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Welcome:

Dear Colleagues,

On behalf of the SSBP chair Dr Petrus de Vries and The Mater Medical Research Institute I would like to welcome you to the 14th Annual Research Symposium and Educational Day in Brisbane Australia.

The Queensland Rugby Club is the venue and is situated in the downtown area of the city with a view over the River and Brisbane's Iconic Story Bridge.

I would like to thank our sponsors:

Queensland Government: Department of Communities

Endeavour Foundation (Educational Day)

I hope you truly enjoy your stay in Queensland and please let us know if there is anything we can do to make your stay more pleasant.

Regards



Associate Professor Helen (Honey) Heussler

On behalf of

Local organizing committee:

Prof Greg O' Brien

Prof. Nicholas (Nick) Lennox

Assoc. Prof Brett McDermott

Prof. Frank Bowling

Prof. Stewart Einfeld

Sponsors



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Mater Medical Research Institute (MMRI) discovers ways to prevent and treat conditions affecting babies, children, adolescents and adults, helping them to lead healthy lives.

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- common diseases affecting children and adults
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- improving health outcomes for mothers and babies
- understanding development from babies through to adolescence and adulthood

<http://research.mater.org.au>



Endeavour Foundation

Endeavour Foundation is one of the largest non-government disability service provider in Australia. The foundation supports more than 3,350 people with a disability, from 230 locations in Queensland and New South Wales

www.endeavour.com.au



Queensland Government

Thanks also to Emma Laurence, Melissa Davis, Barb Makepeace, Jocelyn Sellwood

Scientific Committee

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The Venue – The Strand Rugby Quay.

The Queensland Rugby Club's brand new Brisbane event centre, The Strand at Rugby Quay, boasts an impressive architectural pedigree. The 485 square metre banquet and function venue forms part of Brisbane's Riverside Centre, which was designed by the renowned Harry Seidler, who is arguably Australia's most internationally recognised iconic architect.



For 57 years, Harry Seidler changed and influenced the shape of architecture in Australia - he is best known for buildings that changed the skyline of Sydney's CBD and included the MLC Centre, the controversial Blues Point Tower apartments overlooking Sydney Harbour and most significantly, Australia Square, at one time the tallest light weight concrete building in the world.

The Riverside Centre in Brisbane incorporated ground breaking innovations and an award-winning design which are the hallmark of a Seidler building, and these features have become even more relevant with the passing years. Sun protection awnings, double-glazed windows and in more recent times, efficient water and energy saving initiatives have also been introduced. The entire Rugby Quay development strictly maintains the core integrity of Harry Seidler's vision and the precinct's ongoing commitment to sustainability through its water and waste management strategies.

Plenary Speakers



Prof. John Mattick

"The hidden layer of RNA regulation underpinning human development and cognition"

Professor Mattick was responsible for the development of the IMB with Professor Peter Andrews. In 1988 he was appointed the Foundation Professor of Molecular Biology and Director of the Centre for Molecular Biology and Biotechnology at the University of Queensland.

The Centre was subsequently designated a Special Research Centre of the Australian Research Council (1991-1999) and was re-named the CMCB, with its primary focus being the molecular genetics of mammals and their diseases, including genome mapping, gene regulation, developmental biology and cell biology.

He was responsible for the development of one of the first recombinant DNA-based vaccines, and was the recipient of the 1989 Pharmacia-LKB Biotechnology Medal from the Australian Biochemical Society, and the inaugural (2000) Eppendorf Achievement Award from the Lorne Genome Conference. His current research interest is in the role of non-coding RNAs in the evolution and development of complex organisms. He has published over 100 scientific papers.

Professor Mattick is also, among other things, a member of the Australian Health Ethics Committee and the Research Committee of the NHMRC. He is a foundation member of the recently established International Molecular Biology Network (Asia-Pacific), was a foundation member of the Board of ANGIS (the Australian National Genome Information Service) from 1991-2000 and is currently a member of the Board of the Australian Proteome Analysis Facility. He is a member of the Queensland Biotechnology Advisory Council and on the Scientific Advisory Boards of several institutes nationally and internationally. He was appointed as an Officer in the Order of Australia in June 2001.



Prof. Mark Bellgrove

Cognitive Genetics of Attention and Attention Deficit

Professor Mark Bellgrove completed his undergraduate training at Monash University where he completed a BSc(Hons), majoring in Psychology. He then completed a PhD in Experimental Neuropsychology under the supervision of Professor John Bradshaw at Monash University, examining the perceptual, cognitive and motor deficits of schizophrenia. In 2002 he commenced a post-doctoral period at the Trinity College Institute of Neuroscience Dublin, where he commenced work linking susceptibility genes for ADHD to cognitive deficit phenotypes. In 2005 he returned to Australia and the University of Melbourne, funded by an NHMRC Howard Florey Centenary Fellowship. In 2007 he relocated to the University of Queensland with a joint appointment between the Queensland Brain Institute and the School of Psychology. In 2008 he was awarded a Young Investigator grant from NARSAD, USA and in 2009 was awarded a Career Development Award from the NHMRC and 3 NHMRC Project Grants. He is currently a UQ Principal Research Fellow at the University of Queensland.



Prof. Francis G BOWLING BSc, PhD, MBA, MBBS, FRCPA, FFSc, FHGSA

Molecules and the mind

Frank is the Director of Inherited Metabolic Diseases, Division of Paediatrics, Mater Children's Hospital, Brisbane Australia. He graduated from the University of Queensland, Australia. He trained in Chemical Pathology and Paediatrics at the Mater Children's Hospital Brisbane Australia and did a fellowship in Biochemical Genetics at the British Columbia Children's Hospital, Canada. He completed a PhD in experimental Medicine (Biochemical Genetics), investigating energy metabolism in cystic fibrosis. His major interest is in neurometabolic disorders, including brain energy metabolism and also the molecular basis of psychiatric disorders including autism and psychoses. Prof. Bowling's team has recently identified two sulphate metabolism genes which result in susceptibility to autism. He is an enthusiastic wilderness trekker and photographer, having traversed many remote areas of the world.



Prof Dr Thomy JL de Ravel

What role do CNV's play in neuropsychiatric disorders?

Professor Thomy de Ravel is a Clinical Geneticist at the Centre for Human Genetics at the University Hospitals of Leuven. His field of interest has been the clinical application of molecular karyotyping in individuals with intellectual disability, dysmorphism and other possibly related conditions.

Professor de Ravel received his M.D. from the University of the Witwatersrand in Johannesburg, South Africa, where he thereafter specialized in Paediatrics and then Clinical Genetics. After 10 years as coordinator of the Clinical Genetics Services and also Head of the Cytogenetics laboratory, he moved to Leuven, Belgium. Here he read for his PhD, this relating to the development of molecular karyotyping and interpretation of findings. He is presently Clinical Geneticist and also Clinical Head of the Cytogenetics/ molecular karyotyping facilities at the Centre. His interest lies in the field of interpretation of the influence of a CNV in the expression of disorders, and also clinical genetics in general.



Prof. Anthony John Holland

The Evolving nature of Research into Intellectual Disabilities: Priorities and Possibilities

Tony Holland trained in Medicine at University College and University College Hospital, London, qualifying in 1973. After some years in General Medicine he then trained in Psychiatry at the Maudsley Hospital and Institute of Psychiatry in London. After his psychiatric training, he held a MRC Research Fellowship in Psychiatric Genetics, undertaking a study of the relationship between Down's syndrome and Alzheimer's disease. He held a senior academic post at the

Institute of Psychiatry from 1987 until 1992 and also was Consultant Psychiatrist with the Mental Impairment, Evaluation and Treatment Service at the Bethlam Royal and Maudsley Hospitals. From 1992 to 2002 he held a University Lecturer's post in the Section of Developmental Psychiatry in the University of Cambridge, and in 2002 was awarded the Health Foundation Chair in Learning Disability in the Department of Psychiatry in the University of Cambridge.

Since 2002 he has led the Cambridge Intellectual and Developmental Disabilities Research Group (www.CIDDRG.org.uk) in the Department of Psychiatry at the University of Cambridge. This is a multidisciplinary group that undertakes a broad range of research relevant to people with intellectual disabilities. His specific interests include the eating, behavioural and mental health problems associated with having Prader Willi Syndrome; the relationship between Down's syndrome and Alzheimer's disease, and also clinical/legal issues relevant to the needs of people with intellectual disabilities. In 2010 he was elected a Fellow of the Academy of Medical Sciences. His clinical work is with the Cambridge Learning Disability Partnership and Cambridge and Peterborough Foundation NHS Trust.

