions and three focus groups were held with 10 people in each group. PSI data showed that child factors had a grater impact on the overall stress. Ageing and a lack of competence was identified as main influence on coping. Further Carers reported that due to a lack of knowledge in professionals they were offered limited support and often blamed as bad parents. **Conclusion:** Our hope of a possible better situation in the UK was not found. Further, the difficulty of placing individuals with older carers and in kinship adoption practice in this group may well need further evaluation.

Poster 23: Structure-dependency among individuals with CdLS

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Background: Frambu centre for rare diagnoses and the National autism unit in Norway have collaborated in a project concerning clinically relevant characteristics of individuals with Cornelia de Lange Syndrome (CdLS). Resistance for change and need for structure are some of the key characteristics of autism spectrum disorders (ASD), in this study these traits are explored among individuals with CdLS. **Methods:** 7 individuals with CdLS (age:5-18 yrs) are compared with 14 (age, gender and language competence) matched individuals with idiopathic ASD on a questionnaire containing information on, among other things, the need for structure. 8 questions about the need for structure form a sum "structure-dependent" (Cronbach`s alpha.80) Example of question: He/She react negatively to – change in routine, change in object location, unfamiliar task, new objects. He /She need activities to be administered - at same locations, with same persons. **Results:** Individuals with CdLS score significantly higher on structure-dependency than individuals with Idiopathic ASD. Structure-dependency in the CdLS group is neither significantly related to degree of autism as measured with Social communication questionnaire score (SCQ), nor to level of intellectual disability (ICD-10 F7x diagnosis). But the tendency is that structure-dependency is more prevalent among the least intellectual challenged and the individual with lowest SCQ score. **Conclusion:** Clinicians need to be aware of high degree of structure-dependency and resistance to change in the CdLS group.

Poster 24: Detection of psychiatric disorders and behaviour phenotype in an adult population with intellectual disability and genetic anomalies

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Background: Individuals with intellectual disability (ID) are often observed to exhibit symptoms of psychiatric illness and/or challenge behaviour. Those characteristics are often associated with specific genetics syndromes. The majority of population of adults with ID still lacks a genetic diagnostic. The aim of this study is to establish the genetic origin of mild or moderate ID and its correlation with behavioural and psychiatric phenotype. **Method:** We report our experience testing 100 adult patients affected by mild or moderate ID, associated with psychiatric disorders and/or challenge behaviour and minor dysmorphic features. All patients were recruited from Psychiatric Specialised Service and referred to a clinical geneticist. Genetic analysis included karyotipe (800 G-bands), specific molecular analysis, subtelomeric MLPA (P036 and P070 Kits from MRC Holland) and high-resolution aCGH (Aglient 400K).ABS-RC: 2 test was carried out to analyse adaptive behaviour patterns. PASS-ADD, NPI-DI, Y-BOCS, Checklist of compulsive behaviour and RBQ were administered. ICD-10 Mental Retardation and DC-LD were used as diagnostic criteria. **Results:** Genetic imbalance was detected in 55% of cases. Specific analyses revealed 10 cases with a microdeletion syndrome, 5 cases of fragile-X: 4/5 present psychiatric features -33.3% ADHD, 33% ASD-;from a behavioural point of view shyness was found (3/5). Four cases of VCFS: 100% psychiatric diagnostic; social phobia (1), paranoid schizophrenia (2), schizo-depressive disorder (1), persistent delusional disorder (1). The excessive demand for attention, shyness and behavioural traits were presented in 50% of cases. Other: 2 cases of PWS, 2 Smith-Magenis, 1 Williams, 1 Noonan, 1 Cornellia de Lange. Subtelomeric MLPA detected four cases: del(10q)+dup(15q), del(22q) and one dup(15q) and one dupXpdelXq. A chromosome abnormality was observed (three deletions, two balanced reciprocal translocation, two derivates and one inversion/duplication). Different psychiatric features were observed (anxiety in two cases del15q and 3 cases dup15q and OCD in two del10q).

