

16th SSBP International Research Symposium

The fundamentals of behavioural phenotypes

Programme Book

12–14 September 2013 • Stellenbosch, South Africa



12th – 14th September 2013

The 16th SSBP International Meeting

The Fundamentals of Behavioural Phenotypes

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Welcome

Dear Colleagues,

We are delighted to welcome you to **Stellenbosch, South Africa** for the 16th SSBP International Research Symposium and Educational Day.

The theme for the 2013 meeting is ***'The fundamentals of behavioural phenotypes'***. We deliberately selected the theme because this will be the first SSBP meeting in Africa. Our goal was therefore to present a programme that would represent the global breadth and depth of research and clinical work in the neurodevelopmental and neurobehavioural aspects of genetic disorders and other biologically determined syndromes, but that would also be directly relevant to the needs of clinicians and clinical researchers in Africa.

As you page through the programme book, you will see that topics range from fundamental discussions around autism spectrum disorders, intellectual disability, epilepsy and sleep disorders to targeted presentations about the behavioural phenotypes of specific genetic syndromes. Given that South Africa has one of the highest rates of foetal alcohol spectrum disorder (FASD) in the world, we will also have a mini-symposium on FASD.

We are extremely grateful to our international keynote speakers who agreed to join us in Stellenbosch. We have no doubt that we will have lively discussions throughout the three days of our meeting.

To all our participants who have come from all around the world and from many parts of Africa, we sincerely hope you have a stimulating and inspiring few days in Stellenbosch.

We are pleased to report that all oral abstracts for the Research Symposium and Educational Day have been published in the September 2013 issue of the *Journal of Intellectual Disability Research* (JIDR). The SSBP has had a long-standing collaboration with the JIDR, and we hope to strengthen this relationship over the next few years. For the first time ever, all participants at the conference will have 90 days' free access to all content of JIDR. See page 110 for instructions on how to do this.

For those of you who have not been to South Africa, we hope you will have time to explore some of the beauty of Stellenbosch and surrounding areas while you are here. We will do our best to make you feel at home!

Petrus de Vries

Conference Chair and Chairman: SSBP

Lorna Jacklin

Conference Co-Chair

Andre Venter

Conference Co-Chair

Local Organising Committee

Petrus J de Vries

Sue Struengmann Professor of Child & Adolescent Psychiatry & Chairperson SSBP
University of Cape Town, South Africa
Conference Chair

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Colleen Adnams

Vera Grover Professor of Intellectual Disabilities
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University of Cambridge, United Kingdom

Stellenbosch: a history

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Stellenbosch is a middle-sized town (population about 100,000) about 30 miles (50km) inland from Cape Town. It was founded in 1679 by Simon van der Stel, then Governor of the Cape Colony. Stellenbosch is very much the centre of South Africa's wine industry and the town is surrounded by numerous vineyards and wineries (excellent for food and wine tasting!). It is also home to **Stellenbosch University**, one of the country's oldest universities. This institution has a rich history dating back to 1863 and has 10 **faculties**, including Health Sciences, **Engineering, Commerce, Science** and **Arts**. The Department of Electrical and Electronic Engineering is the only university department in the southern hemisphere which has successfully built a communications satellite **Sunsat** which was launched in 2000 and orbited earth for three years. The University currently has about 25,000 students. Although the official language of the university is **Afrikaans**, most post-graduate courses are presented in **English**.

A look into the Past:

Stone tools dating to the Paleolithic Era have been found at Stellenbosch, first described by **Louis Péringuey** in 1899. Originally, the artifacts were considered the type case for the type of tools known as "Stellenbosch complex", but are now considered to be representative of the **Acheulean Industry**.

The town was founded in 1679 by the Governor of the **Cape Colony**, **Simon van der Stel**, who named it after himself – Stellenbosch means "(van der) Stel's Bush". It is situated on the banks of the Eerste Rivier ("First River"), so named as it was the first new river he reached and followed when he went on an expedition over the Cape Flats to explore the territory towards what is now known as Stellenbosch. The town grew so quickly that it became an





independent local authority in 1682 and the seat of a **magistrate** with jurisdiction over 25,000 square kilometers (9,700 sq mi) in 1685.

The **Dutch** were skilled in hydraulic engineering and they devised a system of furrows to direct water from the Eerste Rivier in the vicinity of Thibault Street through the town along van Riebeeck Street to Mill Street where a **mill** was erected. Early visitors commented on the oak trees and gardens.

During 1690 some **Huguenot refugees** settled in Stellenbosch, **grapes** were planted in the fertile valleys around Stellenbosch and soon it became the centre of the South African **wine** industry.

In 1710 a fire destroyed most of the town, including the first church, all the Company property and twelve houses. Only two or three houses were left standing. When the church was rebuilt in 1723 it was located on what was then the outskirts of the town, to prevent any similar incident from destroying it again. This church was enlarged a number of times since 1723 and is currently known as the “Moederkerk” (Mother Church).

The first school had been opened in 1683 but education in the town began in earnest in 1859 with the opening of a seminary for the Dutch Reformed Church. **Rhenish Girls’ High School**, established in 1860, is the oldest school for girls in South Africa. A gymnasium which was known as *het Stellenbossche Gymnasium* was established in 1866. In 1909 an old boy of the school, **Paul Roos**, captain of the first national rugby team to be called the **Springboks**, was invited to become the sixth rector of the school. He remained rector till 1940. On his retirement the school’s name was changed to **Paul Roos Gymnasium**.

In 1874 Victoria College was created to provide higher education to pupils from the surrounding area. The College was renamed ‘Stellenbosch University’ in 1918. The first men’s hostel to be established in Stellenbosch was Wilgenhof, in 1903. In 1905 the first women’s hostel to be established in Stellenbosch was Harmonie.

The SSBP

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

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

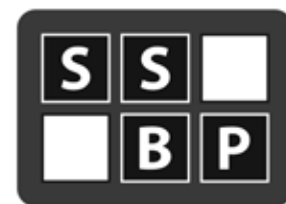
The SSBP Executive Committee

President	<i>Dr Martin Bax</i> (London) (m.bax@imperial.ac.uk)
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International Representatives	Australia – <i>Professor Stewart Einfeld</i> (Camperdown) (s.einfeld@usyd.edu.au)
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International Representatives	USA (West Coast) – <i>Professor Randi Hagerman</i> (Sacramento) (randi.hagerman@ucdmc.ucdavis.edu)

Administrator	Elizabeth Walmsley (ssbpliz@gmail.com)
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Meetings of the SSBP

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

Forthcoming Meetings of the SSBP

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

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

2013	Patricia Howlin
2012	Chris Oliver
2011	Tony Holland
2010	Randi Hagerman
2009	Alcino Silva
2008	Hans-Christoph Steinhausen
2007	Petrus J de Vries

Professor Patricia Howlin

Patricia Howlin is Emeritus Professor of Clinical Child Psychology at the Institute of Psychiatry, London and Professor of Developmental Disorders at the University of Sydney. She is a chartered clinical psychologist with a Ph.D. in Psychology and a Fellow of the British Psychological Society. She was the first person in the UK to be made a Professor of Clinical Child Psychology. A particular focus of her research is on the effectiveness of interventions for individuals with autism and she has been involved in evaluations of a variety of therapies, including early intervention programmes, non-verbal communication training, teaching theory of mind, and supported employment. She has also conducted a number of follow-up studies investigating outcomes in adult life for people with autism, Williams syndrome and developmental language disorders. Professor Howlin was a founder editor of the journal *Autism: The International Journal of Research and Practice* and is on the editorial board of a number of other journals. She has published widely on autism and other developmental disorders. Her latest book is the *Sage Handbook of Developmental Disorders* with Tony Charman & Mohammad Ghaziuddin. In 2011 she received the Autism Association of Western Australia award for services to autism and in 2013 received the International Society for Autism Research (INSAR) Life Time Achievement award.



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.

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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 certificate will be presented to the winner during the SSBP Research symposium.

Patricia Howlin Lecturers

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

Sponsors

SSBP 2013 is extremely grateful to the range of organizations that supported this meeting:



The Paediatric Neurology and Development Association of Southern Africa. PANDA-SA aims to promote communication and networking between professionals in the fields of Paediatric Neurology and child development in Southern Africa.



Sponsorship provided by Novartis in the interest of continuing medical education.



Sponsorship provided by Janssen



Sponsorship provided by Lilly for the afternoon tea on the Educational Day

Keynote Speaker Profiles

(in order of presentation)

Prof Chris Oliver

Chris Oliver is Professor of Neurodevelopmental Disorders at the University of Birmingham and director of the Cerebra Centre for Neurodevelopmental Disorders. He trained as a clinical psychologist at Edinburgh University before completing a PhD on self-injurious behaviour in people with intellectual disability at the Institute of Psychiatry, London. He is currently researching early intervention, behaviour disorders in people with severe intellectual disability and autism spectrum disorder, behavioural phenotypes in genetic syndromes and neuropsychological and behavioural assessment for people with severe intellectual disability. He has published over 100 peer reviewed articles in scientific journals, is Editor in Chief for the Journal of Intellectual Disability Research and serves on a number of scientific advisory committees for syndrome support groups. Sadly, he supports Luton Town Football Club.



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Prof Catherine Lord

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



Prof Colleen Adnams

Colleen Adnams is the Vera Grover Professor of Intellectual Disability, Department of Psychiatry and Mental Health, University of Cape Town, South Africa and is a Chief Specialist in the Intellectual Disability Services, Western Cape Government Psychiatric Hospitals. Prof Adnams completed her medical and specialist training in Paediatrics at the University of Cape Town. From 1994 to 2007 she was head of the Neurodevelopmental Paediatric Clinical Service and teaching unit at the School of Child and Adolescent Health, University of Cape Town and Red Cross War Memorial Children's Hospital. During this time she was instrumental in establishing Neurodevelopmental Paediatrics as a sub-speciality in South Africa. She has contributed to numerous provincial, national and international committees and task groups related to service provision, training, policy and the study of neurodevelopmental disabilities. She has served on the World Health Organization Working Group for the ICD-11 classification of intellectual disability. Her research interests include neurodevelopmental disabilities, health and mental health aspects of intellectual disabilities and fetal alcohol spectrum disorder. She has been active in several National Institutes of Health funded international collaborations examining epidemiological and neurobehavioural aspects of fetal alcohol spectrum disorder. She has published in the areas of fetal alcohol spectrum disorders and developmental and intellectual disabilities in South Africa. In her present capacity, she holds the only chair of intellectual disability in Africa.



Prof Pat Howlin

Patricia Howlin is Emeritus Professor of Clinical Child Psychology at the Institute of Psychiatry, London and Professor of Developmental Disorders at the University of Sydney. She is a chartered clinical psychologist with a Ph.D. in Psychology and a Fellow of the British Psychological Society. She was the first person in the UK to be made a Professor of Clinical Child Psychology. A particular focus of her research is on the effectiveness of interventions for individuals with autism and she has been involved in evaluations of a variety of therapies, including early intervention programmes, non-verbal communication training, teaching theory of mind, and supported employment. She has also conducted a number of follow-up studies investigating outcomes in adult life for people with autism, Williams syndrome and developmental language disorders. Professor Howlin was a founder editor of the journal *Autism: The International Journal of Research and Practice* and is on the editorial board of a number of other journals. She has published widely on autism and other developmental disorders. Her latest book is the *Sage Handbook of Developmental Disorders* with Tony Charman & Mohammad Ghaziuddin. In 2011 she received the Autism Association of Western Australia award for services to autism and in 2013 received the International Society for Autism Research (INSAR) Life Time Achievement award.



Prof Randi Hagerman

Professor Randi Hagerman is a Developmental and Behavioral Pediatrician and the Medical Director of the MIND Institute at UC Davis. She is internationally recognized as both a clinician and researcher in the fragile X field and she is the director of the Fragile X Research and Treatment Center at the MIND Institute and holds an Endowed Chair in Fragile X Research at UC Davis. Professor Hagerman received her M.D. from Stanford University where she also carried out her Pediatric residency. She completed a Fellowship in Learning Disabilities and Ambulatory Pediatrics at UC San Diego and, subsequently, spent the next 20 years from 1980 to 2000 at the University of Colorado where she headed Developmental and Behavioral Pediatrics. She co-founded the National Fragile X Foundation in 1984 in Colorado and developed a world-renowned fragile X research and treatment center. In 2000, Professor Hagerman moved to UC Davis to be the Medical Director of the MIND Institute. Dr. Randi Hagerman and Dr. Paul Hagerman and their team discovered the Fragile X-associated Tremor/Ataxia Syndrome (FXTAS) which is a neurological disorder that affects older carriers of fragile X. Dr. Hagerman's research involves genotype-phenotype correlations in fragile X and the association of fragile X and autism. Her greatest interest is in targeted treatments for fragile X syndrome, autism and premutation medical problems including FXTAS. Professor Randi Hagerman has written over 300 peer-reviewed articles and numerous book chapters on neurodevelopmental disorders. She has written several books on fragile X including a 3rd Edition of *Fragile X Syndrome: Diagnosis, Treatment, and Research* which was published in 2002 by Johns Hopkins University Press. She is editing a new book now regarding targeted treatments for neurodevelopmental disorders to be published by Oxford University Press.