Education Day



Dr Petrus de Vries MBChB, MRCPsych, PhD

Consultant in Developmental Neuropsychiatry, Cambridgeshire & Peterborough NHS Foundation Trust, Cambridge, UK

Dr de Vries is a Child and Adolescent Psychiatrist and is the clinical lead for a multi-agency, multi-disciplinary service for school-aged children with neurodevelopmental disorders. He has a particular 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. He has a particular interest in the molecular mechanisms underlying neurocognitive and neurodevelopmental deficits associated with the TSC1/2-mTOR signalling pathway.

Dr de Vries is a Medical Advisor to the Tuberous Sclerosis Association (UK), a member of the Professional Advisory Board and International Scientific Advisory Panel of the Tuberous Sclerosis Alliance (USA) and a Specialist Advisor to TSDeutschland.

He has been a member of the SSBP since 1998. In 2003 he was elected to the executive committee, in 2007 as Treasurer and in 2008 as Chairman of the society.



Dr Hagerman, Randi J., M.D.,

Medical Director, UC Davis M.I.N.D. Institute; Endowed Chair in Fragile X Research; Professor, Department of Pediatrics, School of Medicine

Dr. Randi Hagerman is a developmental and behavioral pediatrician and the Medical Director of the M.I.N.D. Institute at UC Davis. She is internationally recognized as both a clinician and researcher in the fragile X field. Dr. Hagerman received her M.D. from Stanford University where she also carried out her Pediatric residency. She completed a Fellowship in Learning and 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 M.I.N.D. Institute. Dr. Hagerman and her team discovered the Fragile X-associated Tremor/Ataxia Syndrome (FXTAS) which is a neurological disorder that affects older male and rare female carriers of fragile X. Dr. Hagerman's research involves genotype-phenotype correlations in fragile X and she carries out this research in collaboration with her husband, Paul Hagerman, M.D., Ph.D. Professor Randi Hagerman has written over 200 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. Dr. Hagerman has received numerous awards for her research in fragile X syndrome including the Jerrett Cole Award from the National Fragile X Foundation for unselfish dedication to work with fragile X children and adults, the Bonfils-Stanton Foundation Award for Science

including Medicine, the IASSID Distinguished Achievement Award for Scientific Literature, the 2005 Distinguished Scholarly Public Service Award from UC Davis, and the 2006 Dean's Award for Outstanding Mentoring at UC Davis. In 2004, to honor both Randi and Paul Hagerman in recognition of their work in FXTAS, the National Fragile X Foundation established the Hagerman Award. This award recognizes research accomplishments in the field of FXTAS and is given at the bi-annual International Conference on Fragile X. In 2008, the National Fragile X Foundation again honored Dr. Hagerman with a Lifetime Achievement Award. Dr. Hagerman has worked internationally to establish fragile X clinical programs and research programs throughout the world.

Prof. Pat Howlin

Patricia Howlin is Professor of Clinical Child Psychology at the Institute of Psychiatry, London.

This is the first Chair in Clinical Child Psychology in the UK. She is a chartered clinical psychologist with a Ph.D. in Psychology and a Fellow of the British Psychological Society. Her principal research interests focus on autism and other developmental disorders. She has conducted evaluations of a variety of different intervention programmes, including comparative studies of home and school based treatments; control trials of communication training programmes, and longer term studies of the impact of early interventions. She has also been involved in research on the transition to adulthood by people with autism and individuals with Williams syndrome, developmental language disorders and Fragile X.



Assoc Prof. Brett McDermott

Director Mater Child and Youth, Mental Health Service. Associate Professor Child and Adolescent Psychiatry, University of Queensland.

He is Service Director and a leader of Mater Centre for Service Research in Mental Health he graduated from the University of Tasmania and trained in Sydney and the UK before commencing Clinical practice in Western Australia where he is Professor of Child and Adolescent Psychiatry. He is currently a By-Fellow of Churchill College Cambridge and associate professor at University of Queensland. His research interest include, service delivery of mental health, Trauma, Eating disorders as well as 22q11del syndrome. He is also the chair of the beyond blue NHMRC Youth Depression Clinical practice guideline committee.



Prof Gregory O'Brien

Prof Gregory O'Brien graduated MB Chb from Aberdeen University, M.A from Cambridge University and M.D. from Aberdeen University.

He holds FRCPsych, FRCPC and FRANZCP, and is recognised by the G.M.C. as a certified Specialist in Learning Disability, in Child and Adolescent Psychiatry and also in Forensic Psychiatry. He served as Consultant to UNICEF and to the E.U. Year of Action of Disability. He held office as Associate Dean of the RCPsych, President of Penrose Society, Chair of the MacKeith Meetings Committee, Chair of the Faculty of Learning Disability of the RCPsych, Scientific Director of the Castang Foundation and Associate

Medical Director of NTW NHS FoundationTrust. After a 30 year career in Psychiatry in the UK, he is now Senior Psychiatrist with the Mental Health Assessment and Outreach Team of Disability Services Queensland, and Adjunct Professor of the University of New England. He is Emeritus Professor of Developmental Psychiatry at Northumbria University.

Lifelong research programme explores the cause, natural history and treatment outcomes of behaviour problems among people with intellectual disability. He is especially interested in the long term implications of innate factors, such as the cause and the severity of intellectual disability. This interest has led to his involvement in the development of multimodal research methodologies and instruments and to measure behaviour in this population. This in turn both informs and is informed by his clinical practise, which aims to ameliorate behaviour and optimise social functioning and inclusion among people with intellectual disability. He is author/editor of some 110 publications, including 8 books, towards 30 book chapters and over 80 peer-reviewed academic articles.

Program

Wednesday 5th October 2011

08:00-08:30 Registration

08:30 Welcome Address

Welcome to Country

08:45 Plenary
Prof John Mattick-
The hidden layer of RNA regulation underpinning human development and cognition

09:45 Free Papers:

L Evers: Dopaminergic markers in 22q11 deletion syndrome with moderate to severe Learning disability

Prof. J Harris: Oxytocin and disorders of social engagement

10:25 -10:55 Morning tea

10:55 Plenary
Prof Mark Bellgrove:
Cognitive Genetics of Attention and Attention Deficit

11:55 Free Papers:

Prof. L Nespoli: Quantitative and functional evaluation of circulating T regulatory cells in Down syndrome subjects

Dr L Gilmore: Are motivational Deficits part of the Behavioural phenotype of Down syndrome?

12:35-13:35 Lunch & Poster viewing

13:35-14:35 Free Papers:

Dr F Tassone: AGG Interruptions: risks of expansion to full Mutation

Prof. K Cornish: Carriers of the FMR1 gene- Does size matter?

Dr EJ Evans: Mowat Wilson Syndrome

14:45-15:15 Afternoon tea

15:15-16:55 Free Papers:

Ms L Bull: Temper outbursts in Prader Willi syndrome: Early intervention and Environmental management

Dr D Hocking: Understanding syndrome specific Neuromotor profiles in genetic developmental disorders (Williams)

Dr H Wong/Dr P de Vries: Individuals with TSC1 and TSC2 Mutations show distinct patterns of Intellectual Abilities

Ms L Wilde: Inhibition and Impulsivity in Children with Smith Magenis Syndrome

**18:30-20:30 Cocktail Party
Opening "Celebrating Diversity"
Photographic exhibition**

Thursday 6th October 2011

08:30 Plenary

Prof. Frank Bowling: Molecules and the mind

09:30 Free papers

Dr R Delamont : The modification of apneustic breathing in Rett syndrome with a 5-HT1_A agonist

T Winari: Sertraline improves language developmental trajectory in young children with Fragile X syndrome

10:10 Morning tea

10:30 Plenary

Prof. Thomy de Ravel: What role do CNV's play in neuropsychiatric disorders?