Poster 25: A precocious cerebellar ataxia and combined immunodeficiency revealing ataxia-telangiectasia: a case report

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Background: Ataxia-telangiectasia (A-T) is a complex multisystem disorder characterized by progressive neurological impairment, variable immunodeficiency and oculo-cutaneous telangiectasia. A-T is a member of chromosomal breakage syndromes caused by a mutation in the ataxia-telangiectasia mutated (ATM) gene. Because of a clinical heterogeneity, A-T is often difficult to diagnose in children. **Methods:** We report a case of a 16-months-old-girl affected by A-T who presented with precocious neurological abnormalities and severe combined immunodeficiency. She was referred to our Pediatric Department for a history of repeated episodes of fever of unknown origin and acute enteritis. She was born full-term as a first child of healthy non-consanguineous parents. Our clinical examination revealed ataxic-deambulation with frequent falls, forced right-deviation and left rotation of the head with a left-preferred look and oculomotor-apraxia. The complete blood count (CBC) was normal; serological evaluation were negative. Immunological work-up revealed low levels for age of serum IgG_2 and IgA. Specific antibodies response against tetanus-toxoid and HiB was low. Peripheral blood lymphocyte subsets showed a reduction of T cells with normal B population; cytofluorimetric analysis showed a marked predominance of T cells with a memory phenotype and a corresponding reduction of naïve T cells; NK cells were very increased (41%) with normal activity. In the suspect of a double strands break repair defect, radiosensitivity test was performed, showing an increased number of chromosomal aberrations. Alphafetoprotein (aFP) serum value was tested and was border-line (13 ng/ml, n.v. <10 ng/ml). The characterization of the ATM gene mutations revealed two specific mutations (c.5692C>T/c.7630-2A>C) compatible with A-T diagnose. **Conclusion:** A-T syndrome should be considered in children with precocious signs of cerebellar ataxia and an evidence of cellular immunodeficiency.

Poster 26: Behavioural phenotypes in the classroom: the view of parents and teachers

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Background: The concept of 'behavioural phenotype' and aetiology of intellectual disability may be important with regard to school based interventions. While there are published guidelines in the area of learning and behaviour for a number of syndromes, there is a limited amount of research on the views of parents and teachers with regard to affected children's learning strengths and weaknesses and classroom practices. **Methods:** Parents (n=381) and teachers (n=200) of children affected by 4 genetic syndromes (Fragile X syndrome, Prader-Willi syndrome Williams syndrome, and Velo-cardio-facial syndrome) were surveyed. Areas surveyed included current educational provision, comorbid developmental/medical conditions, perceived knowledge of condition, views on children's learning strengths and weakness and teaching strategies adopted. Qualitative and quantitative methods were used to analyse findings and the views of parents and teachers were compered across syndromes. **Results:** There were few differences in reported attitudes of teachers by parents with regard to general aspects of educational provision. Significant differences emerged between the syndromes with regard to parental views on some aspects of specific learning strengths and weaknesses and some approaches used by teachers in the classroom. Differences between the syndromes also were also found in teacher views on some aspects of student's learning strengths and needs and the use of some teaching strategies. **Conclusion:** There are some significant differences between the syndromes with regard to parent and teacher views on the school related strengths and weakness, approaches adopted to teach the affected children and reported knowledge of parents, teachers and supporting professionals. However, there are also many commonalities across the syndromes. Knowing the aetiology of a child's intellectual disability would appear to be important in relation to some aspects of school functioning. However, significant differences do not exist with regard to the views of parents and teachers in many aspects of functioning and educational provision.

Poster 27: Quality of life outcome measures for investigation of mood and behaviour stabilisers in fragile X syndrome: a single case study