Prof Petrus 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 is also chairman of the Society for the Study of Behavioural Phenotypes (SSBP), an international, interdisciplinary research organization, is a member of the National Executive Committee of Autism South Africa (ASA) and scientific advisor to MONAA (MONaco Against Autism).



Dr Honey Heussler

Honey is a Developmental and Behavioural Paediatrician with dual Sleep Physician accreditation from the RACP. She completed her doctorate in 2008 through the University of Nottingham and has been working at the Mater Children's Hospital since 2003. She is an Associate Professor with the University of Queensland and is Director of Developmental Paediatrics, as well as clinical responsibility in Behavioural and Sleep clinics at the Mater Children's Hospital. She runs a number of specialised clinics for children with genetics syndromes and sees a wide range of children & families dealing with complex Developmental & genetic difficulties. She is on the RACP Training committee for Sleep Physicians and runs a series of workshops training psychologists in the management of sleep disorders around the country. Current primary research interests are in Developmental disorders and sleep difficulties in children at the Mater Research Institute.



Research Symposium Programme.

The 16th SSBP International Meeting:

"The Fundamentals of Behavioural Phenotypes"

Day One Thursday, 12th September 2013

8:00 – 9:00 **Registration & Coffee**

9:00 **Welcome** (*Profs de Vries, Jacklin, Venter*)

9:00 – 11:00 **Session 1** (*Chair: Prof Andre Venter*)

Talk 1: Keynote: *Chris Oliver* – The fundamentals of behavioural phenotypes

Talk 2: *Samango-Sprouse C.A.* – Positive Effects of Short Course Androgen Therapy on the Neurodevelopmental Outcome in Boys with 47,XXY Syndrome at 9 Years of Age

Talk 3: *The Pat Howlin Lecture Prize: Heald M.* – Experimental Analysis of Social and Sensory Reinforcement in Angelman Syndrome.

Talk 4: *Von Gontard A* – Incontinence in Persons with Angelman and Rett Syndrome

11:00 – 11:30 **Morning Coffee**

Put up posters

11:30 – 12:30 **Session 1 (continued)**

Talk 5: *Evers L.J.M.* – Serotonin, Norepinephrenic and Dopaminergic Markers in the 22Q11-Deletion Syndrome

Talk 6: *Huijbregts S.C.J* – Volumetric Abnormalities of Subcortical Brain Regions in Neurofibromatosis Type 1: Associations with Social and Cognitive Problems

Talk 7: *Harris J.C.* – LND Behavioural Phenotype: Cortical Thickness & Volumetric Abnormalities

12:30 – 14:00 **LUNCH**

Poster Viewing

14:00 – 15:00 **Session 2** (*Prof Lorna Jacklin*)

Talk 8: *Hamilton K.* – An Exploration of the Relationships between Autism Spectrum Disorder, Theory of Mind, and the Serotonin Transporter Promoter Length Polymorphism.

Talk 9: *Tassone F.* – Second Hit in FMR1 Premutations May Lead to Autism Spectrum Disorders, Supporting the Two-Hit Model of Phenotypic Variability.

Talk 10: *Meguid N.A.* – Plasma Amino Acids in Saudi and Egyptian Populations with Autism Spectrum Disorders

15:00 – 15:30 **Afternoon Tea**

15:30 – 16:30 **Session 2 (continued)**

Talk 11 Keynote: *Catherine Lord* – The Science of syndromal and non- syndromal ASD

16:30 – 17:00 **General Question and Answer Session**

17:00 – 18:30 **Welcome Reception**

Day Two: Friday, 13th September 2013

8:00 – 9:00	Morning Coffee
9:00 – 10:30	Session 3. Foetal Alcohol Spectrum Disorders – a mini-symposium Talk 12. Keynote: <i>Colleen Adnams</i> – Global perspectives on foetal alcohol spectrum disorder. Talk 13: <i>Donald K.A.</i> – Loss of White Matter Integrity in Infants Prenatally Exposed to Alcohol Talk 14: <i>Jacobson S.W.</i> – Biobehavioural Markers of FASD in Heavily Exposed Children.
10:30 – 11:00	Morning Coffee
11:00 – 11:45	Session 3. (continued) Talk 15: <i>Lindinger N.M.</i> – Fetal Alcohol Spectrum Disorders and Theory of Mind in South African School-age Children Talk 16: <i>Mukherjee R.A.S</i> – Neurodevelopmental Profiles in People Diagnosed with FASD: Experience from a UK National Clinic.
11:45 – 12:30	SSBP Annual General Meeting 2013
12:30 – 13:30	LUNCH Poster Viewing
13:30 – 15:30	Session 4 (Prof Petrus de Vries) Talk 17: <i>Verri A.P.</i> – Late Onset Myoclonic Epilepsy (LOMEDS) in Down Syndrome (DS) Talk 18: <i>Strydom A.</i> – The LonDownS Consortium - Investigating Cognition and Alzheimer's Disease in Down's Syndrome Talk 19: <i>Jansen A.</i> – Tuberous Sclerosis Registry to Increase Disease Awareness (TOSCA) Talk 20: <i>Leclezio L.</i> – The Tuberous Sclerosis Complex Associated Neuropsychiatric Disorders (TAND) Checklist - Pilot Validation of a New Screening Tool for Neuropsychiatric Manifestations in TSC. Talk 21: <i>Wilde L</i> – Persistence of Challenging Behaviour in Tuberous Sclerosis Complex
15:30 – 16:00	Afternoon Tea Take down posters
16:00 – 17:00	Session 4 (continued) Talk 22 The Tom Oppe Lecture: <i>Patricia Howlin</i> – The Importance of Studying Behavioural Phenotypes Thank you and good bye (<i>Profs de Vries, Jacklin, Venter</i>)
18:30	Transfer to Conference Dinner from De Oude Werf Hotel, Church Street, Stellenbosch
19:00 – 22:00	Conference Dinner

Abstracts for Oral Presentations

(in order of presentation)

TALK 1: The Fundamentals Of Behavioural Phenotypes

Oliver C.

Cerebra centre for Neurodevelopmental Disorders, University of Birmingham, Birmingham, UK.

Since the first accounts of behavioural phenotypes appeared there have been significant developments in the breadth and diversity of the behaviours of interest, the descriptions of their causal pathways and their associations with both typical and atypical cognitive and emotional processes. Additionally, variability in genotypes within syndromes has added to the complexity of describing genotype-phenotype correlations and alluded to the need for a more refined approach to characterising behavioural phenotypes. As the field progresses, it is becoming clear that more refined description of behaviour is essential but still insufficient to capture presenting problems. Psychiatric taxonomy is equally compromised in its ability to represent the behaviours that are described. Some of these problems might be overcome by recourse to fine-grained description of behaviour in combination with recognition of informative behavioural correlates, the adoption of a dimensional approach to observed atypicality in a number of key domains and extension of the behavioural phenomena currently considered. Such an approach might cultivate interest in the neuropsychological and structural differences that might underpin difference in these domains. In the meantime, we must still confront the issues of quantifying behaviour in ways that inform understanding and characterisation and begin to address the challenges of neuropsychological and other testing in populations with more severe intellectual disability.

Keywords: behavioural phenotypes; assessment; intellectual disability.

TALK 2: Positive Effects Of Short Course Androgen Therapy On The Neurodevelopmental Outcome In Boys With 47, XXY Syndrome At 9 Years Of Age

Samango-Sprouse C.A.^{1,3}, Stapleton E.J.³, Sprouse C.², Sadeghin T.³, Mitchell F.L.³ and Gropman A.L.^{1,2}

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³ Neurodevelopmental Diagnostic Center for Young Children, USA.

Background: Positive effects of early androgen treatment on neurodevelopmental performance in prepubertal males with 47, XXY have been documented at 36 and 72 months, giving support to the link between neurobiological treatment and neurodevelopmental outcome. The aim is to determine if an early course of androgen treatment (3 injections of testosterone enanthate, 25mg, each) could have a positive impact on XXY boys at 9 years of age.

Method: 59 prenatally diagnosed males with karyotypes of 47, XXY participated with one group (n=22) receiving androgen treatment in infancy and the second group untreated (n=37).

Results: There was a significant positive treatment effect in multiple visual motor domains (VP p=0.0012, MC p=0.0129, VMI p=0.0151). A positive treatment effect was observed on the BOT (Manual Coordination p=0.0003, Bilateral Coordination p=0.0001, Body Coordination p=0.0038, Speed/Agility p=0.0328, Strength p=0.0161 Upper Limb Coordination p=0.0004, and Strength/Agility p=0.0134).

Conclusion: Long-term improved function has been observed in neurodevelopmental performance in XXY males at 36 and 72 months and now at 108 months when treated with a short course of androgen in infancy. An early course of hormonal replacement may have a permanent positive effect on the neurodevelopment outcome in XXY in brain regions with known androgen receptors. These findings suggest early hormonal replacement in XXY males alters selected areas of neurodevelopmental performance for at least 10 years.

Keywords: 47,XXY, androgens, sex chromosome disorders, chromosomal variations, Klinefelter syndrome (KS).

TALK 3: *The Patricia Howlin Prize Lecture* : Experimental Analysis Of Social And Sensory Reinforcement In Angelman Syndrome

Heald M., Adams D., Walls E., Trickett J. and Oliver C.

The Cerebra Centre for Neurodevelopmental Disorders, School of Psychology, University of Birmingham, Birmingham, UK.

Background: The behavioural phenotype of Angelman syndrome (AS) is characterised by high rates of laughing and smiling, unusually strong motivation for adult attention and preference for certain sensory stimuli. Previous research has found that extended teaching periods are needed within this population, potentially due to compromised learning and short attention span. Given the literature on variable preference for stimuli in AS, there is a strong rationale for systematically evaluating the use of preferred sensory and social stimuli as reinforcers to increase rates of learning.

Method: Twenty children with AS aged between two and fifteen years participated. Preferred sensory stimuli were identified in an experimental engagement preference assessment. In subsequent reinforcement assessments, participants were exposed to alternating sensory and social rewards contingent on completion of target behaviours to evaluate speed of acquisition of responding using single case experimental designs.

Results: All participants evidenced acquisition of target behaviours in the presence of either a sensory or social reward. Whilst sensory stimuli functioned as reinforcers for nearly all participants, results from the social reinforcement assessments were variable. Acquisition was more rapid in *specific* conditions of social interaction, particularly in the presence of eye contact. The results also indicate potential genotype-phenotype interactions.

Conclusion: Preferences for sensory and social stimuli in AS may inform effective reinforcement selection. Whilst the effectiveness of sensory reinforcement was consistent across participants, social motivation appears more variable in AS. The findings are discussed within the wider context of developing syndrome specific interventions for children with AS.

Keywords: Angelman syndrome, behavioural phenotype, social motivation, sensory seeking, preference assessment, reinforcer assessment.

TALK 4: Incontinence In Persons With Angelman And Rett Syndromes

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⁴ Department of Clinical Genetics, Academic Hospital/University of Maastricht, Governor Kremers Centre, Maastricht, The Netherlands.

Background: Angelman (AS) and Rett syndromes (RS) are genetic neurodevelopmental disorders. The aim of the two studies was to assess the rate of incontinence and associated problems in persons with AS and RS, which have not been reported so far.

Method: Frequency and type of incontinence were assessed in individuals with AS (n=71; mean age 20.5 years) and in matched controls (n=73; mean age 22.9 years), as well as in females with RS (n=63; mean age 19.3 years) and matched controls (n=26; mean age 21.6 years). Both control groups consisted of individuals with non-specific intellectual disability.