11:10 Free papers

L Gray : The trajectory of Psychopathology in Adults with Autism

Dr L Campbell: How coping skills affect symptoms of Anxiety and Depression in young adults with VCFS

Dr C Smango-Sprouse: Confounding factors affecting Motor Development in Boys with XXY

12:10 Annual General Meeting

13:10 Lunch

Free Papers

14:10 Prof. B Tonge: Testing the extreme male brain theory

Prof. C Oliver: Food related problems in Children with Angelman, Prader willi , 1p36 deletion, Cornelia de Lange and Fragile X syndromes

Prof. A Von Gontard: Elimination Disorders in persons with Prader Willi and Fragile X syndrome

Ms K Eden: Challenging Behaviour in Tuberous Sclerosis Complex

BT Williams, Dr K Gray: Teaching Emotion Recognition Skills to young children with Autism: Evaluation of an Emotion recognition program

- 15:50** **Afternoon tea**
- 16:10** **Conf 2012 Prof. Thomy Ravel**
- 16:20-17:20** **Plenary**
- Prof Tony Holland- The Evolving nature of Research into Intellectual Disabilities:
Priorities and Possibilities.
- Closing remarks**
- 19:00** Conference Dinner -Alchemy Restaurant.

Friday 7th October

Education Day Program:

Dr Randi Hageman: Fragile X: Evolution of new Therapies

Dr Petrus de Vries: New developments in the Neuropsychiatry of Tuberous Sclerosis Complex

Morning tea

Prof. Pat Howlin: Transitions to Adult Care:

Helen Leonard: The Australian Rett syndrome study

Lunch

Assoc. Prof. Brett McDermott: Psychoses and Intellectual Disability

Prof. Gregory O' Brien: Targeted Prescribing for Behavioural and Mental Health problems in Intellectual Disability

Afternoon tea

Social Program:

Tuesday 4th October

**Trip to Lone Pine Koala Sanctuary- Contact Greg O'Brien/
Honey Heussler**

Informal gathering for those that are interested



Wednesday 5th October

Cocktail Party and Opening “Celebrating Diversity”

Artists Talk Rick Guidotti

630pm- 8 pm Brisbane Powerhouse

City Cat from Riverside to New Farm Park – about a 10
minute walk

There is also a bar and 2 restaurants for dinner and snacks
afterwards

119 Lamington St., NEW FARM

www.brisbanepowerhouse.org



Brisbane Powerhouse is both a producer of contemporary performing arts and a multi-arts, dining and conference venue. Nestled on the beautiful banks of Brisbane River (beside New Farm Park) the former power station has become a distinct landmark, both as a stunning industrial creation and as a hub for everything creative, including theatre, music, comedy, film, visual arts, festivals and ideas.



Thursday 6th October

**Conference Dinner Alchemy Restaurant 175 Eagle Street Brisbane (next to the
conference venue on the river) overlooking the Story Bridge.**



Plenaries

The hidden layer of RNA regulation underpinning human development and cognition

Prof. John S. Mattick *Institute for Molecular Bioscience, University of Queensland, Brisbane 4072 Australia*

It appears that the genetic programming of humans and other complex organisms has been misunderstood for the past 50 years, because of the belief that most genetic information is transacted by proteins, leading to the derived assumption that most intronic and intergenic sequences, and the retrotransposed sequences within them, are non-functional debris. Surprisingly, however, the human genome contains only about 20,000 protein-coding genes, similar in number and with largely orthologous functions as those in nematodes that have only 1,000 cells. On the other hand, the extent of non-protein-coding DNA increases with increasing complexity, reaching 98.8% in humans. The majority of these sequences are dynamically transcribed to produce enormous numbers of long non-protein-coding RNAs (ncRNAs) that show dynamic tissue- and cell-specific expression patterns and subcellular location, especially in the brain. There are also enormous numbers of small regulatory RNAs, including microRNAs that regulate almost every aspect of development, as well new classes of small RNAs derived from transcription initiation sites and splice sites that appear to be related to the positioning of nucleosomes in chromatin. The emerging evidence indicates that these RNAs form a massive hidden network of regulatory information to control gene expression at various levels, including the site-specificity of the chromatin-modifying complexes that underpin developmental trajectories, and that these regulatory RNAs are dysregulated in cancer and other complex diseases. It is also becoming evident that animals, particularly primates, have superimposed plasticity on these RNA regulatory systems via RNA editing, and that this is the molecular basis of the environment-epigenome interactions that underpin brain function. Retrotransposons also appear to contribute to genomic, epigenomic and transcriptomic plasticity and somatic mosaicism, especially in the brain. Thus, it appears that most assumptions about the nature and structure of regulatory information in eukaryotic genomes have been incorrect, and that what was dismissed as 'junk' because it was not understood holds the key to understanding human evolution, development, diversity and intelligence.

References:

1. Mattick, J.S. (2001) Non-coding RNAs: the architects of eukaryotic complexity. *EMBO Reports* **2**: 986-991.
2. Mattick, J.S. (2004) RNA regulation: a new genetics? *Nat Rev Genet* **5**: 316-323.
3. Mattick, J.S. (2007) A new paradigm for developmental biology. *J Exp Biol* **210**: 1526-1547.
4. Mattick, J.S. and Mehler, M.F. (2008) RNA editing, DNA recoding and the evolution of human cognition. *Trends Neurosci* **31**: 227-233.
5. Mattick, J.S. (2009) The genetic signatures of noncoding RNAs. *PLoS Genet* **5**: e1000459.
6. Mattick, J.S., Amaral, P.P., Dinger, M.E., Mercer, T.R. and Mehler, M.F. (2009) RNA regulation of epigenetic processes. *Bioessays* **31**: 51-59.
7. Mattick, J.S. (2011) The central role of RNA in human development and cognition. *FEBS Letters* **585**: 1600-1616.

Cognitive Genetics of Attention and Attention Deficit

Prof. Mark A. Bellgrove, PhD. UQ Principal Research Fellow, Queensland Brain Institute and School of Psychology, University of Queensland.

Problems of attention are highly heritable whether they are defined categorically or dimensionally. Although some progress has been made in identifying “risk” genes for conditions such as attention deficit hyperactivity disorder (ADHD), we lack an understanding of the functional impact of these genes for brain and cognition. In this talk I will review work that has attempted to forge links between DNA variation in catecholamine system genes and objective measures of attention from cognitive science. In particular, I will review evidence that a haplotype of the dopamine transporter gene (DAT1) that confers risk to ADHD is associated with abnormalities in directed spatial attention in both ADHD and non-clinical populations.

Thursday 6th October 2011

From Molecules to the Mind

Prof. Francis Bowling Mater Children’s Hospital, Brisbane, Australia. Mater Medical Research Institute

Abstract: Advances in our knowledge about molecular mechanisms associated with specific cognitive and emotional behavioral processes have improved our understanding of psychopathology. The goal is the development of more effective therapeutic methods and the prevention of disease. In psychiatric disease states, the role of genetic variation represents a cornerstone that can either directly, or in concert with environmental factors, facilitate disease onset. The identification of genetic variations associated with disease development can be used to identify at-risk individuals and the biological pathways contributing to disease. However, there is a paradox in the growth of scientific knowledge. As information accumulates in ever more intimidating quantities, disconnected facts and impenetrable mysteries give way to rational explanations and simplicity emerges from chaos. A critic might also say that any such logic must defy composition. The facts are too many and too diverse, the diseases too varied, the homeostasis too complex to be embraced in a set of principles. In 1908, Garrod using an expanded definition of the inborn error of metabolism showed us that all diseases arise out of some condition of incongruence between a chemical constitution and the factors of the environment. Metabolic disorders give us an approach to understanding the molecular basis of many diseases. Biochemical pathways are functional modules that depend on both genotype and the environment to produce a disease phenotype. Disruption of module at any point produces a similar phenotype. Diseases with similar phenotypes will have common modules.

What role do CNV’s play in neuropsychiatric disorders?

Prof. Thomy JL de Ravel, Centre for Human Genetics, University Hospitals Leuven, Belgium

The advent of molecular karyotyping/ array comparative genomic hybridization (CGH) ten years ago has led to the detection of numerous copy number variations (CNV’s) within the DNA of all individuals. The understanding of the origin and role of these CNV’s within the population has revealed that the human genome is far more complex than could ever be imagined. The interpretation of the influence of a CNV in the expression of a disorder is slowly falling into place as the prevalence of each particular CNV in both affected and control populations is being determined through multiple 1000’s of analyses, most of which are entered into large public databases. The last 10 years has also seen more than a 200% increase in the clinical diagnosis of autism spectrum disorders (ASD). The role of inheritable factors in this and many

other neuropsychiatric disorders has long been known from not only twin and family studies but also from macroscopically visible numerical and structural chromosome aberrations, eg trisomy 21, Prader Willi syndrome, and the velocardiofacial syndrome (22q11.2 deletion syndrome). CNV's and point mutations involving genes such as *SHANK3* on chromosome 22q13.3 substantially increase the probability of the carrier individual having an autism spectrum disorder. Recurrent CNV's involving chromosomes 15q11.2q13, 16p11.2, 16p13.11 and 17q12, amongst others, are also more frequently associated with ASD. Next generation sequencing technology, assisted by array CGH and the more traditional FISH technique, is further unravelling the complexity of the human genome, and in so doing, the understanding of susceptibility factors in leading to expression of disorders and also therapeutic responses.