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Background: There is currently little evidence for the use of already available, tried and tested, medications for developmental and behavioural challenges experienced by children and young people with fragile X syndrome, despite novel medications now being explored and promoted. **Methods:** An open trial, naturalistic, exploratory, single case study design was applied to a boy with fragile X syndrome who was experiencing multiple, longstanding and debilitating ADHD, autism spectrum and oppositional defiant features in association with his intellectual disability. Regular carbamazepine, as a mood and behaviour stabiliser, was prescribed with before, after and long term evaluations using the Developmental Disability Behaviour Checklist, Conners Parent Rating Scale, KINDL Child Quality of Life Measure and Sheffield Parental Quality of Life Outcome Scale. **Results:** Commencement of regular oral carbamazepine coincided with clinical improvements in disruptiveness, self-absorption, anxiety, autisticness, sleep disorder, oppositionality, inattentiveness and hyperactivity. Initial longstanding emotional and behavioural dysfunctions, and subsequent improvements on carbamazepine, were reflected in both symptom checklist and quality of life measures with parents reporting their child's and their own qualities of life as having improved substantially. Improvements continue to be maintained long term at two year follow-up. **Conclusion:** Already available medications hold the potential to improve psychological functioning and quality of life for young people with fragile X syndrome and their carers in cost-effective, evidence-based, readily available and clinically safe fashions.

Poster 28: De novo microdeletion in chromosome 8q12.3q13.2: association with mild intellectual disability and a rare form of epilepsy

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Background: Nowadays, whole genome microarray techniques are the primary tool for the etiological assessment in intellectually disabled patients. This had led to the discovery of several novel microdeletions that could be causatively related to the disorder. Interpretation of array results is facilitated through the use of databases such as the European Cytogeneticists Association of Unbalanced Chromosome Abberations (ECARUCA). **Methods:** An extensive neuropsychological, neurological, neuropsychiatric and genetic workup was performed in a 9-years-old female patient with a history characterized by delay of psychomotor and speech development, mild to moderate intellectual disability and persistent sleep disturbances since the age of two. **Results:** Several dysmorphic features were noticed including hypertelorism, downslanting palpebral fissures, a long, pear shaped nose, and low set, posteriorly rotated ears. Furthermore, she had a pectus excavatum, bilateral flat feet, and a sandal gap. Besides lowered intelligence, neuropsychological functioning disclosed impaired attentional capacities and executive control as well as weak motor skills. MRI-scanning of the brain revealed no abnormalities. EEG demonstrated frequent epileptiform activity centroparietal bilaterally with marked increase during sleep corresponding with continuous spike-waves during slow sleep (CSWS) syndrome, more specifically Electrical Status Epilepticus in Sleep (ESES). Array-CGH demonstrated a 3.57 Mb de novo microdeletion in chromosome 8q12.3 encompassing 27 genes. Adequate treatment with the anti-epileptic sulthiame in combination with clobazam resulted in a marked improvement of the sleep pattern of the patient and consequently of her behaviour. **Conclusion:** This de novo 8q12.3q13.2 microdeletion syndrome is characterized by a specific combination of a rare form of juvenile epilepsy (ESES/CSWS), neuropsychological dysfunction, impaired language and motor skills.

Poster 29: Atypical BIPOLAR disorder as psychopathological phenotype of Phelan-McDermid syndrome

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Background: Phelan-McDermid or 22q13.3 deletion syndrome (OMIM: 606232) is characterized by global intellectual disability, childhood hypotonia, severely delayed or absent speech, and features of autism spectrum disorder, without any major dysmorphisms or somatic anomalies. Haploinsufficiency of the SH3 and multiple ankyrin repeat domains 3 (SHANK3) gene is thought to be causative for the neurobehavioural characteristics and the expression of its phenotypical characteristics appears to be linearly related to the deletion size. It is typically diagnosed before adolescence and data about adult patients are virtually absent. **Methods:** Detailed examination of the developmental and behavioural antecendents of three adult intellectually disabled patients in whom etiological investigations had recently demonstrated the genetic etiology. **Results:** In two brothers aged 29 and 31 years, an identical 2.15 Mb 22qter deletion was found, and in a 70-years-old female a 610 kb deletion in the distal end of the long arm of chromosome 22 was demonstrated. In all three patients, early development was characterized by severe delay of language and speech. Furthermore, there were perseverations with associated features from the autism spectrum. Careful analysis of their histories revealed a longlasting unstable pattern of mood and behaviour with, in the two brothers, recurrent episodes with depressive spectrum symptoms, most prominent in the youngest. Given the fluctuating intensity of mood instability and behavioural abnormalities, a diagnosis of unstable mood disorder was made. Under maintenance therapy with mood stabilizers, psychiatric symptoms remitted and functioning of the patients substantially stabilized. **Conclusion:** Apart from delayed or absent speech and perseverations with associated features from the autism spectrum, thought to be key elements of the behavioural phenotype of the Phelan-McDermid syndrome, its psychopathological phenotype comprises oscillating abnormalities in mood and behaviour which can be attributed to an atypical bipolar disorder.