Results: Persons with AS had significantly less daytime urinary incontinence (DUI) than controls (54% vs. 78%) and less faecal incontinence (FI) during the day (46% vs. 75%). They had similar rates for nocturnal enuresis (NE) (89% vs. 84%) and nocturnal FI (57% vs. 54%). While children with AS had similar rates of DUI, adults with AS were less incontinent than controls (DUI at ages 5-12 years: 90% vs. 87%; at ages 31-55 years: 17% vs. 84%). Most females with RS (as well as controls) were affected by DUI (96.8% vs. 96.2%), NE (98.4% vs. 96.2%), daytime FI (72.1% vs. 88.5%) and night-time FI (57.4% vs. 57.7%). All groups showed high rates of lower urinary tract symptoms (LUTS).

Conclusion: The study shows that incontinence is a major problem in persons with AS and RS. Due to the high rates of incontinence and lower urinary tract symptoms (LUTS), paediatric or urologic assessment and treatment are recommended.

Keywords: Angelman syndrome, Rett syndrome, nocturnal enuresis, daytime urinary incontinence, faecal incontinence.

TALK 5: Serotonin, Norepinephrenic And Dopaminergic Markers In The 22q11-Deletion Syndrome

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³ Department of Psychiatry and Psychology, Maastricht University, Maastricht, The Netherlands.

Background: 22q11-deletion syndrome (22q11DS) is a genetic syndrome caused by a microdeletion on chromosome 22q11.2. Besides several physical features it is characterized by a variety of psychiatric problems such as psychosis, mood and anxiety disorders. In this study, we investigated in addition to the dopaminergic system, for the first time the serotonergic system in people with 22q11DS.

Method: We collected urine samples from 65 patients with 22q11DS and 29 healthy controls. Dopamine, serotonin, norepinephrine and its metabolites homovanillic acid (HVA), 5HIAA, and vanillylmandelic acid (VMA) were determined and compared between the groups. In a regression analysis we looked at the influence of present IQ (TIQ), presence (life-long) of psychosis, age and gender.

Results: T-tests showed significantly higher HVA ($p=0.0016$) VMA ($p=0.0314$) and serotonin ($p=0.0052$) in the controls, compared to patients with 22q11DS. Regression analysis showed a significant effect of TIQ on dopamine ($p=0.0001$), HVA ($p=0.0001$) serotonin ($p=0.026$) and norepinephrine ($p=0.001$) with lower values for the lower IQ's. Gender, age and presence of psychosis show no influence on any of the neurochemical markers.

Conclusion: We found lower levels of dopaminergic metabolites and serotonin in 22q11DS patients compared to controls. After regression analysis low TIQ is correlated with low dopamine, low serotonin and low norepinephrine. Patients with 22q11DS are haplo-insufficient for approximately fifty genes. Among them are the COMT, SEPT5 and GP1Bbeta genes. COMT encodes for an enzyme involved in the metabolism of dopamine and norepinephrine; SEPT5 and GP1Bbeta play a role in thrombocyte metabolism. Platelets are responsible for serotonin transport. Previously a disturbed dopaminergic metabolism is reported in healthy adult patients with 22q11DS. In particular, the serotonergic findings are novel.

Keywords: Neurotransmitters, 22q11 deletion syndrome, serotonin, dopamine, norepinephrine.

TALK 6: Volumetric Abnormalities Of Subcortical Brain Regions In Neurofibromatosis Type 1: Associations With Social And Cognitive Problems

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Background: Neurofibromatosis Type 1 (NF1) is often accompanied by social and cognitive problems. Magnetic Resonance Imaging (MRI)-studies have shown different abnormalities in the brains of NF1-patients, including T2-hyperintensities, white matter microstructural abnormalities, and greater white and grey matter volumes, but results regarding associations with cognitive abnormalities have been inconsistent, whereas associations with social problems have not yet been studied.

Method: 21 NF1-patients (mean age 12.5 years, SD 2.7) and 18 healthy controls (mean age 13.3 years, SD 3.8) were compared, using analyses of (co-)variance, on cognitive, behavioural and social outcomes. Instruments included the Social Responsiveness Scale, the Child Behaviour Checklist, the Social Skills Rating System, and the Behaviour Rating Inventory of Executive Function. 15 of the NF1-patients and 18 healthy controls underwent MRI-scanning. Volume measurements were performed on 3T 3D-T1-weighted images, using the *Integrated Registration and Segmentation Tool*-algorithm of FMRIBs Software Library (FSL). Pearson correlations were used to examine associations between brain region volumes and cognitive, behavioural and social outcomes.

Results: NF1-patients showed more social problems and autistic traits (mean in clinical/severe range), and poorer social skills, emotion and behaviour regulation than controls (all $p < .001$). After correction for age and intracranial volume, significantly larger grey matter volumes in subcortical regions were observed in NF1-patients compared to healthy controls. Within the group of NF1-patients there were significant positive correlations between left and right putamen-, right pallidus-, and right amygdala-volumes and social problems, autistic traits, lack of social skills, and behaviour/emotion regulation problems (r -range: .49-.73).

Conclusion: Lack of control over cellular growth in subcortical brain regions may (partly) explain social and cognitive problems in NF1.

Keywords: Neurofibromatosis Type 1, Cognitive and Social functioning, Magnetic Resonance Imaging, Voxel-based morphometry.

TALK 7: LND Behavioural Phenotype: Cortical Thickness & Volumetric Abnormalities

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² Kennedy Krieger Institute, USA.

³ Emory University, USA.

Background: Lesch Nyhan syndrome has a characteristic neurological and behavioural phenotype. We seek to determine the underlying neural substrates for the phenotype.

Method: 3T MRI Brain scans were conducted in 7 adult males and 1 adult female with Lesch-Nyhan disease (LND), and 16 age and sex matched healthy controls. Cortical reconstruction and volumetric segmentation were performed and segmentation was applied to the subcortical white matter (WM) and deep gray matter regions of interest (ROIs). Cortical thickness measurements were obtained and total intracranial volume (TICV) was calculated. Comparisons were made by group using a MANCOVA controlling for age, gender and TICV.

Results: Univariate analyses revealed decreases in total cortical volume ($F(4, 23) = 30.6$; $p < .0001$) among LND patients. Significant decreases in subcortical gray volume in multiple areas and structures were identified. Significant areas of cortical thickening were found in patients with LND in right ($F(4, 23) = 4.6$; $p = .009$) and left ($F(4, 23) = 8.4$; $p < .0001$) anterior cingulate, and the right ($F(4, 23) = 3.8$; $p = .02$) and left ($F(4, 23) = 4.6$; $p = .009$) medial orbital frontal regions.

Conclusion: Volumetric findings are consistent with previously reported findings including widespread cortical volume loss with additional volume loss in the striatum and associated enlargement of the inferior lateral ventricles and decreased size of the superior lateral ventricles. Lesions of striatal and ventral diencephalon structures with volume reductions are associated with motor impairments in the LND neurological phenotype including chorea, dystonia, ballismus, and extrapyramidal movements. Behavioural outcomes in humans and animals secondary to lesions in regions where we noted cortical thickening, include mood disturbance, socially inappropriate behaviour, hyperactivity, impulsivity, difficulties learning, and resistance to extinction. Further examination of the association between cortical thickening in these regions and behaviour is a focus for future study.

Keywords: Lesch Nyhan syndrome, MRI, behavioural phenotype, cortical thickening

TALK 8: An Exploration Of The Relationships Between Autism Spectrum Disorder, Theory Of Mind, And The Serotonin Transporter Promoter Length Polymorphism

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Background: This study investigated relationships between Autism Spectrum Disorder (ASD), Theory of Mind (ToM), and the serotonin transporter promoter length polymorphism (5-HTTLPR). ASDs are characterised by restricted and repetitive behaviours and interests, deficits in social competence, and deficits in communication. ToM is the ability to recognise independent mental states in others. Deficits in ToM are proposed as underlying the social awkwardness typical of ASD, and a positive correlation between ToM ability and social competence is recognised in typically developing children. 5-HTTLPR is a candidate gene for ASD due to its role in serotonergic neurotransmission, and is implicated in ToM due to the role of serotonin in social behaviour.

Method: 70 children with current ASD diagnoses (8-14 years old) were recruited. DNA samples were collected with buccal cheek swabs. Parents provided information regarding ASD symptoms. Parents completed the Autism Social Skills Profile, the Social Communication Questionnaire, and the Repetitive Behaviour Scale - Revised. 53 children underwent ToM testing using the UCT Autism Research Group ToM Battery. The variations in ASD symptoms across 5-HTTLPR genotypes were assessed ($n = 70$), as were the relationships between ASD symptoms and ToM ($n = 53$), and ToM and 5-HTTLPR genotypes ($n = 53$).

Results: We predicted positive relationships between: i) the LL genotype and rates of restrictive and repetitive behaviours and interests; ii) a short allele (i.e. LS or SS genotypes) and impairment in social competence; iii) ToM and social competence; and, iv) a short allele and impaired ToM. Further, we predicted that ToM would mediate the influence of 5-HTTLPR genotypes on social competence.

Conclusion: The relationships between ASD symptoms, ToM, and 5-HTTLPR provide valuable insight into ASD.

Keywords: Autism Spectrum Disorder, Theory of Mind, 5HTTLPR.

TALK 9: Second Hit In FMR1 Premutations May Lead To Autism Spectrum Disorders, Supporting The Two Hit Model Of Phenotypic Variability

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Background: Autism spectrum disorder (ASD), seizures and behaviour problems including ADHD and anxiety have been observed in children with the FMR1 premutation. The phenotypic variability is not fully explained by the number of CGG repeats or FMRP deficits and may be the result of a second genetic or environmental insult. The two-hit model suggests that an additional hit, in combination with the first, is sufficient to cause a disorder, here ASD or seizures. The model was first used to explain genetic variability of large CNVs in families, and showed that additional CNV hits led to more severe phenotype. Here, we expand the model and allow hits to include the inherited *FMR1* premutation risk allele.

Method: We sought to explore the genetic contribution of CNVs to ASD and seizures in the context of the *FMR1* premutation. Genomic DNA from 50 premutation carriers (with ASD, seizure and ASD, without ASD or seizure) was hybridized to custom high-density arrays targeted to ~120 hotspot regions of frequent genomic rearrangement mediated by unequal crossing-over (one probe every 2.5kbp) with a lower density genomic backbone (one probe every 35 kbp) (Nimblegen 12-plex 135K arrays).

Results: Results suggest an enrichment of large CNVs in the premutation carriers. We found that 20% of the premutation carriers harbour novel genomic events not observed in over 8,000 normal individuals. CNVs found include Xp22.31 dup, 10q26.3 dup, 21q21.2 del, and 6p22.3 dup.

Conclusion: Our findings support the two-hit model and suggest a contribution from rare CNVs, particularly duplications, to ASD and seizures in the background of an *FMR1* premutation. While these copy-number mutations are likely contributory to clinical phenotype, additional studies are needed to characterize phenotypic variability in individuals with an *FMR1* premutation. These studies should explore not only CNV but all sequence variants.

Keywords: FMR1 premutation, ASD, CNV, two-hit.

TALK 10: Plasma Amino Acids In Saudi And Egyptian Populations With Autism Spectrum Disorders

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Background: Autism spectrum disorders are complex developmental disorders with increasing incidence and poorly understood etiology. Imbalance of amino acids profoundly influences the brain functions, and is thought to be one of the key players in the pathophysiology of autism. This study aims to measure the plasma amino acid profiles of 20 Egyptian and 20 Saudi autistic patients in comparison to age, gender and ethnic matching healthy controls in a trial to clarify the role of impaired amino acid concentrations in the etiology of autism.

Method: Plasma amino acids profiles were measured using high performance liquid chromatography (HPLC). The resultant peaks are compared with those of standards, and the level of each amino acid is automatically calculated.

Results: While plasma levels of glutamic, aspartic, and glycine recorded the most significant percentage elevated amino acids, glutamine, asparagine, arginine, tyrosine and isoleucine recorded the most remarkable percentage decrease in autistic patients from both populations compared to control healthy subjects. Among the calculated relative values, only acidic/basic, and glutamate/glutamine ratios were significantly higher in autistics compared to controls. Nonessential/essential and glucogenic/ketogenic ratios were unaltered in autistics compared to control.

Conclusion: The present study suggests that plasma glutamate/glutamine ratio, together with glycine, arginine, aspartate, asparagine, and acidic/basic amino acid ratio can serve as a diagnostic tool for the early detection of autism. These findings mostly indicate that glutamatergic abnormalities in the brain may be associated with the pathobiology of autism. The changes in amino acid profile in both populations were discussed in relation to genetic makeup, and defective transport mechanism.