The increasing availability of high technology genetic analysis raises ethical and societal questions regarding the desirability of worldwide screening, management of the personalized data, and issues relating to access hereof.

THE EVOLVING NATURE OF RESEARCH INTO INTELLECTUAL DISABILITIES: PRIORITIES AND POSSIBILITIES

Prof. Holland A.J.

Cambridge Intellectual and Developmental Disabilities Research Group, Academic Department of Psychiatry, University of Cambridge, 18b Trumpington Road, Cambridge, CB2 8AH, UK.

Background: The 20th Century saw significant positive changes in the attitudes towards people with intellectual disabilities and the way in which they were supported. For many high resource and democratic countries the focus was very much towards an inclusive social model, challenging the prejudices and pre-conceptions of the past. At the same time rapid advances in genetics and neuroscience, made possible by developments in technologies, were opening up new research possibilities.

Methods: As part of a Foresight project on *mental capital and wellbeing* initiated by the UK Government priority areas of research specific to ID were identified. The focus of the review was on the likely need for research and also on technological advances that might enable questions to be addressed that previously may not have been possible to answer. In this overview specific priority areas identified in the Foresight review are selected because of their relevance to behavioural phenotype research. Results In the above report three broad themes for future research in ID were identified including a) human rights, citizenship and access to justice; b) developmental processes, resilience, and the prevention, management and treatment of associated behaviour problems and psychiatric disorders; and c) changing demographics and delivery of health care in community settings. Of particular relevance to theme *b*, advances in understanding epigenetic processes and in the neurosciences, either individually or in combination, offer the possibility of significant new insights.

Conclusions: The study of *behavioural phenotypes in organic genetic disease* are at a pivotal stage moving from the characterization of the behavioural phenotype associated with a given syndrome to be able to investigate the underlying brain mechanisms. Such an approach should in turn enable novel treatments to be developed focusing on the prevention or treatment of the behavioural and psychiatric problems associated predominately with one syndrome or another.

Research Symposium Abstracts

DOPAMINERGIC MARKERS IN 22Q11 DELETION SYNDROME WITH MODERATE TO SEVERE LEARNING DISABILITY

Evers L.J.M.^{1, 2}, Amelsvoort Van T.A.M.J.³, Bakker J.A.², Abeling N.G.G.M.⁴, Bierau J.² and Curfs L.M.G.²

¹Koraalgroup, MFCG, Heel, The Netherlands. ²Department of Clinical Genetics, Maastricht University Medical Centre, Maastricht, The Netherlands. ³Department of Psychiatry, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands. ⁴Department of Genetic Metabolic Disorders, Academic Medical Centre, Amsterdam, The Netherlands.

Background: 22q11 deletion syndrome (22q11DS) is a genetic syndrome caused by a microdeletion on chromosome 22q11.2. Patients with 22q11DS are haploinsufficient for COMT, a gene coding for an enzyme involved in dopaminergic neurotransmission. Disrupted dopaminergic neurotransmission was previously reported in high functioning 22q11DS adult patients. To date no one has studied patients with 22q11DS who suffer from chronic psychotic symptoms and severe cognitive deterioration (DET) or 22q11DS patients with a pre-existing low IQ (PRE). Therefore we determined dopaminergic markers in adult DET and PRE 22q11 patients. **Methods:** Blood and urine samples were collected from 16 DET patients and 12 PRE patients, 12 high functioning 22q11DS patients and 12 control subjects (CONT) to determine concentrations of dopamine and its metabolites. **Results:** ANOVA analysis show significant differences for dopamine between PRE vs VCFS ($p = 0,03$) and PRE vs VCFS ($p < 0,01$), for VMA between DET vs CONT ($p < 0,01$) Det vs VCFS $p < 0,01$), for HVA for PRE vs CONT ($p = 0,02$) PRE vs VCFS ($p = 0,01$) DET vs CONT ($p < 0,01$) and DET vs VCFS ($p < 0,01$). Dopaminergic markers in PRE and DET were in all cases lower than in VCFS and CONT **Conclusion:** Different dopaminergic outcomes for the different subgroups were registered with lower dopaminergic outcomes in groups with low IQ's. Further characterisation of these subgroups is important and we will discuss the implications of these findings.

OXYTOCIN AND DISORDERS OF SOCIAL ENGAGEMENT

Harris J.C. The Johns Hopkins University School of Medicine.

Background: Oxytocin is a neuropeptide involved in social bonding, social cognition, processing of social signals (e.g., eye contact), social memory and resilience to stress. Polymorphisms of the oxytocin receptor (OXTR) have been associated with both autism and depression. There are ongoing treatment trials with intranasal oxytocin in persons with diagnoses of autism spectrum disorder. **Methods:** Critical review and synopsis of published literature on the role of oxytocin in social behavior, genetic and epigenetic findings in ASD, and treatment studies with intranasal oxytocin administration. **Results:** Four candidate genes studies in children from diverse ethnic groups demonstrate that SNPs and haplotypes in the OXTR gene confer risk for the diagnosis of an ASD and social communicative deficits. Exogenous oxytocin treatment in patients with autism may be associated with reduction of repetitive behaviors and increased retention of social cognitive skills. **Conclusion:** The role of oxytocin in social behavior is well established and candidate genes studies are promising in disorders of social engagement. Examination of the role of oxytocin in neurogenetic disorders with behavioral phenotypes is called for and a promising area for study.

QUANTITATIVE AND FUNCTIONAL EVALUATION OF CIRCULATING T REGULATORY CELLS IN DOWN SYNDROME SUBJECTS

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Background: Higher rates of autoimmune disorders (AD) are characteristics of Down syndrome persons (DS). Treg cells contribute to the immune surveillance which prevents AD. To establish a possible correlation between Tregs and AD in DS we studied their phenotypes and their functions in DS.

Methods: In a group of 29 DS patients (15 M, mean age 11.4 yrs, range: 1.4-22.8) and 29 age and sex matched healthy controls we numbered the circulating Treg (CD4+CD25^{high}CD127^{low}) by flow cytometric analysis. In vitro cell proliferation assays were set up in which DS Treg were co-cultured with CD4+CD25⁻ T-cells and stimulated by a pan-T stimulus (anti-CD2, anti-CD3, anti-CD28 coated beads) for 4 days at 37 °C in RPMI culture medium. **Results:** The CD4+CD25^{high} cells in DS and control group were 2,7% and 1,2%, respectively (P=.0007) with a percentage of FOXP3 expressing cells of 79,2% and 59,7%, respectively (P=.0015). While the proliferative capacity of DS T cells was not significantly altered, a reduced inhibitory activity of DS Treg was clearly observed. **Conclusion:** An increased number of circulating Treg are present in our DS population, but they express a reduced suppressive activity in in vitro assays. This observation is in accordance with the observed higher incidence of AD in these persons.

ARE MOTIVATIONAL DEFICITS PART OF THE BEHAVIOURAL PHENOTYPE OF DOWN SYNDROME?

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Background. Motivational deficits are generally accepted to be part of the behavioural phenotype associated with Down syndrome (DS). A motivational profile comprising low or inconsistent levels of task persistence, avoidance of challenging activities and over-dependence on adult direction has been described. However, comparisons are usually made between children with DS and those who are developing typically, without the inclusion of samples with intellectual disability (ID) from etiologies other than DS. Such comparisons are needed to determine the extent to which motivational deficits are specific to DS, as opposed to being a feature of ID generally. **Method.** The current study collected data about the personality-motivation profiles of children in three groups matched for mental age. They consisted of 80 typically developing (TD) 3-7 year old children, 62 children with DS aged 7-15 years, and 54 children with moderate ID aged 7-15 years. Parents completed the 37-item EZ-Personality Questionnaire (EZPQ; Zigler et al., 2002), a measure of personality-motivational functioning. **Results.** There were significant differences between TD children and those with ID on all EZPQ scales. In most respects children with DS did not differ significantly from others with moderate ID, although they were rated as having greater expectancy of success and fewer negative reactions. **Conclusions.** The finding that children with DS are less motivated than TD children of the same mental age is consistent with previous studies in which parents have rated motivation. It seems, however, that motivation difficulties are associated with ID more generally, rather than being specific to those with DS. The study raises questions about phenotypic versus experiential effects on motivation for children with ID.