Poster 30: Does gender role perception affect psychopatology in Klinefelter syndrome (KS)?

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Background:KS is the most common abnormality of sex chromosomes in humans. Cognitive, behavioural dysfunctions affect social functioning in KS. Previous studies assessed gender role perceptions and found lower scores for masculinity and femininity in KS (Ratcliffe, 1982).We addressed the question whether social dysfunctions might be related to problems in perceiving gender role. Gender role is defined as the outward manifestations of personality that reflect the gender identity. **Methods:**The sample was composed by 48 subjects (mean age=23.5 yrs, range:1-55) with sex chromosome aneuploidies (SCAs). Among them 20 typical KS individuals (age range 19-55) were evaluated on gender role perception and psychological states. All patients assumed testosterone replacement therapy.After IQ was assessed using WAIS, we considered finally 15 typical KS subjects with IQ in the normal range: mean IQ 100.6, VIQ 99.9, PIQ 102.4.Patients completed the Bem Sex Role Inventory (BSRI) and Symptom Checklist-90 Revised (SCL-90R). Caregivers completed a comprehensive questionnaire detailing developmental and psychological history (Tartaglia, 2008).21 control subjects, matched on sex and age, completed BSRI. **Results:**Between groups analysis didn't identify significant differences between KS group and control group on BSRI profiles. Statistical analysis revealed a positive correlation between feminine profile KS and interpersonal sensitivity (.75, $p<.05$), positive correlation between feminine profile and phobic anxiety (.80, $p<.05$). **Conclusion:**We found higher levels of interpersonal sensitivity and phobic anxiety in KS patients with a feminine role perception. It appears that feminine role perceptions in KS subjects might be related to feelings of personal inadequacy and inferiority, discomfort during interpersonal interactions and persistent fear response to specific situations. Social adaptive problems in KS might be associated to difficulty in perceiving gender role.

Poster 31: Clinical experience with the complex behavioral phenotype of sex chromosome aneuploidy

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Background: Sex chromosome aneuploidy (SCA) conditions are associated with a broad behavioral phenotype including language, cognitive, and social deficits, anxiety, and autism spectrum disorders. This study reports presenting clinical concerns and diagnostic conclusions in a multidisciplinary clinic for individuals with SCA. **Methods:** 92 individuals aged 3-26 with SCA (XXY; XYY; XXYY; XXXY; XXX) underwent team evaluation. Presenting clinical concerns and diagnoses were gathered through retrospective chart review. Social concerns were subcategorized into immature versus atypical social skills. Frequencies of diagnoses were calculated for the entire group by presenting concerns. **Results:** The most prevalent clinical concerns across all SCA groups were social skills (66.3%), behavioral dysregulation (62.9 %) and academic problems (59.6%). Across presenting concerns, language disorders and ADHD were the two most frequent diagnoses (47.5-58%). Among patients with social concerns, ASD was the next most frequent diagnosis (37.5%) and, for those with academic concerns, learning disabilities was the third most frequent (30%). Conduct disorders presented in only 1.8% of the total sample. A diagnosis of ASD occurred more frequently in the atypical social skills group (73.7%) versus the immature group (8.8%; X2, p<.001). Analyses for each SCA syndrome will be presented. **Conclusion:** Regardless of presenting concerns, the high frequency of language disorders and ADHD in this clinical SCA sample suggests that characteristics associated with these two disorders may underlie the behavioral presentation. Significant externalizing behavior disorders were not prevalent. Atypical social presentation, but not social immaturity, was significantly associated with a diagnosis of ASD. Results emphasize the importance of a broad-based, team evaluation to help elucidate factors contributing to behavioral presentation.