Keywords: Autism, Amino acids profile, Egyptian, Saudi.

TALK 11: The Science Of Syndromal And Non-Syndromal Autism Spectrum Disorders (ASD)

Lord C.

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An extraordinary amount of research has been carried out in the last 10 years concerning the etiology and phenomenology of Autism Spectrum Disorders. This talk will summarize major findings and future directions particularly in the study of the behavioural phenotypes that characterize and modify ASD across development. Individuals with ASD who have known genetic or etiological syndromes, those at risk for ASD because of known genetic relationships (e.g., siblings) and idiopathic cases will all be considered in terms of what they can tell us about the relationship between brain function, genetics and behaviour, and what we can learn that may affect prognosis and treatment planning.

Keywords: syndromal autism, non-syndromal autism, behavioural phenotypes, aetiology of ASD

TALK 12: Global Perspectives On Fetal Alcohol Spectrum Disorder

Adnams C.M.

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Fetal Alcohol Spectrum Disorder (FASD) is recognised as the most common preventable cause of intellectual disability worldwide and constitutes a major public health problem in many countries. There is a large body of knowledge about neurobehavioural manifestations in children who are prenatally exposed to alcohol. However, a neurobehavioural profile specific to FASD phenotype has not been determined and identification of children with less severe forms of FASD remains difficult. I will comment on the current state of neurobehavioural research in FASD with respect to high and low-middle income countries. Biological and environmental factors influence neurocognitive outcomes in children with FASD. The relationship between poverty and low socio-economic status and cognitive developmental outcome is well documented and will be discussed in the context of FASD. Research findings from a cohort of children in South Africa will be presented to demonstrate this association. Longitudinal studies are beginning to provide insights into lifespan neurobehavioural trajectories in FASD. Children and adults with FASD are at increased risk for mental health disorders and the interface of environment, neurocognitive phenotype and mental health will be examined in relation to FASD using data from South African and other studies. Interventions in FASD remains an under-researched area and internationally, but particularly in low- and middle- income settings, further translational research is required to develop evidence-informed and cost-effective ways to improve outcomes of primary and secondary cognitive and neurobehavioural disabilities in children with FASD.

Keywords: Fetal alcohol spectrum disorder, neurobehavioural phenotype, disability, poverty, longitudinal trajectory, interventions.

TALK 13: Loss Of White Matter Integrity In Infants Prenatally Exposed To Alcohol

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³ Combined Universities Brain Imaging Centre, University of Stellenbosch.

⁴ Laboratory of neuroimaging, UCLA.

Background: Globally, substance use and substance disorders contribute a significant proportion of the burden of disease in low, middle, and high income countries. In particular, South Africa has one of the highest prevalences of alcohol abuse disorders and foetal alcohol syndrome world-wide. Neuroimaging studies of prenatal alcohol exposure have reported differences in the structure and metabolism of many brain circuits, but little has been reported on the impact in early infancy. Diffusion tensor imaging (DTI) has proved to be a particularly useful tool in the investigation of the more subtle effects of the spectrum of alcohol on the developing brain.

Method: Infants aged 2-4 weeks of age were imaged using DTI sequences on a Siemens Magnetom 3T system. Eleven healthy unexposed infants (mean age: 22.3 days SD 7.2; 7 males, 4 females) and 20 alcohol exposed infants (mean age: 20.2 days SD 4.5; 11 males, 9 females) were included in this preliminary tract-based spatial statistics (TBSS) analysis.

Results: When comparing fractional anisotropy (FA) between alcohol-exposed and healthy infants, significant decreases ($p < 0.05$) in FA were found for the following white matter regions: the inferior cerebellar peduncle, fornix, corona radiata, cingulum, cerebral peduncle and internal capsule.

Conclusion: These results indicate that even in newborn infants the neurobiological effects of alcohol are observable in reduced white matter integrity. The location of the findings is consistent with previously reported findings in older children. However, this has not been previously reported in infants at this age when the confounding post-natal environmental influences on infants and children from these backgrounds have not yet come into play.

Keywords: alcohol, infants, neuroimaging, fetal alcohol spectrum disorder.

TALK 14: Biobehavioural Markers Of FASD In Heavily Exposed Children

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² University of Cape Town, Cape Town, South Africa.

Background: Identification of children with fetal alcohol spectrum disorders (FASD) is difficult because prenatal exposure information is often unavailable, many affected children lack the distinctive fetal alcohol syndrome (FAS) facial anomalies, and no behavioural phenotype has yet been identified. In our UCT Longitudinal Cohort, we have examined two promising FASD biobehavioural markers--eyeblink conditioning (EBC) and magnitude comparison (MC)--and used 3-D photography to successfully identify affected children.

Method: Mothers were recruited prospectively during pregnancy, and children were assessed on EBC and number processing at 5 and 9 years, examined by expert dysmorphologists, photographed at 9 years using 3-D technology, and scanned at 9 years using functional magnetic resonance imaging. Results: Not a single child with FAS met criterion for conditioning compared with 75% of controls at 5 years; two-thirds with partial FAS (PFAS) and non-syndromal children also failed to condition. A similar pattern was seen at school-age. Fetal alcohol also predicted a specific deficit in MC, a core element in arithmetic, a domain among the most frequently affected in FASD. An innovative methodology involving dense surface modelling and shape signature analyses of 3D facial photographs identified children with FAS and PFAS and also discriminated two groups of non-dysmorphic alcohol-exposed children--those with subtle facial dysmorphism resembling the features of children with FAS and PFAS vs. those whose facial features were more similar to controls.

Conclusion: These new biobehavioural markers and 3-D methodology have considerable potential for advancing understanding FASD pathophysiology, which can contribute to development of treatments targeted to specific FASD deficits.

Keywords: fetal alcohol spectrum disorders, fetal alcohol syndrome, biobehavioural markers, EBC, number processing, 3D-photography.

TALK 15: Fetal Alcohol Spectrum Disorders And Theory Of Mind In South African School-Age Children

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² Wayne State University, Detroit, MI, USA.

Background: 'Theory of mind' (ToM) refers to the ability to understand and make inferences about other people's intentions, feelings, and beliefs. Although children with fetal alcohol spectrum disorders (FASD) are known to have deficits in social-cognitive function, little is known about ToM in FASD.

Method: ToM ability including affect recognition was assessed using a developmentally sensitive ToM battery. The cohort consisted of 63 Cape Coloured children (9-11 years; 8 fetal alcohol syndrome (FAS), 19 partial FAS (PFAS), 17 nonsyndromal heavily exposed (HE), 19 born to abstaining or light drinkers), whose mothers were prospectively recruited during pregnancy.

Results: No differences were found on First- and Second-order False Belief, Strange Stories and NEPSY-II Affect Recognition tasks at this age, but the Faux-Pas task just missed significance. By contrast, FAS and PFAS groups performed more poorly than controls on the Reading the Mind in the Eyes (RME) test, even after control for IQ and numerous tests of executive function. In general, children with FAS and PFAS performed similarly on all tasks and more poorly than HE and Control groups, and Controls did not perform better than the HE group on any task.

Conclusion: The REM findings indicate a specific alcohol-related deficit that does not merely reflect poorer cognitive or executive function. Moreover, deficits in higher order ToM function may play a significant role in the social-cognitive behavioural impairment often described in children with FAS and PFAS.

Keywords: Theory of mind, fetal alcohol spectrum disorders, fetal alcohol syndrome, social cognition, affect recognition, Reading the Mind in the Eyes.

TALK 16: Neurodevelopmental Profiles In People Diagnosed With FASD: Experience From A UK National Clinic

Mukherjee R.A.S.

UK National FASD Specialist Behaviour Clinic, Surrey and Border's Partnership NHS Foundation Trust, Oxted, Surrey, UK.

Background: Fetal Alcohol Spectrum Disorders (FASD) represent a range of disorders causing neurodevelopmental consequences. As part of a national clinic in the UK neurodevelopmental and cognitive profiles are collected to better understand the different range of presentations seen in people with FASD.

Method: The National UK FASD clinic is based on a neurodevelopmental clinic model. It uses a MDT approach to diagnosis after CGH array has ruled out other disorders. Having grown organically since 2009, it now offers comprehensive assessment and diagnosis of FASD in Children and Adults aged 6 and above. Measures currently collected include, Canadian Guidance approach to FASD diagnosis, SCQ, ADHD DSM IV screen, DISCO assessment for Autism, WAIS/ WISC iv, CELFIV, Delis Kaplan Executive function tests, Vineland II, Developmental Behaviour Checklists, Short Sensory Profiles, Parental Stress inventories, as well as qualitative history of function and ability. Analysis of data collected and analysed using SPSS 21.

Results: Over 70 cases have been seen since 2009. The presentation will deliver the most up to date analysis of the data from the clinic including the proportion of ASD, ADHD and correlate as far as possible this to underlying neurocognitive assessment and function. Taking account of comorbid risk factors such as neglect and poly substance abuse.

Conclusion: Preliminary findings have shown a high presentation of both ADHD and ASD. Deficits in executive functioning and the vulnerability of prefrontal cortical functioning through direct and indirect damage will also be discussed as well as compound effects of neglect and environmental learning on psychiatric presentation.

Keywords: FASD, Neurodevelopmental profiles, comorbid presentations, Cognitive profiles, Psychiatric comorbidity.

TALK 17: Late Onset Myoclonic Epilepsy (LOMEDS) In Down Syndrome (DS)

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Background: Specific forms of epilepsy may be found at various ages in DS and a sharp increase in the incidence of epilepsy with age has been documented. A type of myoclonic epilepsy associated with cognitive decline has been reported as “senile myoclonic epilepsy” or “LOMEDS”.

Method: We recently reported a case of LOMEDS, documented by clinical and neurophysiological evaluation and psychometric assessment (DSDS and DMR) (Verri, 2012).

Results: MF, male, affected by DS, was referred in 2004 at 40 years of age; he had no personal or familial history of epilepsy. Since one year, the patient presented cognitive deterioration, characterized by regression of language abilities, loss of memory, and loss of sphincters control. A brain TC showed mild brainstem and sub-cortical atrophy. In 2006, myoclonic jerks involving upper limbs occurred mainly after awakening. EEG showed a low voltage 8 Hz background activity with diffuse slow activity, intermingled with spikes or polyspikes, persisting during NREM sleep. MF was initially treated with clonazepam and after with topiramate, resulting in partial seizures control. MRI (2008) demonstrated diffuse brain atrophy, associated with marked ventricular enlargement. At the psychometric evaluation, onset of dementia was evident late in 2004, with transition to the middle stage in 2006. Last assessment (2009) showed the clinical signs of a late stage of deterioration, with loss of verbal abilities and autonomous ambulation. Using levetiracetam till 2,000 mg/die, myoclonic jerks decreased but are still present every day after awakening. On the EEG slow and poorly organized background activity with bilateral polyspike-wave discharges was recorded.

Conclusion: A video-polysomnography is recommended in DS with dementia.

Keywords: Myoclonic epilepsy, DS, dementia.

TALK 18: The Londowns Consortium - Investigating Cognition And Alzheimer's Disease In Down's Syndrome

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Background: The amyloid precursor protein (APP) gene on chromosome 21 is thought to account for the increased prevalence of Alzheimer's Disease (AD) in Down's Syndrome (DS). Amyloid plaques suggesting neuropathological signs of AD are present in the brains of nearly all individuals with DS at the age of 30. However, not all individuals with DS show the clinical signs of AD, with significant cognitive decline being observed in just a third aged 30 and over. We aim to identify the protective factors that prevent many people with DS from developing dementia.

Method: The LonDownS consortium is a multidisciplinary effort combining clinical, developmental, genetic, cellular and mouse model studies to understand AD in DS. We will recruit 200 older adults (focusing on extremes of phenotype; i.e. young adults with AD, older adults without AD) and use a variety of cognitive tasks to profile their individual abilities. We will also recruit 150 younger adults (aged 16-30 years), using the same battery of cognitive tasks. A third cohort will consist of infants (6-36 months) with DS, profiled with comparable cognitive tasks. We will investigate general cognitive abilities, in addition to those relating to functions of frontal, temporal, hippocampal and cerebellar regions (such as executive functioning, language, memory and motor co-ordination respectively). We will also compare electroencephalogram (EEG) recordings of brain activity and sleep patterns between individuals, and collect samples for DNA analysis and for generation of induced pluripotent stem cells. We will relate differences in individual cognitive and clinical profiles to genetic, molecular and cellular differences to identify predictive phenotypes for AD in DS, and combine these with mouse model studies to identify underlying mechanisms.