DEVELOPMENTAL TRAJECTORIES OF VISUAL ATTENTION IN YOUNG CHILDREN WITH FRAGILE X SYNDROME: DEVELOPMENTAL DELAY OR DEVELOPMENTAL FREEZE?

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Background: Neurodevelopmental disorders with a clear genetic aetiology provide important glimpses into the complex world of gene-behavior associations. Fragile X syndrome (FXS) is a monogenic disorder diagnosed early in childhood and associated with a well-documented pattern of cognitive and attentional difficulties, as well as with a high risk of poor outcomes across multiple behavioural dimensions. However, striking variability in outcomes is evident even in young boys with the condition. Based within a three-year prospective longitudinal design, our core aim was to explore how basic attention processing develops in FXS boys from as young as four years old and trace its impact on the wider behavioural landscape. Specifically whether, and if so, how, attentional processes impact on variable outcomes across boys with FXS. **Method:** In the largest such study, 52 medication naive boys with FXS aged between 4 and 10, and 40 typically developing control boys of equivalent non-verbal ability were assessed three times over 24 months. Using novel paradigms of visual and auditory attention alongside standardised measures of IQ and behaviour we assessed participants across three time points spanning 24 months.. **Results:** While non-verbal IQ seemed to decline, there were significant improvements in non-verbal growth scores and in markers of cognitive attention across the visual and auditory modality. In contrast, behavioural difficulties such as autistic symptomatology, hyperactivity and inattention remained stable over this time-frame. **Findings:** Teasing apart predictors of individual differences in outcomes within our cohort, preliminary analyses suggest that cognitive attentional markers in both the visual and auditory modality predicted classroom behaviour, whereas auditory markers alone predicted autistic symptomatology.

AGG INTERRUPTIONS: RISKS OF EXPANSION TO A FULL MUTATION

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Background: Fragile X syndrome normally arises from expansions of a (CGG)(n) trinucleotide repeat (>200 CGG) in the *FMR1* promoter. Many *FMR1* alleles contain AGG sequences interspersed among the CGG repeats. These AGG "interruptions" are thought to confer DNA stability and reduce the risk of expansion. It has been theorized that pure CGG repeat length is the underlying factor. The smallest premutation alleles documented to expand to full mutations have lacked AGG interruptions. **Methods:** We used a novel CGG Repeat Primed PCR-based approach to identify AGG interruptions in 269 mothers of children with an expanded allele (>44 CGG). We looked for association between presence of AGG interruptions and *FMR1* transcription levels, measured by qRT-PCR, within the mothers. **Results:** Modeling the probability of transmission, we found the optimal cutoff for total CGG length as a predictor of transmission status to be 70 while the pure stretch was determined to be 65. The risk for expansion increased as a function of 3'-continuous CGG repeat length. No association between presence of AGG interruptions and transcriptional levels was observed. **Conclusion:** We have used a novel approach to assess the AGG structure in 269 premutation women, representing 373 transmissions. Our findings point to a relevant role of AGG interruptions in the stability of the CGG repeats in mothers. The risk of expansion in equally sized alleles is determined by pure CGG stretch. Knowledge of the AGG structure in

intermediate and premutation alleles is of great importance in determining risk stratification for women and improving genetic counseling.

CARRIERS OF THE *FMR1* GENE: DOES SIZE MATTER?

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Background: Recent findings suggest that males with the fragile X premutation show a cognitive signature of inhibitory and working memory decline that progressively deteriorates with increasing age. Fragile X premutation males have moderate expansions of the trinucleotide CGG repeat region of the *FMR1* gene that may have neurotoxic effects in specific neural regions. Some carriers of the fragile X premutation are at-risk for a late-onset neurodegenerative disorder, fragile X-associated tremor/ataxia syndrome (FXTAS). To further characterise the cognitive signature in premutation carriers prior to the onset of FXTAS, we determined whether males with the fragile X premutation show a higher CGG repeat threshold within which a subgroup may be especially vulnerable to selective cognitive impairments.

Methods: Forty males with the fragile X premutation aged 18-69 years underwent neuropsychological tests of inhibition and working memory. Multiple regression analyses were conducted to examine the moderating role of CGG repeat length on the relation between age and performance on inhibition and working memory tasks. **Results:** These results demonstrate that an age-related decline in inhibitory control and working memory may only become discernible in an at-risk subgroup with expansions in the range of 100 CGG repeats and above. Males in the lower premutation range between 55 and 100 CGG repeats were relatively risk-free from any cognitive aging effects associated with CGG repeat expansions.

Conclusion: We conclude that specific executive markers may incur variable degrees of risk for the later onset of FXTAS and that selective brain networks may be especially vulnerable to the neurotoxic effects of *FMR1* gene expansions.

Temper outbursts in Prader-Willi syndrome: Early intervention and environmental management.

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Background : Temper outbursts in Prader-Willi syndrome (PWS) can be triggered by change to routine/expectation. We addressed two issues relevant to reducing this behaviour. 1) Is the length of time a person is exposed to a routine related to the resulting behavioural reaction when routine is changed? 2) Can an environmental cueing technique reduce temper outbursts?

Methods: 1) Twelve individuals with PWS played four novel games that allowed routines to be established. Routines were established for different lengths of time for each game, before unexpected changes were imposed. 2) Five individuals with PWS and their parents/carers were taught to use a novel cue to reliably signal when a change to routine or expectation would occur.

Results: 1) Significantly more temper outburst behaviour was shown when changes were imposed to games that participants had been exposed to for 40-80 minutes, compared to 10-20 minutes. 2) Participants were able to learn to associate the presentation of an arbitrary novel cue with the subsequent

occurrence of a change to routine or expectation. Early data suggest that use of the cue can be successful in reducing temper outburst behaviour.

Conclusions: 1) Early intervention focused around introducing deliberate changes and reducing the rigidity of routines from an early age may be effective in reducing subsequent difficulties with temper outbursts; 2) Using a novel cue to reliably signal change in a person's routine or expectation may be effective in reducing temper outbursts triggered by change to routine/expectation in individuals with PWS.

UNDERSTANDING SYNDROME-SPECIFIC NEUROMOTOR PROFILES IN GENETIC DEVELOPMENTAL DISORDERS

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Background: Despite early reports of delayed motor development in Williams syndrome (WS), a rare genetically based developmental disorder, there has not yet been any systematic investigation of the neuromotor signature as an indication of brain-cognitive associative patterns. The core aim of this study was to employ experimentally-driven neuromotor measures in adults with WS to determine whether the neuromotor profile resembles other movement disorders with known involvement of specific neural regions. **Methods:** Ten adults with WS were compared to age- and IQ-matched individuals with Down syndrome (DS) and typically developing controls. The spatiotemporal characteristics of gait and foot placement variability were measured using the GAITRite walkway while participants crossed a small ground based obstacle in the travel path. **Results:** The results showed that adults with WS adopted a more conservative obstacle crossing strategy, with late adjustments to spatiotemporal gait characteristics alongside specific deficits in adaptation to the spatial constraints of the obstacle. In contrast, the adults with DS showed longer step duration and more variable gait during the crossing and recovery steps after the obstacle. Although the controls were able to reduce the variability of foot placement across the obstacle crossing trials, both the WS and DS groups did not become more consistent with practice. **Conclusion:** We conclude that locomotor planning during tasks requiring visuomotor transformations may be especially compromised in affected individuals with WS. These findings are discussed in terms of the importance of a cross-syndrome perspective in the investigation of neuromotor profiles in genetic developmental disorders.