Poster 32: Reducing temper outbursts in people with Prader-Willi syndrome: the roles of emotion and increasing predictability

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Background: Temper outbursts are prevalent and challenging in Prader-Willi syndrome (PWS). The potential role of emotion has received little systematic investigation. Unexpected changes to routines/expectations comprise a common trigger for these outbursts. We addressed the role of emotion in these temper outbursts and evaluated the efficacy of a cueing strategy for reducing outbursts triggered by changes. **Methods:** Sixteen individuals with PWS (9-48 years), showing outbursts following changes, participated. Caregivers (n=14) completed a semi-structured interview on outbursts. Structured games manipulated participants' exposure to routines and associated changes, while behaviour, heart rate and activity was measured (n=15). During training, a distinctive card was reliably paired with changes. Caregivers subsequently used the card to cue changes in the natural environment (n=11). Diaries tracked behaviour over baseline and intervention, and naturalistic observations were conducted when imposed changes were cued or not. **Results:** Caregivers reported that temper outbursts included behavioural indicators of heightened emotion. In structured games, increased outburst behaviour was associated with increased physiological arousal (available from n=13). Increased outburst behaviour followed changes to routines that participants had been exposed to for longer, but this relationship was not evident in six participants who showed most distraction (not attending to the games). Increased engagement in distraction was associated with increased outburst behaviour. Behaviour diaries (currently n=7) demonstrated pre to post cueing intervention reductions in temper outbursts in 4 individuals, no change in 2 (though low baseline levels), and an increase in 1. Structured observations (n=5) consistently demonstrated reduced outburst behaviour following cued versus non-cued changes. **Conclusion:** Emotion plays an important role in temper outbursts in individuals with PWS. For some individuals, engagement in an ineffective emotion regulation strategy involving self-distraction may be linked to temper outbursts. Predictably signalling changes reduced the outburst behaviour following imposed changes, and reduced the frequency of temper outbursts in a majority of individuals.

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

Autism and Asperger Syndrome

CHARGE Syndrome (or Association)

Coffin-Lowry Syndrome

Coffin Siris

Cornelia de Lange syndrome

Cri du Chat Syndrome

Foetal alcohol syndrome/ Alcohol related neurodevelopmental disorder

Fragile X Syndrome

Klinefelter syndrome (49,XXY)

Lesch-Nyhan Disease (LND)

Neurofibromatosis Type 1 (NF1)

Noonan Syndrome

Prader-Willi Syndrome (PWS)

Rett Syndrome/ Rett Disorder / RTT

Triple-X syndrome (47,XXX)

Tuberous Sclerosis Complex (TSC)

Turner syndrome

Velo-Cardio-Facial Syndrome

Wolf-Hirschhorn Syndrome

XYY Syndrome

Angelman Syndrome

Alternative names

Although the term 'happy puppet syndrome', proposed by Bower and Jeavons in 1967 has been 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'. Until the 1980s relatively few patients were reported, when it became apparent that electro-encephalography and cytogenetic testing could greatly contribute to identifying affected patients. Clinical diagnostic criteria rest on physical and behavioural features (Williams et al. 1995).

Genetic aspects

Angelman syndrome is caused by a disruption of the maternally inherited proportion of chromosome 15q 11-13 (Clayton-Smith & Laan, 2003; Knoll, Nicholls & Lalande, 1989) via four known genetic mechanisms (Jiang, *et al.*, 1999; Louise *et al.*, 2001). Williams, Lossie and Driscoll's (2001) review suggests that approximately 68-75% of individuals with Angelman syndrome have a deletion on the maternally derived chromosome 15q 11-13; 2-7% have uniparental disomy (where both copies of chromosome 15 are paternally inherited); 2-5% have an imprinting defect and 8-11% have a mutation in the UBE3A gene (which lies at the 15q 11-13 locus; Jiang *et al.*, 1999). 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 *et al.*, 2003; Laan *et al.*, 1998; Lossie *et al.*, 2001; Williams *et al.*, 2001). The genetic association between Angelman syndrome and Prader-Willi syndrome has evoked interest in genomic imprinting and within these individuals (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 rocesses. 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 incriminated in Rett syndrome. According to the mechanism of inheritance, the recurrence risk may be close to 0 or to 50%.