Results: We will present our planned investigations and protocol.

Conclusion: Treatment and care for individuals with DS may be improved with this multidisciplinary approach.

Keywords: Down's syndrome, Alzheimer's Disease, Protocol.

TALK 19: Tuberous Sclerosis Registry To Increase Disease Awareness (TOSCA)

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² Brighton and Sussex University Hospital Trust, United Kingdom.

³ TOSCA Consortium.

Background: TOSCA, a noninterventional, multicenter, international retrospective and prospective disease registry, will assess manifestations, interventions, and outcomes in patients with tuberous sclerosis complex (TSC). The information collected from this large cohort of TSC patients aims to address gaps in the clinical course of TSC and outcomes of therapeutic interventions.

Method: Patients (any age) with a diagnosis of TSC, documented visit for TSC disease within the last 12 months, or newly diagnosed individuals are eligible for inclusion in the registry. The initial enrolment period will be 24 months with a follow-up observation period of up to 5 years. All patients (or legal guardians) are required to provide written informed consent before enrolment. Objectives of this study include mapping the course of TSC manifestations and their prognostic role, identifying patients with rare symptoms and co-morbidities, recording interventions and their outcomes, creating an evidence base for disease assessment and therapy, measuring quality of life, and collecting information on neurocognitive development and organ-related manifestations in patients with TSC. General information on patient's background, including demographics, family, prenatal, vital signs and disease features are collected in the 'Core' section of the registry at baseline and updated yearly, if available. Additional detailed data related to specific disease manifestations are collected in subsections of the registry and will be updated yearly, if available. The TOSCA Post-Authorization Safety Study, a drug safety sub study, will provide data for the European Medicines Agency that assesses the long-term safety and tolerability profile of Votubia® in the treatment of TSC patients residing in the European Union for the licensed indications. Therefore, retrospective and prospective data are collected from both patient characteristics and disease-specific information from subjects enrolled in the registry. It is estimated that ~2000 patients meeting eligibility criteria will be enrolled from roughly 250 sites in more than 30 countries.

Keywords: tuberous sclerosis complex; autosomal dominant genetic disorder; disease registry; everolimus; mTOR pathway.

TALK 20: The Tuberous Sclerosis Complex Associated Neuropsychiatric Disorders (TAND) Checklist - Pilot Validation Of A New Screening Tool For Neuropsychiatric Manifestations In TSC

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Background: Tuberous Sclerosis Complex (TSC) is a multi-system disorder that includes a range of neuropsychiatric manifestations. The majority of individuals with TSC will have some neuropsychiatric problems, with lifetime prevalence rates close to 90%. Survey results unfortunately suggest a vast gap between need and actual assessment/treatment. At the 2012 International TSC consensus conference the Neuropsychiatry panel coined the term TAND (TSC-Associated Neuropsychiatric Disorders) and advised that all individuals with TSC should be screened for TAND annually. To aid in the systematic enquiry of the behavioural, psychiatric, neuropsychological and psycho-social difficulties experienced by individuals with TSC, a 'TAND Checklist' was developed to act as an 'aide-memoire' to clinicians.

Method: Mixed-methods were used across three stages in the pilot validation of the TAND Checklist. In stage 1 we gathered feedback on the checklist from 16 international TSC experts and 42 parents/carers. The aim was to examine face and content validity. Stage 2 involved the administration of the refined TAND Checklist concurrently with four other validated assessment tools to 15 South African parents of individuals with TSC. The aim of this stage was to examine concurrent validity and to obtain qualitative feedback. Stage 3 involved the collection of demographic and clinical data about the individuals with TSC evaluated in Stage 2.

Results: At the time of submission, we were in the process of data collection for stages 2 and 3. Here we will present results from all three stages of validation including external validity and perceived subsequent validity.

Conclusion: Early results suggest that expert clinicians as well as families consider the TAND Checklist to have good face and content validity. Results of other aspects of validity and qualitative feedback will be used to shape the checklist in order to be both clinically meaningful, and to be a useful research tool for future studies.

Keywords: TSC, TAND.

TALK 21: Persistence Of Challenging Behaviour In Tuberous Sclerosis Complex

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² Division of Child & Adolescent Psychiatry, University of Cape Town, Cape Town, South Africa.

Background: Tuberous Sclerosis Complex (TSC) is a multisystemic genetic disorder associated with increased risk of challenging behaviour. The study examined the three year persistence of challenging behaviour in adults and children.

Method: Forty-seven participants responded (64% response rate). Prevalence of challenging behaviour at time 2 (t2) is compared to time 1 (t1) to establish persistence. Utility of t1 risk markers to differentiate between persistent (present t1 and t2), transient (t1 or t2 only) and absent (neither t1 nor t2) challenging behaviour is evaluated.

Results: Persistence rates were 82% for self-injurious behaviour (SIB) and 67% for aggression. Ability, impulsivity and over-activity discriminated persistent, absent and transient SIB groups. The persistent SIB group were less able and more impulsive and over-active than absent or transient SIB groups, who did not differ from each other. The persistent aggression group were more also impulsive and over-active than the absent group, but did not differ from the transient group, who were more over-active than the absent group. Finally, these variables also *predicted* persistence of SIB and aggression.

Conclusion: SIB and aggression were persistent in over two-thirds of those showing these behaviours at t1, suggesting these behaviours require early intervention, being likely to persist over time. Key risk markers differentiate those with persistent challenging behaviour from those without and have predictive power in identifying those with persistent challenging behaviour. Replication with a larger sample is needed to determine utility of these risk markers in identifying those with TSC at risk of persistent challenging behaviour.

Keywords: Tuberous Sclerosis Complex, challenging behaviour, self-injury, aggression.

TALK 22: *The Tom Oppé Distinguished Lecture:* **The Importance Of Studying Behavioural Phenotypes**

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Until the mid-19th century almost anyone born with significant intellectual delays would be classified as “feeble minded” (or some other even less desirable term) and “treatment” would generally be the same as that meted out to anyone with a severe psychiatric or cognitive impairment. However, the recognition of Down syndrome and Tuberous sclerosis in the latter part of the 19th century as distinct conditions with variable outcomes, heralded the beginning of the scientific study of the causes and trajectories of different types of developmental disorder. Subsequent research into the factors that can cause specific developmental disorders (e.g. phenylketonuria, congenital hypothyroidism, rubella or measles encephalitis) has resulted in significant reductions in certain conditions, at least in areas of the world with well-developed health systems. Nevertheless, (although figures vary from study to study and country to country) it is estimated that up to 15% of children in the US have an identifiable developmental disorder (Boyle et al., 2011). These conditions have very different causes, trajectories and outcomes; levels of intellectual impairment vary widely, and the severity of associated problems (e.g. specific learning difficulties, sensory and motor difficulties, and emotional and behavioural problems) is also highly variable. Understanding the behavioural phenotypes associated with different developmental disorders is crucial for successful intervention; for helping parents to develop effective management techniques, and for teachers to make use of appropriate educational strategies. This presentation will summarise research into the cognitive and behavioural characteristics of different behavioural phenotypes and how this knowledge can help to improve management and outcomes.

Keywords: behavioural phenotypes; developmental disorders; individualized treatments

Abstracts for Poster Presentations

(in alphabetical order of primary author)

POSTER 1: The Behavioural Phenotype Of Foetal Alcohol Spectrum Disorder (FASD): Intra-Familial Variability In Three Brothers

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Background: FASD involves several conditions resulting from gestational exposure to alcohol with the two most common being Foetal Alcohol Syndrome (FAS) and Alcohol-Related Neurodevelopmental Disorder (ARND). The variability of neurobehavioral outcomes of prenatal alcohol exposure is likely to have genetic and environmental influences. To study the environmental factors, clinical researchers need to identify dose, pattern and developmental timing of alcohol consumption. All such information is best ascertained from parents. However, because many children with FAS and ARND are adopted or fostered, information about their biological mothers' drinking patterns during pregnancy is often not available. The objective of this paper is to describe a family of 3 siblings presenting with phenotypic variability of FASD/ARND.

Method: We describe 3 male siblings with the same biological parents who were removed and placed in different children's homes at different stages of their lives. The first born, age 18 years old was not referred to clinical services and was therefore not included in this report.

Results: The youngest child, aged 4 years, received an early diagnosis of FASD, intellectual disability, hearing and speech problems at the age of 3 years and later presented with severe symptoms of Attention Deficit Hyperactivity Disorder (ADHD), hyperactive-impulsive subtype. The 7 year old presented with ADHD combined type and average Intellectual ability. The 13 year old presented with stuttering and Intellectual Disability, and attended special needs school but had no evidence of ADHD. The 7 year old responded well to methylphenidate treatment while the 4 year old was particularly challenging because of his age of presentation and controversies surrounding use of stimulants in children with FASD.

Conclusion: These 3 siblings presented with phenotypical variability of FASD and raises both the challenges of clinical management in real life, and in the scientific study of the aetiological contributors to the spectrum of FASD.

Key words: FASD, ARND, Phenotypes, variability, Africa.

POSTER 2: Variable Phenotype In 16p Duplication Within A Family

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Background: More individuals are now being identified with very rare genetic syndromes. We present a family with an inherited duplication of 16p11.2 to 16q12.1 in ring formation. Three of the four children, (aged 15 months to 10 years), mother, uncle, and grandmother are affected. Our aim was to provide preliminary evidence of possible phenotypic patterns of learning and behaviour associated with this chromosome anomaly.

Method: Psychometric assessments were undertaken with all four children. The mother and uncle also agreed to participate in the study. Measures of development (Bayley or Mullen), intellectual ability (WISC-IV or WAIS-III), academic achievement (WIAT-II), adaptive behaviour (Vinelands), and other relevant aspects of functioning (e.g., Children's Memory Scale) were administered.

Results: The first-born child is the only one who is unaffected. Her intellectual ability was assessed as being within the superior range. The second child experienced early difficulties with speech and motor skills. Although his intelligence is average, he has learning difficulties and significant auditory memory problems. The third child's speech and motor milestones were markedly delayed. He has a complex medical history that includes a vitamin B12 deficiency. On the Mullen Scales at age 4 his scores ranged from average to very low. The development of the youngest child (aged 15 months), who also had a B12 deficiency but was treated early, was assessed as being within typical limits.

Conclusion: There is considerable developmental variability among the three children with this inherited 16p duplication. We discuss the intriguing similarities and differences, considering common features that may reflect phenotypic patterns and speculating about possible explanations for the variable presentations.

Keywords: 16p duplication; behavioural phenotype; rare chromosome disorders.

POSTER 3: Health Related Quality Of Life (HRQoL) In 22q11 Deletion Syndrome: The Child's Perspective

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Background: 22q11 Deletion Syndrome (22q11DS) is a genetic syndrome of high prevalence that manifests an extensively varied phenotype. There are periods of severe illness, early in life where medical and surgical emergencies are often present. As the child ages the focus shifts to an impairment model which attempts to maximize the quality of life of the individual with a high prevalence of cognitive and mental health difficulties.

Method: In this study we recruited individuals between the ages of 8 and 18 with a positive genetic diagnosis of 22q11DS (n=30) and a parent of the child. Participants were asked to complete the PedsQL 4.0™ questionnaire. Results were correlated with other clinical measures. We were interested in measuring the HRQoL from the perspective of the child and also as a proxy measure from the parent. Comparisons were made with a typical population (n=5972) of healthy individuals.

Results: In all domains of the PedQoL children with 22q11DS had a significantly poorer HRQoL (Mean 52.17(95% CI 47.98-56.3) than the typical population (Mean 82.2 (CI 82.54-83.2)) in all domains. Parents perceived the child's HRQoL as significantly lower than the children themselves in the social domain only. Correlations with cognitive level and mental health are made.

Conclusion: Children and parents both perceived the child's quality of life was poorer than for their typically developing peers. It is important to recognise that children may have different views to their parents however in this study the children had very similar views to their parents except in the social subdomain where they believed they had less problems with social skills.

Keywords: 22q11ds, Quality of Life, children.

POSTER 4: The Experiences Of Adults With ASD, Their Employers And Co-Workers In The Workplace In KwaZulu-Natal

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University of KwaZulu-Natal.

Background: In South Africa, research done on Autism Spectrum Disorder (ASD) mainly focused on children. However, little is known about the job opportunities and the challenges faced by adults with ASD in the workplace. Therefore, this study aims to gain a better understanding of the experiences of adults with ASD and their employers and co-workers in KwaZulu-Natal.