MOWAT-WILSON SYNDROME

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Background: Mowat-Wilson syndrome (MWS) is caused by a mutation or deletion of the *ZEB2* gene. It is associated with a characteristic facial appearance, intellectual disability, and variable medical features which include seizures, microcephaly, and Hirschsprung disease. This study investigated the behavioural

phenotype of MWS. **Methods:** Participants were 71 individuals with MWS and their parents or carers. Parents and carers completed questionnaires, including the Developmental Behaviour Checklist (DBC), and DBC data were compared with those for individuals selected from an epidemiological sample of people with intellectual disability from other causes. In addition, for a subset of participants, parent and carer interviews and direct assessments were conducted. Unstructured data from observations of behaviours and from carer reports was also collated. **Results:** The behaviours associated with MWS included a high rate of oral behaviours, an increased prevalence of repetitive behaviours, and an under-reaction to pain. Other aspects of the MWS behavioural phenotype are suggestive of a happy affect and sociable demeanor. Despite this, those with MWS displayed similar levels of behavioural problems as those with intellectual disabilities from other causes, with over 30% showing clinically significant levels of behavioural or emotional disturbance. **Conclusion:** These results may inform management options to enhance the independence and quality of life for people with MWS.

INDIVIDUALS WITH TSC1 AND TSC2 MUTATIONS SHOW DISTINCT PATTERNS OF INTELLECTUAL ABILITIES

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Background: Tuberous Sclerosis Complex (TSC) is a multi-system genetic disorder associated with mutations in either *TSC1* or *TSC2*. In contrast to the normal IQ distribution in the general population (Mean = 100, Standard deviation (SD) = 15), 30% of individuals with TSC are profoundly impaired ('P phenotype', IQ<20) while the remaining 70% are normally distributed, with the mean IQ shifted downward ('ND phenotype'). Genotype-phenotype studies to date have concluded that *TSC2* is 'more severe' than *TSC1*. However, only two studies have utilized standardized measures of intelligence; both had significant limitations. The first study was very 'categorical', simply comparing impaired vs non-impaired IQ in *TSC1* vs *TSC2* mutations; the second used a range of neuropsychological measures but collapsed them into a composite score of unknown neurocognitive significance. Here we examined the psychometric properties of *TSC1* and *TSC2*. **Methods:** We studied a total sample of 100 individuals with TSC. The majority were from a sequentially ascertained sample for molecular genetics studies at the Institute of Medical Genetics, Cardiff University. The remaining subjects were identified for a separate study in Cambridge, UK. All had intellectual assessments using hierarchical measurements to capture a best estimate IQ score, and detailed mutational analysis. **Results:** Of the overall sample (*TSC1* = 26; *TSC2* = 74) 72% of individuals fell in the normal distribution and 28% showed the P phenotype (*TSC1* = 3; *TSC2* = 25), essentially identical to the population-based TSC expectation. When P phenotype individuals were excluded, those with *TSC1* mutations had IQs indistinguishable from the general population (mean = 97.5; SD = 19.1). In contrast, IQs of those with *TSC2* mutations had significantly lower mean and wider standard deviation (mean = 71.6; SD = 27.1; *TSC1* vs *TSC2* $p < 0.001$). No gender-specific effects were observed. **Conclusion:** *TSC1* and *TSC2* clearly present with distinct patterns of intellectual abilities. The majority of individuals with *TSC1* fall on a normal distribution identical to the general population and ~10% have profound intellectual disability. In contrast, a substantial proportion of *TSC2* mutations (34%) are associated with profound intellectual disability, and the remainder show a pattern of IQ significantly more variable and shifted to the left than in *TSC1* or the general population. Our results suggest that differences in the functional consequences of individual mutations should be explored further as predictors and determinants of the intellectual manifestations of TSC.

Inhibition and impulsivity in children with Smith Magenis syndrome.

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Background: Children with Smith Magenis syndrome (SMS) are described as highly impulsive, yet there is limited research of this aspect of the behavioural phenotype. As inhibition has been identified as a possible cognitive endophenotype of impulsivity, in this study we examined inhibition and impulsivity in children with SMS, using children with Down syndrome (DS) and a normative sample as contrast groups

Methods: Children were tested using three cognitive tasks measuring response inhibition. Participants with SMS (n =13 for two tasks, 12 for one) were individually matched on mental age (MA) to DS participants and group performance was compared. Each syndrome group was then compared to individually MA matched typically developing (TD) participants from a normative database. Caregiver report measures of inhibition and impulsivity were also used.

Results: No differences were found between SMS and DS groups on inhibition tasks. In comparisons with the normative sample, children with SMS scored lower on one task, children with DS on two. Caregiver reports suggested children with SMS had greater deficits in inhibition and emotional control but were not more impulsive than those with DS. In SMS, but not DS, impulsivity was strongly negatively correlated with emotional control.

Conclusion: Compared to MA matched TD children, those with SMS and DS demonstrated impairment in cognitive assessments of inhibition; however syndrome groups did not differ from each other on these assessments or on caregiver ratings of impulsivity. This contrasts with caregiver reports that inhibition was more impaired in SMS than DS. The correlation between emotional control and impulsivity in the SMS group only suggests a possible motivational, rather than cognitive, influence on impulsive and disinhibited behaviour in SMS.

Thursday 6th October

The modification of apneustic breathing in Rett Syndrome with a 5-HT1-A agonist.

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Aim: Breathing dysrhythmias are a major clinical component of Rett syndrome (RTT). The three major cardiorespiratory phenotypes include apneustic breathing, feeble breathing and forceful breathing types. They are associated with major cardiovascular, autonomic and metabolic effects. Serotonin has been shown to modulate breathing control in animals and humans. The aim of this study was to assess the effects of the 5-HT1-A receptor agonist (Buspirone) on the apneustic breathing phenotype.

Methods: The study population consisted of eight RTT girls well defined genetically and neurophysiologically & who had an apneustic breathing phenotype. Full corticobulbar neurophysiology was performed at baseline and repeated at 2 days, 2 weeks and one month after buspirone treatment commenced. The respiratory traces were compared.

Results: There was a significant reduction in combined breath holds and protracted inspiration (apneusis) and an increase in normal breath holds with buspirone but no change in other breathing dysrhythmias or any effect on normal breathing.

Conclusions: The reduction in severe breathing dysrhythmias with the associated metabolic disturbances opens the way for targeted treatment strategies for patients with RTT based on their respiratory phenotype. This may have a significant benefit on mortality, metabolic status and functional abilities. Further studies to assess other neuromodulating agents and their long term use are needed.

SERTRALINE IMPROVES LANGUAGE DEVELOPMENTAL TRAJECTORY IN YOUNG CHILDREN WITH FRAGILE X SYNDROME

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Background: Young children with FXS often experience anxiety, irritability, and hyperactivity related to sensory hyperarousal and an enhanced sympathetic response to sensory stimuli. However there are currently no medication recommendations with documented efficacy for children under 5 years old with FXS. **Method:** An observational retrospective analysis of the longitudinal changes in the Mullen Scales of Early Learning (MSEL) assessments over time in young children with FXS aged 12-50 months at baseline and longitudinal assessment who have clinical problems with anxiety and or autism spectrum disorder (ASD) compared to children who were not treated with sertraline. **Result:** We followed 45 children 12-50 months old with FXS. Eleven children were treated with sertraline at an early age with baseline assessment ranging from 18-44 months (mean 26.9, SD 7.99) were retrospectively compared to a group of 34 children who were not treated with sertraline. Mean rate of improvement in both expressive and receptive language development were significantly higher in the group treated with sertraline ($p < 0.0001$ and $p = 0.0071$, respectively). **Conclusion:** The result of this observational retrospective study provides support for a controlled trial of early sertraline treatment in children with FXS who have problems with anxiety, ASD or significant language delays. **Key word:** Sertraline, FXS, language development, developmental trajectory.

THE TRAJECTORY OF PSYCHOPATHOLOGY IN ADULTS WITH AUTISM

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Background: High rates of psychopathology (behaviour and emotional problems) have been consistently reported in children and adolescents with autism. Elevated rates of mental health problems have also been reported in adults with autism. Little however is known about the longitudinal development of psychopathology in adults with autism. **Methods:** This study followed a cohort of 119 children and adolescents over 18 years with five waves of data collection. The mean age of the sample at Time 1 was 8.7 years (sd 4.3), and 24.8 years (sd 4.7) at Time 5. Participation has been consistently high throughout the study, with 77% of the original sample participating at Time 5. **Results:** Change in rates of psychopathology from Time 1 to Time 5 will be reported. Outcomes will be reported in relation to psychopathology, social inclusion, living arrangements and employment, and social competence. The relationship between Time 1 outcome (psychopathology) and Time 1 individual factors (age, gender, IQ, psychopathology at Time 1) and environmental factors (schooling, socio-economic disadvantage, family environment, social networks) will be explored. **Conclusion:** A better understanding of change over time in psychopathology will facilitate the development of specific interventions to help young people with autism. Associations between adult outcomes and individual and environmental childhood factors will be discussed in relation to approaches to early intervention.