Incidence/prevalence

Prevalence estimates range significantly, but many suggest a current prevalence estimate of 1 in 40,000 live births (Buckley, Dinno, & Weber, 1998; Clayton-Smith, 1993).

Physical phenotype

Craniofacial features include microbachycephaly, short, hooked nose, prognatism, wide smiling mouth and widely spaced teeth. Hypopigmented hair, skin and eyes relative to other family members can be seen. Axial hypotonia is present from birth. Limb hypertonia predominating at the lower extremities appears in infancy. Developmental milestones are delayed. Movements may be ataxic. Most patients develop walking. Gait is typical, with medially rotated, extended lower limbs, flexed elbows and out-turned wrists. Scoliosis may develop, especially in less mobile patients. Over 80% of patients have a seizure disorder, which may be severe, including convulsive and non-convulsive status epilepticus. The EEG shows highly characteristic features in almost all cases (Boyd et al. 1988).

Behavioural aspects

The behavioural phenotype is reviewed extensively by Horsler and Oliver (2006a). Of note are the presence of raised levels of laughing, smiling and happy demeanour, excessive sociability, little or no speech, sleep

disturbances, hyperactivity and aggression in 6-10% (Summers, Allison, Lynch, & Sandler, 1995). There is very little literature describing the behavioural phenotype of adults with Angelman syndrome, but it is suggested that many of these behaviours may decrease in frequency as the individual ages. Sixty (94%) out of the 64 studies reviewed by Horsler and Oliver identified elevated levels of laughing and smiling behaviours. Early work suggested that these behaviors were neurologically driven, and therefore environmental factors were not influential (e.g. Dooley, Berg, Pakula, & MacGregor, 1981; Williams & Frias, 1982). However, careful experimental manipulation of the environment identified that both the frequency and duration of these behaviors are related to environmental context (e.g. Horsler & Oliver, 2006b; Oliver *et al.*, 2007).

Cognitive aspects

Cognitive functions are severely to profoundly impaired in all cases. Early social interaction is usually not delayed, but vocalisation is poor or absent. Attention span short. Patients exceptionally acquire more than 5 words and one third of individuals have no words. Speech impairment is partly related to oral dyspraxia. Receptive verbal language is usually better than expressive speech. Non- verbal communication can be developed to some extent. Patients have relatively good visuo-spatial skills.

Life expectancy

Probably close to normal, as health is generally good, expect for seizure disorder which is not usually severe beyond childhood.

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Chris Oliver, 2010

Autism and Asperger Syndrome

Classification

Autism and Asperger Syndrome are the two principal conditions included by DSM-IV & ICD-10 in the category of Pervasive Developmental Disorders (PDD). The others include atypical autism and PDD Not Otherwise Specified (PDD NOS). There has been continuing debate as to whether autism and Asperger syndrome are distinct conditions and lack of consistency in differentiating between Asperger syndrome and high functioning autism, or between PDD-NOS and atypical autism have resulted in the draft proposals for DSM-V suggesting an over-arching classification of Autism Spectrum Disorder in which there will be no differentiation between these categories. In addition, whereas current diagnostic criteria require specific impairments in 3 domains (Social, Communication, and Restricted, Repetitive and Stereotyped behaviours/interests [RRSB]) the proposed criteria will be based on just 2 domains, Social –Communication impairment and RRSB. Additionally, a dimensional rating of severity of disorder is also proposed.
First described: Autism by Kanner in 1943 and Asperger syndrome by Asperger in 1944. Both accounts note the abnormal patterns of communication and social development and the presence of ritualistic and stereotyped behaviours that are now recognised as the core symptoms of Autism Spectrum Disorders (ASD) (van Engeland & Buitelaar, 2008). Both Kanner and Asperger also described a variety of other behavioural difficulties and they included individuals of normal/above average IQ, as well as those with more severe cognitive impairments.

Associated conditions

There is a significant association between autism and Tuberous Sclerosis and a lesser association with Fragile X. Links with other conditions have also been described (e.g. rubella, cytomegalovirus, phenylketonuria) but the phenotype in these cases tends to be atypical. Epilepsy, often with onset in early teens, occurs in around 20-30% of individuals with comorbid intellectual disability, but in under 19% of those with normal IQ (Bolton, et al., 2010; Levisohn, 2007).