Method: A qualitative phenomenological case study design was used. Participants were identified using a non-probability convenience sampling technique. Individual semi-structured interviews were conducted. The study population consisted of 6 individuals with ASD, 3 employers and 2 co-workers. Thematic analysis was used to identify common themes from the data obtained.

Results: Results revealed that participants with ASD had difficulties maintaining employment for longer than 3 months due to changes in routine, difficulties with communication and social interaction, and becoming bored with job tasks. Disclosure of ASD and employers lack of awareness of ASD sometimes resulted in poor confidence in the individual's abilities to complete tasks. Participants with ASD presented with verbal and nonverbal communication skills that limited their ability to express themselves appropriately, resulting in increased stress and decreased task completion. Difficulty understanding the rules of social interaction resulted in participants with ASD not enjoying or seeing the purpose of socializing, leading to poor working relationships, inappropriate behaviour, disputes and dismissals. Social support systems helped individuals with ASD to cope with functions related to employment.

Conclusion: Social and communication profiles significantly impacted on the completion of job tasks, job maintenance and maintaining social relationships. Fears related to disclosure played a key role in the negative experiences of the participants. Implications include the importance of early identification, exploring tertiary qualifications, and roles of other health professionals in the management of ASD in the workplace. Limitations of the study will be presented.

Keywords: Autism Spectrum Disorder, Employment, Employers, co-workers.

POSTER 5: Prospective Memory Impairment In Children With Fetal Alcohol Spectrum Disorders (FASD)

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Background: Prospective memory (PM; the ability to realize and act on delayed intentions) is reliant on declarative memory and executive functions (EF), both of which are impaired in FASD. This study investigated PM in a prospective longitudinal cohort of children with heavy prenatal alcohol exposure (PAE) and examined the impact of potential confounding variables, IQ, EF, or declarative memory.

Method: 89 children ($M_{age}=11.1$ years; 29 fetal alcohol syndrome (FAS) or partial FAS (PFAS), 32 heavy exposed nonsyndromal (HE), 28 controls born to abstainers/light-drinkers) completed two versions (Focal/Non-Focal) of the *Dresden Cruiser*, a computerized car-racing game that measures event-based PM at two difficulty levels (easy/difficult).

Results: The FAS/PFAS group had more PM failures than the HE or Control groups, with HE=Control. PAE had an independent effect on PM after control for potential confounders, EF, and declarative memory. However, WISC-IV Full Scale IQ, Perceptual Reasoning, and Verbal Comprehension indices, partially mediated effects of PAE on PM.

Conclusion: These findings indicate a distinct PM impairment independent of sociodemographic variables and difficulties with EF and/or declarative memory in children with FAS and PFAS. The finding that this effect was independent of previously-documented effects on EF indicates impairment, by fetal alcohol exposure, of a new domain of cognitive control not previously identified in the literature. These results therefore provide a novel contribution to defining the neurocognitive profile of FASD.

Keywords: Prospective memory, fetal alcohol spectrum disorders, fetal alcohol syndrome, IQ, executive function, heavy prenatal alcohol exposure.

POSTER 6: An Investigation Of Single Nucleotide Polymorphisms (SNPs) In Differential-Expressed Candidate Genes: Is There A Correlation Between SNPs And ASD Phenotypes In South Africans?

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Background: Autism spectrum disorder (ASD) is a complex trait that is the result of the interplay of genes, epigenetic and environmental factors, and is an early onset developmental disorder with deficits in communication, behaviour and social interactions. Many studies link specific genes to ASD, but these gene mutations are rare and occur at very low frequencies in a population. ASD is a quantitative genetic trait with highly variable phenotypes that is the result of the additive effects of a number of different genes, in a number of different combinations. SNPs (Single Nucleotide Polymorphisms) in a number of genes are correlated with ASD and are reflected in both candidate gene (CG) or genome wide association studies (GWAS). A recent paper, using RNA expression data, identified over 4000 genes that are differentially expressed, but only when the controls were compared to specific phenotype variants of ASD.

Methods: This project aims to identify novel SNPs in candidate genes that are differentially expressed in ASD. Using a bioinformatics approach, we identify SNPs in differentially expressed genes by searching the Human HapMap Project and SNP database hosted by NCBI using web based platforms such as Galaxy and SNPinfo Webserver.

Results: We describe the methods used to identify these SNPs, and to demonstrate the utility of this approach, we show genotyping data for genes identified in this manner. We report novel SNP data for a selected set of genes that were previously identified as candidate genes using either differential expression, GWAS or other criteria.

Conclusion: We demonstrate a bioinformatics-based approach to find SNPs potentially associated with ASD and measure the frequencies of these SNPs in a South African population.

Keywords: Autism spectrum disorder; Single Nucleotide Polymorphisms; Genotyping

POSTER 7: The Effects Of Early Hormonal Replacement On The Anthropometric Measurements Of Boys With XXY

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Background: 47,XXY is the most common sex aneuploidy and occurs 1 in 500-1000 births. Individuals with XXY often present with various characteristics including tall stature and cognitive and language deficits of varying severity. Early hormonal replacement (EHR) was shown to improve neurodevelopmental performance in XXY at 36 and 72 months. The question has been posited that EHR may alter growth in boys with XXY. The purpose is to investigate effects of an EHR on the height, weight and head circumference (HC) in XXY.

Method: Height, weight and HC were collected at 36, 72, and 96 months of age on 35 prenatally diagnosed XXY males; twelve received EHR and 23 were untreated.

Results: The results showed no statistically significant difference in the height, weight or HC of participants who received EHR versus participants who did not at any of the time points.

Conclusion: Few publications have studied the physical effects of EHR, especially in the paediatric population. Our study is the first to look at the physical effects of EHR. The physical phenotype in young boys with XXY was not altered significantly by EHR. Our study further demonstrates that boys with XXY improved in neurodevelopmental performance while not sustaining any interruptions to height, weight or HC. Further investigation into the effects of EHR on neurodevelopmental performance and growth parameters in XXY is underway.

Keywords: Early Hormonal Replacement Therapy, XXY, Growth.

POSTER 8: Expanding The Phenotypic Profile Of Boys With XXY: Mathematic Capabilities

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Background: Males with XXY have been characterized by developmental dyspraxia, language based learning disorders, executive dysfunction and attentional deficits. This is the first systematic evaluation of XXY and math capabilities in a large and homogenous group of boys with XXY. Ascertainment bias and insufficient study subjects have confounded previous research of XXY neurodevelopmental profiles. The aim was to assess the impact of familial learning disorders (FLD) on the phenotypic profile of mathematic capabilities in the child with XXY.

Method: 103 boys with XXY diagnosed prenatally who did not receive hormonal replacement had comprehensive mathematics evaluations.

Results: There was significant difference between the group with learning disabilities (N=40) and those without (N=63) on the total test ($p=0.0033$) and multiple subtests of the KeyMath3 including, numeration ($p=0.0026$), algebra ($p=0.037$), geometry ($p=0.0305$), measurement ($p=0.0021$), data analysis/probability ($p=0.0071$), basic concepts ($p=0.0037$), mental computation/estimation ($p=0.0019$), addition/subtraction ($p=0.0419$), operations ($p=0.0069$), foundation of problem solving ($p=0.0208$), applied problem solving ($p=0.0072$), applications ($p=0.0026$).

Conclusion: Our study demonstrates the significant influence of FLDs on mathematic performance of boys with XXY. Our findings suggest that boys with FLDs have an increased incidence of mathematical disabilities. Our study further expands on previous findings and the significant influence of FLDs on neurodevelopment and behaviour. FLDs may increase the vulnerability of the child with XXY and further study is underway to examine the interaction between the many salient factors effecting neurodevelopmental progression in XXY.

Keywords: Klinefelter syndrome; XXY; mathematics; familial learning disorders; genetics.

POSTER 9: Focal Epilepsy And Severe Neurological Features Associated With Tetrasomy Of 22q11.1q11.21 Region

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Background: The 22q11 region is susceptible to chromosomal rearrangements, leading to various types of congenital malformation and intellectual disability. Several genomic disorders have been well described, including Cat Eye syndrome (CES) caused by extra copies of the most proximal region, DiGeorge/Velocardiofacial syndrome due to deletion of 22q11.21, 22q11.2 duplication syndrome and distal 22q11.2 microdeletion/microduplication syndrome. We present a clinical observation of a 28 yrs old male with a tetrasomy of the region q11.1q11.21 of the chromosome 22, corresponding to the CES region.

Method: clinical, neurophysiological and neuroradiological instruments Laboratory studies included array-CGH, conventional cytogenetic and FISH analysis.

Results: Born from non consanguineous parents after a normal pregnancy. Weight at birth: 3350 grams, height 54 cm. A cardiac total anomalous pulmonary venous connection was corrected at birth. Developmental milestones were severely delayed: first steps after 3 years, no development of language. Since two years the patients developed daily atypical seizures, characterized by loss of contact and motor stereotypies, which are refractory to treatment. At clinical evaluation he presents turricephaly, corrected nasal fistula, spastic tetraparesis. Brain MRI documented thinning of the corpus callosum, hypomyelination of the semioval centers. On the EEG slow and poorly organized activity without specific abnormalities. The cognitive phenotype is characterized by severe learning disabilities, and specific language impairment. Behavioural phenotype is characterized by an exaggerated response to threatening stimuli, presence of ritualistic behaviours. Array-CGH detected the tetrasomy of about 1,55 Mb on chromosome 22q11.1q11.21, due to the presence of a bisatellited small dicentric supernumerary chromosome.

Conclusion: We underline the severity of the neurological and clinical picture that can be associated with CES.

Keywords: Epilepsy, ID, CES.

The 2013 SSBP Educational Day Programme

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Educational Day: Saturday, 14th September 2013

8:00 – 9:00	Registration & Coffee
9:00	Welcome (<i>Profs de Vries, Jacklin, Venter</i>)
9:00 – 10:00	Educational Day Talk 1: <i>Randi Hagerman, USA</i> – Molecularly targeted treatments in genetic disorders
10:00 – 11:00	Educational Day Talk 2: <i>Petrus J de Vries, South Africa</i> – The Neuropsychiatric journey of discovery from molecules to medicines in Tuberous Sclerosis Complex
11:00 – 11:30	Morning Coffee
11:30 – 12:30	Educational Day Talk 3: <i>Honey Heussler, Australia</i> – Management of sleep disorders in Neurodevelopmental disorders and genetic syndromes
12:30 – 13:30	LUNCH
13:30 – 14:30	Educational Day Talk 4: <i>Chris Oliver, UK</i> – Management of challenging behaviours in neurodevelopmental disorders and genetic syndromes
14:30 – 15:00	Afternoon Tea
15:00 – 16:00	Educational Day Talk 5: <i>Catherine Lord, USA</i> – Update on diagnosis of Autism Spectrum Disorders
16:00 – 17:00	Educational Day Talk 6: <i>Patricia Howlin, UK</i> – Update on treatments for Autism Spectrum Disorders
	Good byes (<i>Profs de Vries, Jacklin, Venter</i>)

EDUCATIONAL TALK 1: Molecularly Targeted Treatments For Genetic Disorders

Hagerman R.

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Background: The development of animal models for genetic syndromes with intellectual disability (ID) have lead to trials of targeted treatments that reverse the neurobiological abnormalities.

Method: Review of the literature and the organization of treatment trials in Fragile X syndrome (FXS), Angelman syndrome (AS), Autism Spectrum Disorders (ASD), Rett syndrome (RS) and Down syndrome (DS) will be discussed.

Results: In several disorders glutamate and GABA imbalance have lead to ID and behavioral problems. Typically there is enhanced glutamate activity and lowered GABA as seen in FXS, AS, ASD and RS but this is not the case in DS. The use of metabotropic glutamate receptor 5 (mGluR5) antagonists have been shown to be helpful in animal models of FXS and ASD and expected in AS. Human trials have been somewhat helpful in FXS. Excessive protein up-regulation can be documented in FXS and AS and the use of minocycline that lowers matrix metalloproteinase 9 (MMP9) and stalls translation of mRNAs have demonstrated efficacy in FXS and AS, particularly in young patients. The use of a GABA agonist has demonstrated benefits in the animal models of ASD and FXS and arbaclofen (a GABAB agonist) has been beneficial to a subgroup of children with FXS and ASD. Ganaxolone, a GABAA agonist also looks promising for FXS and perhaps ASD. In DS the use of a GABAA alpha5 inverse agonist has been beneficial in animal models and is currently in trials in patients with DS.