HOW COPING SKILLS AFFECT SYMPTOMS OF ANXIETY AND DEPRESSION IN YOUNG ADULTS WITH VCFS

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Background: Coping refers to the thoughts and actions we use to deal with stress and our coping strategies have an important role in promoting good mental health. In the general population it has been found that maladaptive coping strategies and personality traits such as social withdrawal increase the risk of developing mental health problems such as anxiety and depression in adolescence and young adulthood. In addition, coping strategies are amenable to change and, if identified, targeted interventions can be utilized to teach better coping skills and reduce the risk for future mental health problems. Hence, the current study aims to investigate the relationship between coping strategies and mental health, and the influence of individual factors such as social functioning, dependency and self-efficacy among young people with VCFS. **Methods:** Coping strategies, social functioning, dependency, self-efficacy, anxiety and mood disorders were assessed in 19 participants with VCFS (12 females) and 16 healthy controls (10 females) aged between 15-24 years in a questionnaire/semi-structured interview design. **Results:** The analyses identified significantly higher levels of anxiety (VCFS mean= 18.4, SD =9.7; Controls mean= 9.8, SD=5.5) and depression (VCFS mean= 9.4, SD =5.8; Controls mean= 3.6, SD=2.3) in the VCFS cohort ($p<0.01$). There was no between-group differences in the utilization of maladaptive/adaptive coping skills ($p>0.05$). In the VCFS group only there were significant correlations between maladaptive coping and anxiety ($r=0.37$, $p<0.05$) and with depression ($r=0.54$, $p<0.004$). In addition, there was a strong correlation between anxiety and depression in the VCFS group ($r=0.85$, $p<0.0005$). Social functioning and self-efficacy was significantly lower in the VCFS group whilst dependency scores were

higher ($p < 0.005$), however these factors did not mediate the relationship between maladaptive coping and anxiety/depression. **Conclusions:** The current study suggests that while maladaptive coping strategies are not more common in the VCFS cohort, when maladaptive coping occur it is more likely to be linked with high levels of anxiety and or depression.

CONFOUNDING FACTORS AFFECTING MOTOR DEVELOPMENT IN BOYS WITH XXY

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Background: Research literature in boys with XXY has revealed motor development disturbances however, the findings have been flawed by small sample size and ascertainment bias. The variability of symptoms of the boys with XXY has been perplexing and poorly understood. This study investigated the effect of learning dysfunction in first degree relatives to boys with XXY and its effect on the neuromotor profile. **Methods:** 90 boys with XXY were evaluated to ascertain motor function. Standardized assessments were administered including Wechsler Intelligence Scales, Bruininks Osteretsky Motor Proficiency Test-2 and Visual Motor Integration. Data was gathered regarding the presence of learning disability. The data was bifurcated by XXY/LD and XXY/n-LD. Data was analyzed comparing the two groups using appropriate biostatistics measures. **Results:** Data revealed significant differences on multiple domains between XXY/n-LD and XXY/LD. WISC results revealed statistically significant differences in processing speed quotient ($p=0.028$), coding ($p=0.016$), symbol search ($p=0.028$). Bruininks-Osteretsky Test-2 revealed significance at $p < .05$ on four out of 12 subtests and the Visual Motor Integration were significantly different on all three domain at $p < .05$. Demographics between the groups revealed no significant differences. **Conclusion:** Our findings demonstrate that the complexity of the neurodevelopmental profile in boys with XXY may be confounded by multiple factors that have not been considered previously. These results support that the wide variability of performance in motor domain in boys with XXY may be related familial learning disabilities and not exclusively to the presence of additional X. Further investigation is warranted to determine if presence of learning disability in mother, father or sibling is more detrimental to the neurodevelopmental processes in boys with XXY.

TESTING THE “EXTREME MALE BRAIN THEORY”

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Background: The ‘extreme male brain’ was first suggested by Hans Asperger in 1944 when he first described the presentation of Asperger Disorder. Almost 60 years later, Baron-Cohen proposes that the behaviours of Autism Spectrum Disorder are an exaggeration of typical sex differences and proposed the “Extreme Male Brain Theory”. Arguing that males and females empathise differently, Baron-Cohen and associates have suggested that ASD is linked with sexual dimorphism by this difference in empathy and that exposure to high levels of prenatal androgens might cause this exaggeration. Indeed, patients with ASD have higher serum androgen levels. However, neural mechanism(s) through which androgens may act to cause this difference are not understood. We will describe a mouse model with hormonal disturbances which would be a useful tool to test this hypothesis. **Methods:** The aromatase knockout (ArKO, an estrogen-deficient model) mouse model was characterised by a battery of behavioural tests.

Results: We have pilot data to indicate that the aromatase knockout (ArKO, an estrogen-deficient model) mouse has behavioural phenotypes consistent with the spectrum of autistic symptoms. The male ArKO mice present a short-term spatial reference memory deficit in the Y-maze test; develop repetitive behaviour such as excessive water-spray triggered grooming and wheel-running activities. These ArKO phenotypes may be analogous to the reported characteristics of Autism Spectrum Disorder patients. More importantly, the young (6 week-old) male ArKO mice exhibited social interaction deficits but not the young female ArKO. **Conclusion:** Oestrogen deficiency in the brain may lead to the presentation of autistic-like symptoms predominately in male mice.

FOOD RELATED PROBLEMS IN CHILDREN WITH ANGELMAN, PRADER-WILLI, 1P36 DELETION, CORNELIA DE LANGE AND FRAGILE X SYNDROMES

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Background: Food related problems are commonly reported in Prader-Willi syndrome with occasional reports of excessive appetite in 1p36 deletion and Angelman syndromes. We compared the level of food related problems in these groups to two contrast groups: Cornelia de Lange and Fragile X syndromes.

Methods: As part of a larger survey, data were collected using the informant measure the Food Related Problems Questionnaire for children under 16 with Prader-Willi (25 males; mean age = 10.73 years; n = 37), Angelman (17; 10.51; 35), Cornelia de Lange (22; 10.3; 33), Fragile X (29; 13.7; 30) and 1p36 (7; 7.57; 21) syndromes.

Results: As expected, comparison of group means, using analysis of variance, revealed significantly higher scores for the Prader-Willi syndrome group than other groups on most subscales. The Angelman syndrome group also scored significantly higher than other groups on some subscales and at levels comparable to those for Prader-Willi on the 'composite negative behaviour' subscale and the 'preoccupation with food' subscale. These differences remained when level of ability was used as a covariate. **Conclusion:** The elevated levels of food related problems in Angelman syndrome, that are comparable to those reported in Prader-Willi syndrome, are notable and warrant controlled investigation. The greater degree of intellectual disability in Angelman syndrome may mean these problems are easier to manage, and hence less likely to be reported as a feature of the behavioural phenotype, but nevertheless problematic for people with Angelman syndrome.

ELIMINATION DISORDERS IN PERSONS WITH PRADER-WILLI AND FRAGILE-X SYNDROMES

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Background: Elimination disorders are common in typically developing children: 10% of 7 year olds wet at night (nocturnal enuresis - NE), 2-3% during daytime (diurnal urinary incontinence - DI) and 1-3% soil (faecal incontinence - FI). Only few studies have addressed elimination disorders in persons with intellectual disability - and even fewer studies in those with specific syndromes. The aim of the study was to investigate the rates of elimination disorders in persons with Prader-Willi (PWS) and Fragile-X syndromes (FXS) in a large sample. It was hypothesised that the rates would be increased and associated with behavioural symptoms. **Methods:** 358 persons with PWS or FXS were recruited through

parent self-help groups. Questionnaires regarding elimination symptoms, as well as the Child Behavior Checklist (CBCL) or the Young Adult Behavior Checklist (YABCL) were filled out by parents or caregivers. **Results:** The sample included 116 persons with FXS (92.2% male) with a mean age of 15.4 years (range 4.0 to 46.1), as well as 192 persons with PWS (54.2% male) with a mean age of 20.1 years (4.3 to 52.7). 29.5% (49) of the persons with FXS had NE, 28.3% (47) DI and 27.7% (46) FI. Combinations were common and only 50.6% (84) were not affected. 21.4% (41) of persons with PWS had NE, 12.0% (23) DI and 12.0% (23) FI. 67.2% had no elimination disorder. 56.0% (93) of persons with FXS and 64.1% (123) with PWS had clinically relevant total behaviour scores (CBCL/YABCL). Elimination disorders were associated with higher rates of clinically relevant behavioural symptoms: in FXS with NE (68.1%), with DI (71.0%) and with FI (67.4%); in PWS with NE (63.4%), with DI (63.3%) and with FI (78.3%). **Conclusion:** Elimination disorders are very common in persons with FXS and PWS and are associated with other behavioural symptoms. They persist into adulthood - even though effective modes of therapy are available. Early assessment and treatment are recommended.