Genetics

The risk of ASD in siblings of probands is significantly increased and there is an exceptionally 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. However, although ASDs are clearly highly heritable, attempts to identify specific susceptibility genes have thus far met with limited success. Genome- wide association studies have identified regions of suggestive and significant linkage on a number of different chromosomes including 5p,15q, 16p, and 22q but various other sites have also been implicated (Abrahams & Geschwind, 2008; Weiss et al., 2009) Recent research suggests that many (possibly the majority) cases of autism may be due to de novo mutations occurring first in the parental germ line and which have high penetrance in males (Zhao et al., 2007) There is no evidence that single environmental factors (e.g. MMR or other vaccines) cause autism although more complex environmental risk factors (e.g. abnormalities in the immune system of individuals with ASD, or pre- natal perturbations) cannot be ruled out. The role of gene-environment interaction must also be considered (Rutter et al., 2006).

Prevalence

Although once thought to be a rare condition, detailed epidemiological research (Baird et al., 2006) now indicates that up to 1% of the child population may have an autism spectrum disorder. Prevalence figures for autism = approximately 40 per 10.000 (95% Confidence Interval 30-48); for other ASD's= 77 per 10,000 (CI= 52-102); total prevalence= 116 per 10,000 (CI=90-142).

Physical Phenotype

This is usually normal although minor physical anomalies are not uncommon. One of the most consistent anatomical findings is an enlarged head circumference and patterns of cerebellar development also seem to be atypical (Van Engeland & Buitelaar, 2008).

Life expectancy/natural history

Life expectancy appears normal. Many individuals, especially those who are more able do show improvements with age. Outcome depends partly on innate factors, such as IQ, and partly on the adequacy of educational, occupational and other support systems (Howlin et al., 2004).

Behavioural and cognitive characteristics

Autism and Asperger syndrome are identified by a "triad" of impairments: qualitative abnormalities in the development of social skills and communication, and the presence of ritualistic and stereotyped behaviours/interests. Onset of language is usually significantly delayed in autism but by definition there are no marked delays in Asperger syndrome. Although frequently associated with cognitive delays, recent studies suggest that up to 70% of individuals with ASD may in fact be of normal intellectual ability. IQ in Asperger syndrome is, by definition, within the normal range (≥ 70). In children with autism, 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 (Hutton et al., 2008).

Websites

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

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Patricia Howlin, April 2010

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: p90**RSK2**, 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.

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 & 0'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 $GABA_B$ 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 usuallly 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 has been used. Lesch-Nyhan Disease (LND) and hypoxanthine-guanine phosphoribosyl transferase (HPRT) deficiency are most commonly used to describe this disease.

First description

It is interesting to speculate that the first description of Lesch-Nyhan Disease may very well have been in the year 1267. Beck (Euro J of Ped Surg 1991) identified an original description of what is most probably 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 was written by Jacobus de Voragine from secondary sources (Golden Legend). Incidentally, de Voragaine thought the origin of the disease might somehow be related to the murder of St. Thomas and the "wrath of God". Commonly accepted as the first description of the familial nature of the disease was by Nyhan and Lesch who published data in 1964.

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 purine metabolism associated with cognitive impairment, hyperuricemia, renal involvement, and the hallmark symptom of severe and involuntary self-injurious behaviors. The disease involves the near absence of the enzyme HPRT. There are probably a few thousand individuals with this disease in the world. The mutation is in the HPRT1 gene located on the long arm of the X chromosome. Remarkably, 218 different mutations have been identified in 271 different families (O'Neill). The product of the normal gene is the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) which recycles purines from DNA and RNA. Even though there are many different types of mutations that affect this gene, the outcome is always a very low level of the enzyme. Because it is an X-linked recessive mutation, it generally occurs only in males, but there have been several documented cases in females thought to be a consequence of events explained by the Lyon Hypothesis. Because of the lack of this enzyme, there is an over-production of uric acid which leads to the production of uric acid (and Xanthine) renal stones. Unfortunately, treatment of the high serum uric acid with allopurinol does not have an impact on the neurobehavioral manifestations of the disease but does minimize renal injury.