Conclusion: There are a number of targeted treatments currently in human trials that are likely to change the face of ID in our generation. The use of enhanced learning programs to take advantage of the improved synaptic connections is critical for the successful reversal of ID.

Keywords: targeted treatments.

EDUCATIONAL TALK 2: The Neuropsychiatric Journey Of Discovery From Molecules To Medicines In Tuberous Sclerosis Complex

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The last decade has seen rapid and exciting progress in Tuberous Sclerosis Complex (TSC) from molecules and molecular discoveries to medicines and molecularly targeted treatments. TSC has become one of the first genetic disorders with a licenced targeted treatment. The journey has been particularly rapid for angiomyolipomas (AML) and subependymal giant cell astrocytomas (SEGA) with facial angiofibromas following closely behind. Neuropsychiatric manifestations represent some of the greatest concerns to individuals with TSC and their families, and represent a significant proportion of the burden of disease. Approximately 90% of individuals with TSC will have some neuropsychiatric manifestations, yet fewer than 20% of those receive assessment and appropriate treatments. Whilst molecularly targeted treatments therefore hold great hope for neuropsychiatric features of TSC, there are many unanswered questions and many risks to consider. In this presentation we will discuss our neuropsychiatric journey from molecules to medicines, from mouse to man, and will review critically the numerous gaps, obstacles and challenges to consider along this journey of discovery.

Keywords: rapamycin, mTOR, targeted treatments, everolimus

EDUCATIONAL TALK 3: Management Of Sleep Disorders In Neurodevelopmental Disorders And Genetic Syndromes

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Children with Neurodevelopmental disorders often have problems with sleep. These problems can be many and varied depending on both medical problems and behavioural phenotype. As many as 80% of children presenting with a neurodevelopmental disorder such as Autism, ADHD or various developmental syndromes will present with a sleep difficulty. This has far reaching implications on child presentation and family function. These disorders are commonly thought of as disorders of initiating or maintaining sleep as well as sleep related breathing disorders. Management presents significant challenges in that our knowledge of sleep in specific syndromes is limited however basic principles can be applied especially when adapted with knowledge of the individual behavioural phenotype and medical issues. Evidence based therapies suggest that problems are able to be modified and are not that different from the age specific problems in the typically developing population and with moderate adaptations can be successful in the population with developmental disability. Practical solutions often need to be explored on an individual basis but with sound knowledge of sleep interventions. Examples of specific disorders with unique problems include children with Smith Magenis and Angelman's syndrome and these groups often require specific adaption of sleep strategies.

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Keywords: Sleep, paediatrics, behaviour, genetics

EDUCATIONAL TALK 4: Management Of Challenging Behaviours In Neurodevelopmental Disorders And Genetic Syndromes

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Four decades of research on challenging behaviour have generated a large but disparate body of knowledge about causes, assessment and intervention. A striking characteristic of the published literature is the lack of integration of both empirical findings and theoretical perspectives with implications for the conceptualisation of challenging behaviour, intervention research and service delivery. This lack of integration frequently runs alongside a quest for a single causal model that can account for different forms of challenging behaviour across the total population of people who have intellectual disability. It is clear that this combination is not proving fruitful because: 1) there are few, if any, good quality group based intervention studies, 2) the prevalence of challenging behaviours, such as self-injury, appears to be unchanged for over twenty years and 3) policy has stagnated. One way ahead is to use robust empirical findings to build and test models of well defined behaviours shown by clearly delineated subgroups of people with intellectual disability. Groups may be defined by broad characteristics, such as degree of intellectual disability, aetiology, in particular genetic syndromes, and behavioural characteristics. Models for different groups may give varying degrees of emphasis to biological, psychological and environmental characteristics in order to increase the explanatory power of a model for a given behaviour shown by a group. It is these models for specific behaviours shown by well defined groups that should be tested in intervention studies at a group level. Supportive evidence for this strategy is provided by the results of behavioural phenotype studies, the association between some forms of challenging behaviour and other behavioural characteristics and empirically derived models of challenging behaviour in genetic syndromes.

EDUCATIONAL TALK 5: Diagnosis Of Autism Spectrum Disorders (ASD): Where Is The Diagnosis Of ASD Going? And What Will We Do When We Get There?

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This talk will outline the changes that DSM5 includes as we move from Pervasive Developmental Disorder to Autism Spectrum Disorder. Information regarding the nature of these changes, the research on which they are founded and the implications for clinical practice will be discussed.

Keywords: DSM-5, diagnosis of ASD, autism spectrum disorder

EDUCATIONAL TALK 6: Update On Treatments For Autism Spectrum Disorders

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In recent years there has been a significant improvement in the quality of intervention research for young children with autism. The number of randomised control trials is increasing steadily and there is now much better evidence for the effectiveness of a range of different treatment approaches, including those with a focus on parent management style, early, intensive behavioural intervention, social communication, joint attention and play programmes, and augmentative communication systems. Overall, group results indicate moderate, but encouraging improvements for children involved in each of these interventions. However, at an individual child level, outcome is much more variable, with some children in each programme showing considerable change, others only minor improvements and some showing no improvement, or even deterioration over time. Identification of the children who respond most to specific types of intervention remains a major challenge for research in this field in the future. The presentation will summarise the evidence base for therapies for young children with autism and will highlight the need to improve interventions for older children and adolescents in order to improve long-term outcomes.

Keywords: autism, interventions, randomized control trials

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.

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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 electroencephalography 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 processes. This expression is normally determined epigenetically by a methylation pattern which is specific to the maternally inherited chromosome. Abnormal imprinting in various regions of the brain and the cerebellum are probably responsible for most of the phenotype. Angelman syndrome phenotype has been associated with mutations in the X-linked methyl-CpG-binding protein 2 (MECP2) which has been 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 microbrachycephaly, short, hooked nose, prognathism, 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 Spectrum Disorder

Classification

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

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

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

environmental factor; is associated with another neurodevelopmental, mental or behavioural disorder, or with catatonia.

Sub-categories of disorder that were included in DSM-IV such as Asperger syndrome or Pervasive Developmental Disorder no longer appear, although DSM-5 criteria specify that “Individuals with a well-established diagnosis of autistic disorder, Asperger’s disorder or Pervasive Developmental Disorder should be given a diagnosis of Autism Spectrum Disorder”

Associated conditions

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

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

Genetics

The risk of ASD in siblings of probands is significantly increased and there is a high concordance rate in monozygotic twins. Family studies indicate that the “Broader Autism Phenotype” (i.e. having problems related to social, language and/or cognitive functioning) occurs in up to 20% of first-degree family members. Although ASD is clearly highly heritable, attempts to identify the specific genes involved have met with limited success (Rutter, 2013). Currently, up to 15% of cases of ASD appear to be associated with some form of genetic mutation and it is suggested that the identification

of rare mutations (e.g. SHANK 3) and Copy Number Variations (CNV's; i.e. submicroscopic chromosomal deletions or substitutions) may provide evidence of the neural systems that underlie autism (Geschwind, 2011). However, Rutter (2013) notes that these may be related to intellectual disability as much as to autism. It is evident, too, that both common polymorphic variations and rare mutations play a role; there are also genes that are intermediate between rare and common. "The relative importance of rare, common and intermediate frequency genes has yet to be established" (Rutter, 2013).

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

Prevalence

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

Physical Phenotype

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

Life expectancy/natural history

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

Behavioural and cognitive characteristics

As noted above, ASD is defined by impairments in reciprocal social communication and the presence of ritualistic and stereotyped behaviours/interests. Onset of language is typically delayed but significant delays in language are less common in children of average or above IQ. Although frequently associated with intellectual impairment, recent studies suggest that up to 50% of individuals with ASD may be of average intellectual ability (Baird et al., 2006). In children, non-verbal IQ is frequently higher than Verbal IQ, although this pattern may be reversed in older, more able individuals.

Outcome

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

Websites

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

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Patricia Howlin, 2013

CHARGE Syndrome (or Association)

First Description

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

Genetics/aetiology

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

Incidence/prevalence

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

Physical phenotype

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

CHARGE has become the most common cause of congenital deaf-blindness (after "other" and "unknown"). Vestibular difficulties are present due to missing or malformed semi-circular canals and otoliths. Swallowing difficulties are common due to cranial nerve dysfunction. Other problems include gastroesophageal reflux, airway difficulties, chronic otitis media, sinusitis, detached retina, scoliosis, chronic constipation with megacolon, and sleep disturbances. Cranial nerve anomalies are common in CHARGE with as many as 92% having symptoms of at least one anomaly. It is speculated that in some cases all 12 cranial nerves might be affected, but the most common are I, V, VII, VIII, and IX/X.

Behavioural and psychiatric characteristics

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

Neuropsychological characteristics

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

Useful websites/associations for more information

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

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Timothy S. Hartshorne, April, 2010

Coffin-Lowry Syndrome

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

Genetics and molecular biology

The *RPS6KA3* gene encodes a growth factor regulated serine-threonine protein kinase, Rsk2 (alternate names: 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; Bhuiyan *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, Kliever 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.
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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). Niebuhr 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 (Niebuhr, 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.
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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 dysmorphism and /or growth retardation (3). ARND replaced the old term Fetal Alcohol Effect (FAE). FAS Spectrum Disorders, an umbrella term, was introduced by O'Malley & Hagerman in 1998, refined to Fetal Alcohol Spectrum Disorders (FASD) by Streissguth & O'Malley in 2000 (4,5).

Genetics and molecular biology

Both FAS and ARND are teratogenic conditions, but recent research is beginning to study the epigenetic effects of prenatal alcohol exposure. For example, the major liver pathway of oxidative metabolism which produces acetaldehyde by cytotoxic alcohol dehydrogenase is also accompanied by a reduction in NAD to NADH. There is a subsequent alteration in the cellular redox triggered by a change in the NAD/NADH ratio which may result in gene activation resulting in a change in gene expression.

Incidence/ prevalence

The recognition and incidence for FAS has been shown to be increasing. Original estimates varied from 3 per 1,000 live births in the USA to 40 per 1,000 births in South Africa. More recent studies in Lazio, Italy and Cape Town, South Africa, have suggested much higher rates of 35/1000 to 890/1000 respectively (6,10,13). Methodological issues, genetic differences in the susceptibility to alcohol based on the mother's liver metabolism, as well as differences in population drinking patterns may account for some of the variance(7). As a result, whilst the exact incidence for any one population differs greatly and is unknown

the rates are considered potentially higher than previously thought. No documentation of decreased life expectancy exists.

Physical features and psychiatric characteristics

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

Infants can demonstrate Primary Regulatory Disorders characterized by difficulties in tolerating environmental stimuli (i.e. habituation problems), co-ordinating basic motor movements (i.e. sucking), or interacting with parents or care-providers. Secondary psychiatric disorders appear due to environmental stressors such as PTSD after physical or sexual abuse, or Reactive Attachment Disorder of Infancy or Early Childhood related to separation from birth mother or multiple foster home placements. FASD increases the vulnerability to many common psychiatric disorders, such as ADHD, Mood Disorder, Anxiety Disorder, Alcohol or Drug Dependence, PDD and Schizoaffective Disorder. Personality Disorders seen are, Avoidant, Dependent, Schizoid, Passive/Aggressive and Borderline. Presence or absence of facial dysmorphism 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 heterotopias (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.fasaware.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 unmethylated 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 is not known.

Incidence/prevalence

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

Physical features and natural history

Although 47,XXY is associated with a characteristic pattern of physical differences, the degree to which an individual is affected can vary widely. Prior to puberty physical differences can be minimal, including increased height and proportional leg length. These are thought likely related to dosage effects of the additional chromosome. Studies of testosterone levels during the perinatal period have had mixed results. During adolescence and adulthood physical features related to hypogonadism become more

prominent, including small, firm testes; gynaecomastia, low testosterone levels and other abnormalities in endocrine response. Testicular histology may appear normal until puberty, but then demonstrates increasing hyalinization of the seminiferous tubules, disappearance of Sertoli cells, hyperplasia of Leydig cells, with loss of spermatogenesis. Islands of normal testicular tissue may remain in some individuals. Other areas of increased risk developing over adulthood include low energy and libido; osteoporosis; thromboembolic disease, obesity, and diabetes mellitus. Individuals with a mosaic form are usually less affected and may have normal fertility.

Behavioural and psychiatric characteristics

Individuals with 47,XXY are at increased risk for behavioural problems and psychiatric disorders. School aged children frequently show problems with anxiety and mood disorders, self-esteem, and socialization.

Socialization problems frequently relate to inhibition and anxiety, and may become more pronounced during adolescence. Adults are at greater risk of depression related to low testosterone. 47,XXY individuals are considered to be at greater risk for psychosis. Brain imaging data has shown abnormal brain activation patterns and decreased brain volumes, particularly in frontal and temporal regions.

Neuropsychological characteristics

The effects on neurocognitive function widely, with many 47,XXY individuals having normal or above average cognitive capacity. On a group level mean IQ values fall within the normal to low normal range, and are depressed approximately 10 points below what would be expected based on siblings. Verbal ability may be more severely affected than nonverbal. 70-80% of 47,XXY individuals across several studies have had identified language problems. Some studies have reported relatively more pronounced deficits in verbal IQ than performance IQ, although this is not universal. Executive function capacities such as attention and impulse control may be impaired, although available

studies are sparse. Several studies have reported impairments in both fine and gross motor skills.

Available guidelines for behavioural assessment/treatment/management

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

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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 Voragine 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 be 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 injure 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 performat 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 (Wingbermhühle 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 Wingbermhühle, 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 *FOXP1* have been separately reported as leading to very severe developmental disorders, still to be fully characterised but with similarities to Rett disorder.

Management

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

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

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Alison M Kerr, 2010

Triple-X Syndrome (47,XXX)

First description and alternative names

In 1959 Jacobs (Jacobs *et al.* 1959) first described triple-X syndrome in an infertile patient. The term “super female” is considered to be controversial and the term triplo-X syndrome is old fashioned. The terms triple-X syndrome, trisomy-X syndrome and 47,XXX syndrome are generally preferred. After the first description there was a period of research in biased populations, e.g in institutions, asylums and forensic psychiatric hospitals (Olanders 1975). In 1974 200,000 newborns were screened for chromosomal disorders in several hospitals. The triple-X cases in this study have been evaluated several times for at least 20 years. These newborn-screening studies yielded unbiased data (Robinson *et al.* 1990).

Genetics and molecular biology

In triple-X syndrome there is an extra X chromosome in all cells or, in mosaic cases, in almost all cells. Most of the cases are diagnosed through prenatal diagnostic examinations. In 46,XX females one X chromosome is silenced. The extra X chromosome in triple-X women is also silenced through Lyonization. In 46,XX females one-third of the genes on the X chromosome escape silencing (Migeon 2007). The so-called ‘late-replicating’ X chromosome is found on the second X chromosome. In cases of an extra X chromosome there is another late-replicating chromosome, so replication time increases during each cell division (Barlow 1973). The extra X chromosome might also have some influence on the nuclear architecture and on epigenetic processes (Kelkar and Deobagkar 2010). The question of whether incomplete silencing of the extra X chromosome, the prolonged cell cycle during division or epigenetic phenomena are relevant during development in 47,XXX requires further research.

Incidence/prevalence

1/1000 females have an extra X chromosome (Jacobs 1979).

Physical features and natural history

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

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

Behavioural and psychiatric characteristics

Low self-esteem seems to be the most common feature, and shyness is also common in triple-X females. Receptive and expressive language disorders are common. These language disorders may be responsible for social problems, as is challenging behaviour, although this behaviour is less common. Both individuals living in a stable family and controls in unstable families function better than triple-X girls do (Netley 1986). The triple-X girls seem to be less able to cope in a stressful environment. After leaving school, most of the girls will find a job that reflects their non-verbal abilities (Robinson *et al.* 1990).

There seems to be a higher prevalence of psychiatric illness in general, especially in cases of less severe global intellectual disability. More specifically, there is a higher prevalence of psychotic disorders and adjustment disorders (Olanders 1975). Newborn-screening studies have not continued to the age

at which psychotic disorders could have become noticeable. Further psychiatric research with standardised psychiatric diagnostic tools is warranted in these females.

Neuropsychological characteristics

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

Data on intelligence are consistent, indicating that Full Scale IQs are almost 20 points lower than would be expected in the family. Whether the girls show problems in reading or arithmetic is not uniformly reported in the case reports. Mild or serious academic problems are quite common. In individual cases support may be necessary and beneficial. Further research is needed to determine whether there are attention problems due to receptive language disorder, auditory processing disorders or attention deficit disorder (ADD). Clinical experience in treating ADD with medication suggests that the treatment is less effective than in 46,XX cases; however, controlled treatment studies are lacking (Leggett *et al.* 2010).

Available guidelines for behavioural assessment/treatment/management

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

Useful websites/associations for more information

- The Dutch parents' support website: <http://triple-x-syndroom.nl/> .
This website shows many links to scientific papers and useful links, e.g. links to international chat pages for parents and triple-X girls/women. Scientific papers and syndrome sheets are available in English, French, Spanish, German and Dutch.
- <http://www.rarechromo.org/information/Chromosome%20X/Triple%20X%20FTNW.pdf> provides a syndrome sheet with information on physical and behavioural developmental issues.

- The KS&A (Klinefelter Syndrome and Associates) website <http://www.genetic.org> . Parents and triple-X-girls/women in the United States have the opportunity to meet experts, other parents and triple-X girls/women.

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Maarten Otter, summer 2010

Tuberous Sclerosis Complex (TSC)

First description and alternative names

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

Genetics and Molecular Biology

Occurs as a spontaneous mutation in 70% of cases. Autosomal dominantly inherited in the remaining 30% of familial cases. The disorder is associated with mutations in one of two genes, TSC1 (on 9q34) or TSC2 (on 16p13.3). The TSC1-2 protein complex acts as a heterodimer linking a number of intracellular signalling pathways including the AMPK pathway, the MAPK pathway and the PI3K pathway. The TSC1-2 complex functions upstream of mTOR (mammalian Target Of Rapamycin). TSC mutations causes mTOR overactivation, leading to dysregulation of cell growth, proliferation and various other fundamental neurobiological processes (de Vries, 2010, Kwiatkowski *et al.*, 2010).

Incidence/prevalence

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

Physical features and natural history

Wide variability of expression. The previously used "diagnostic triad" (of epilepsy, intellectual disability and characteristic facial skin lesions) is seen in only about 30% of people with the disorder. TSC is multi-system and can include hamartomatous growths affecting the brain, skin, kidneys, heart, eyes, teeth, bones, lungs and other organs. About 80% of affected people have a lifetime history of epilepsy. Diagnosis is based on

meeting clinical criteria for the disorder (Roach *et al.*, 1998). Mutations are identified in 80-90% of individuals with clinically confirmed TSC.

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

Behavioural and psychiatric characteristics

Tuberous sclerosis complex is associated with high rates of various disruptive behaviours, sleep problems and self-injurious behaviours. Developmental disorders including autism and autism spectrum disorders (ASD) in 40-50%, ADHD and attention-related disorders in 30-50% and intellectual disability in ~50% of individuals. TSC is one of the medical conditions most commonly associated with ASD. In adolescents and adults, very high rates of anxiety and mood-related disorders are reported. Psychotic disorders should raise the possibility of seizure-related psychopathology (Prather & de Vries, 2004; Kwiatkowski *et al.*, 2010).

Neuropsychological characteristics

Global intellectual abilities show a bimodal distribution in TSC. 30% of individuals with TSC have profound global intellectual disability (IQ equivalent <20) and do not show significant developmental gains over time. The remaining 70% fall on a normal distribution curve, shifted to the left. In clinical practice, more than 50% of individuals with TSC will have global intellectual abilities in the normal range. There are, however, high rates of specific neuropsychological deficits in those with normal global intellectual abilities. Specific deficits are most prominent in attentional, executive and visuo-spatial skills. These specific cognitive deficits may be associated with significant scholastic difficulties and impair functional abilities in daily life (Prather & de Vries, 2004; Kwiatkowski *et al.*, 2010; Tierney *et al.*, 2011).

**Available guidelines for behavioural assessment/
treatment/management**

- International consensus guidelines were drawn up for the assessment of cognitive and behavioural problems in TSC (de Vries *et al.*, 2005).
- There are currently no TSC-specific treatments available for the neuropsychiatric manifestations of TSC. Clinicians should therefore use evidence-based interventions as for the general population.
- Targeted treatments using mTOR inhibitors are currently in clinical trials for the neurocognitive and neurodevelopmental features of TSC (de Vries, 2010), but these should not be used outside formal trials.
- The diagnostic criteria and management guidelines for TSC were revised in 2012 and are expected to be published in 2013/2014.

Useful websites/associations for more information

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

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Petrus de Vries, August 2010

Revised 10/07/2013

Turner Syndrome

First description

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

Genetics and molecular biology

In humans, partial or complete loss of either of the sex chromosomes results in the condition. A phenotype arises because of haploinsufficiency for genes that are normally expressed from both X- chromosomes in females (or 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

XYY Syndrome

First description and alternative names

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

Genetics and molecular biology

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

Incidence/prevalence

The prevalence of 47,XYY is currently estimated at approximately 1/1000 males. As it is typically not associated with marked phenotypic characteristics it is frequently 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

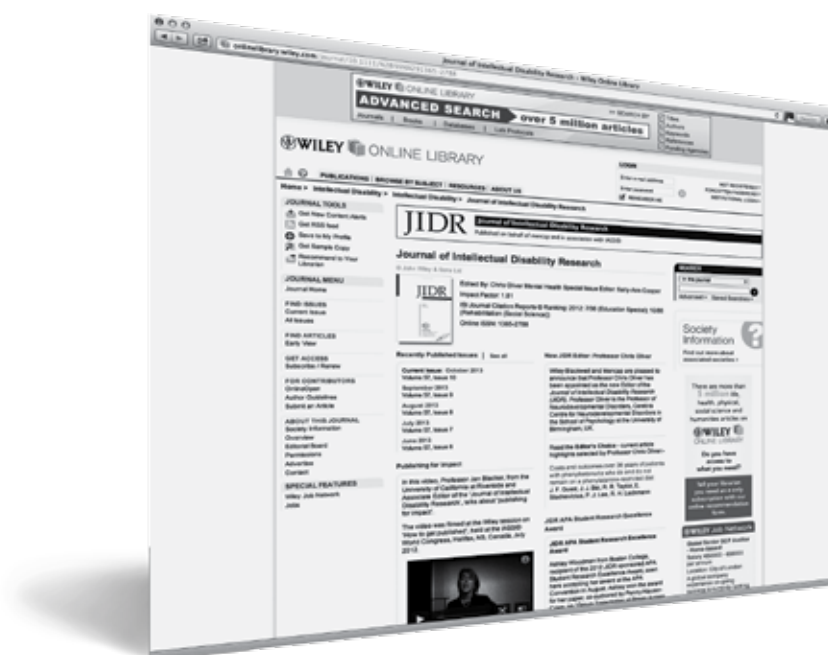
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Rhoshel K Lenroot, 2010

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Acknowledgements

We are extremely grateful to the wide range of people who contributed to this conference.

A few specific acknowledgements are warranted:

- **Liz Walmsley**, the SSBP Administrator, in her first year with the Society
- **Heather Windram**, the former SSBP Administrator, for her ongoing support
- **Rehana Effendi** and **Loren Leclezio** from UCT, for lots of behind-the-scenes organising and advice
- **Jo Venter** and the **STIAS conference team**
- **Our sponsors** PANDA-SA, Novartis, Janssen and Lilly
- **Deborah**, our graphic designer from Department of Shapes & Colours
- **Magda de Vries**, for arranging entertainment
- **Members of the Scientific Committee**, for review of abstracts and posters
- **All keynote speakers**, for their time and expertise
- **Chris Oliver** and the **JIDR team**
- **SSBP Trustees and Executive Committee**



The 17th SSBP International Research Symposium

Research Symposium 10–12 October 2014 • Educational Day 13 October 2014 • New York City, USA

Developmental Trajectories of Behavioural Phenotypes

The Society for the Study of Behavioural Phenotypes (SSBP) is pleased to announce that the 17th International Research Symposium and Educational Day will be held at New York University, Colleges of Dentistry and Nursing, New York City, USA.

This will be the third SSBP meeting in the USA. Previous meetings in the US were in Baltimore (1998) and Lake Tahoe (2007). The overarching theme will be on developmental trajectories in behavioural phenotypes produced by genetic disorders. Behavioural phenotypes to be highlighted include: Autism Spectrum Disorders, Williams Syndrome, deletion 22q (VCFS), and Wolf-Hirschhorn Syndrome.

Registration and abstract submission open: April 2014

Deadline for online abstract submission: 31 May 2014

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