Physical phenotype

The motor syndrome found in 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. 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. Interestingly, if CP is defined as a non- progressive movement disorder, LND could then be classified as a dystonic form of cerebral palsy with hypotonia. Affected individuals are generally non-ambulatory. The basal ganglia is now known to be involved in the regulation of areas other than the motor circuits. Personality, cognition, emotion as well as movement are all potentially regulated by the basal ganglia (see Visser, Bar, and Jinnah).

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 that the IQ scores obtained by professionals are artificially low and reason that low performance is secondary to LND behavior.

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.

Treatment

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 would violate the autonomous rights of the patient. In Lesch-Nyhan Disease self-injury far exceeds that associated with other developmental disabilities and is a consequence of the neurotransmitter abnormality 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.
Recently, Deep Brain Stimulation (DBS) has been tried with several patients with LND in Japan, Switzerland/France, India and the United States. 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. This procedure may very well be an ideal treatment for this disorder.

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 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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Gary E. Eddey, 2010

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

Rett Syndrome/ Rett Disorder / RTT

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% 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 occasionally self-injurious behaviours. Developmental disorders including autism and autism spectrum disorders (ASD) (40-50%), ADHD and attention-related disorders (30-50%) are seen at high rates. 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 cognitive abilities show a bimodal distribution. 30% of individuals with TSC have profound global intellectual disability 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 cognitive 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 lead to significant scholastic difficulties and impair functional abilities in daily life (Prather & de Vries, 2004; Kwiatkowski et al., 2010).

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.

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

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 the Y in males). Early degeneration of the ovaries leads to oestrogen insufficiency. Knowing the genetic sequence of the X chromosome should lead to 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.

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 which gives a 'Michelin Man' appearance, but 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 to oromotor immaturity. There are low-set ears, a low hairline, and occasionally a webbed neck (this latter feature is much rarer than textbook descriptions would suggest). The eyes may have a strabismus and slight ptosis. The chest is typically broad, with widely spaced breasts. When standing with arms at her side, the arms turn out at the elbows (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 otitis media, exacerbated by anatomical anomalies of the Eustachian tube. This is extremely common in girls with Turner syndrome, particularly in infancy and early childhood. Aggressive treatment of infections is appropriate. The majority (50-90%) of women with Turner syndrome will also develop early sensorineural (nerve) hearing loss and may require hearing aids earlier than the general population.

Because of the small stature, which is almost invariably 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.

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 (by endocrine management). These factors combine with specific deficits in social cognitive competence, which is severe in at least 30% of cases. Forming and maintaining peer relationships are often problematic, especially as these become more complex in later life. As adults, many women cannot function effectively in complex 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, which may not be obvious to the paediatricians or endocrinologists who manage the syndrome in childhood and adulthood.
Many females with Turner syndrome have poor self-esteem. This is largely due to their difficulty in establishing satisfactory social relationships, the latter being misattributed to associated short stature or infertility. This is rarely the true explanation, and undermines the possibility of effective treatment, but it is the prevailing view in the United States, where the attribution of social maladjustment to fundamental problems with social-cognitive processing is strongly resisted by both women with Turner syndrome and their doctors.

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 recognizing facial expressions of emotion. Socio-cognitive anomalies in Turner syndrome extend to deficits in mentalizing skills; typical performance in 'reading the mind from the eyes' is *more* impaired in Turner syndrome than in Autism Spectrum Disorders (ASD). Because of their superficially good and engaging social skills, learned from imitation, the underlying Theory of Mind deficits are not readily appreciated, but they lead to major functional impairment in a substantial minority of females with Turner syndrome.

Available guidelines for behavioural assessment/treatment/management

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- Gravholt C.H. "Turner – know your body!" Editor –Published by Novo-Nordisk. Available as a 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, 2010

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

Wolf-Hirschhorn Syndrome

First description

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 idiosyncratic 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 are 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 Canners 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 11 q22-25 (Jacobsen syndrome).

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Gene S Fisch, March 2011

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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The 16th SSBP International Research Symposium

Research Symposium 12-13 September 2013; Educational Day 14 September 2013 • Stellenbosch, South Africa

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