Challenging Behaviour in Tuberous Sclerosis Complex

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Background: Tuberous Sclerosis Complex (TSC) is a multisystemic genetic disorder. Evidence is emerging for an association between TSC and high rates of challenging behaviours. This study reports the prevalence rates of self injury, aggression and destruction of property in TSC and investigates the association between challenging behaviour and factors previously identified as predictive of challenging behaviour in other genetic syndromes.

Methods: Informant based questionnaires were completed by carers on: ability, autism spectrum disorder, challenging behaviour, mood, activity, repetitive behaviours, communication and pain. Results from 67 individual with TSC, recruited through the Tuberous Sclerosis Association, were compared to those from an existing dataset on children and adults with Down, Angelman, Cornelia de Lange, and Fragile-X syndromes and Autism Spectrum Disorder.

Results: For individuals with TSC under the age of 16 and those 16 and over, the prevalence rates for self injury were 27% and 31%, aggression; 50% and 37.9% and destruction of property; 33.3% and 17.2% respectively. These were high but not significantly different to the prevalence rates reported in Down syndrome. Factors previously shown to be predictive of challenging behaviours in other genetic syndromes were associated with challenging behaviour in TSC. For example, low mood, high activity levels, stereotyped and repetitive behaviours, impulsivity, characteristics of autism spectrum disorder and pain were all associated with challenging behaviour.

Conclusion: These results quantify the risk of challenging behaviour in TSC compared to other syndromes. Challenging behaviour in TSC was shown to be associated with person characteristics previously identified in other syndrome groups. This has implications for early intervention and targeting of recourses for those most at risk of challenging behaviour.

EDUCATION DAY

New developments in the neuropsychiatry of Tuberous Sclerosis Complex (TSC)

Dr Petrus de Vries, Consultant in Developmental Neuropsychiatry, Cambridgeshire & Peterborough NHS Foundation Trust, and Developmental Psychiatry Section, University of Cambridge, UK

The neuropsychiatric aspects of TSC lead to some of the greatest burden of care for families living with TSC. We can describe these manifestations across a number of 'levels of investigation' including behavioural, psychiatric, intellectual, scholastic and neuropsychological. Over the last five years we have seen significant developments in the neuropsychiatry of TSC across most of these levels. Apart from a range of studies elaborating descriptive and correlational work, there has also been exciting progress in the translational neuroscience of TSC - to start understanding the actual mechanisms underlying the neuropsychiatric disorders of TSC. Most importantly, theoretical predictions and evidence from TSC animal models have shown that there are direct molecular pathways from genetic defect to neurocognitive and neurodevelopmental deficits. These discoveries have led to pre-clinical and clinical trials investigating the possibility of reversing some of the neuropsychiatric deficits in TSC.

In this presentation we will describe examples of new developments across the different levels of investigation. In particular, we will discuss new findings in adults with TSC, experimental studies of autism in TSC, and explore progress in clinical trials of mTOR inhibitors specifically aimed at the neurocognitive and neurodevelopmental manifestations of TSC.

Overview of Treatment Research in Fragile X Syndrome

Randi Hagerman, MIND Institute at University of California at Davis Medical Center, Sacramento, CA

The focus of treatment research in those with fragile X syndrome (FXS) is targeted treatment which means the use of medications that have the potential to reverse the neurobiological abnormalities seen in FXS. The research on the knock out (KO) mouse has demonstrated metabotropic glutamate receptor 5 (mGluR5) dysregulation, GABA A receptor down regulation, and elevation of matrix metalloproteinase 9 (MMP9), all of which has been targeted with specific therapies. The use of mGluR5 antagonists, GABA agonists and minocycline which lowers MMP9 have all been beneficial in the KO mouse model. Currently there are trials taking place in both children and adults with FXS with mGluR5 antagonists including AFQ056 from Novartis, and R049 from Roche. In addition Arbaclofen, the right isomer of Baclofen, has demonstrated efficacy in children and adults with FXS who have autism or significant social deficits. These results have led to a larger controlled trial of Arbaclofen in children and adults with FXS and in idiopathic autism. A controlled trial of minocycline is showing positive results after treatment of 40 children with FXS and will continue until completion of 60 patients. Ganaxolone, a GABA A agonist, is currently being studied in a controlled trial of children 6 to 17 years with FXS. The trials of mGluR5 antagonists are taking place in the US and internationally and these studies include Australia. As studies of FXS continue additional pathways are found to be dysregulated including P13K and mTOR and new treatments are being studied in animal models of FXS. Lastly, a number of medications that are currently available by prescription or over the counter are also being studied in FXS including lithium, aripiprazole, antioxidants, and memantine.

Psychosis in Intellectual Disability

Brett McDermott

This paper will briefly consider the development of the current classification system for Schizophrenia. From the perspective of intellectual disability it will be noted that individuals have an elevated risk for psychosis; conversely individuals with Schizophrenia have an increased risk of neurocognitive deficits prior to illness onset. The breadth of disorders with psychotic features as part of the phenotype will be reviewed, so too typical reasons for misdiagnosis of psychosis and the implications of this. Finally, the current evidence for psychopharmacological and other interventions for psychosis in intellectually disabled groups will be reviewed.

Targeted Prescribing for Behavioural and Mental Health problems in Intellectual Disability

Gregory O'Brien

My starting point whenever I address the subject of drug treatment in this area is driven by basic Hippocratean principles – which translated for today go something like “when in doubt, don’t” mingled with “when it is needed, do”. Certainly, given that the socially and developmentally crippling behaviour we encounter among people with intellectual disability is best addressed by interventions which are aimed at the underlying cause, medication is not the only answer. Essentially, the trick lies in knowing when to reach for the prescription pad, as part of a wider plan of intervention.

This presentation will suggest guidelines to be followed in prescribing medication for behavioural and mental health problems in this population. These are based on the available evidence, augmented by clinical consensus. The word “targeted” in the title of the presentation is one key. Notably, the evidence base is strongest in respect of clear-cut mental illness – but so much of what we see in our clinical practice is more complex than this. Nevertheless, there is emerging recent evidence of the value of psychopharmacological intervention in this population. Interpretation of the evidence base can be daunting – parents and carers will typically ask about this or that new “miracle cure” they have encountered on some commercial website. Consequently, the need for the kind of inclusive and participatory approach to working in partnership which is so highly valued throughout the Disability world is stressed most keenly in our approach to the use of drugs for behaviour among the people whom we serve.

In line with current contemporary concerns, the presentation will include an overview and survey concerning the issue of “Chemical restraint”. It will be argued that the best approach to this matter is to follow the kind of approach recommended generally.

Hippocrates counselled us to follow principles of non-maleficence, beneficence, justice and autonomy. How he would have incorporated evidence-based adherence and health economics into his thinking is anyone’s guess. But he would have probably been content to know that our use of potentially toxic substances is still guided by his watchphrase – “but first do no harm”.

Posters

WELL-BEING AND BURDEN IN FATHERS' OF YOUNG CHILDREN ATTENDING AN AUTISM-SPECIFIC EARLY INTERVENTION SERVICE

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Background: Despite decades of research on family adaptation in the context of having a child with autism, the well-being of fathers remains poorly understood. Emerging research suggests that fathers experience unique challenges and that factors related to stress may differ from that of mothers (Hastings, 2005). Fathers have distinct psychological profiles from mothers (e.g., Davis & Carter, 2008) and make unique and direct contributions to children's development (Flippin & Crais, 2011). The present research seeks to investigate fathers' well-being and burden in a particularly vulnerable time; when children with ASD are young. **Methods:** Participants were fathers of children aged between 2:6 and 6 years who were attending an autism-specific early intervention centre. A mixed methods design was used, which involved the completion of a mailed survey and a telephone interview. The survey included standardised measures assessing the constructs of the double ABCX model of family adaptation (McCubbin & Patterson, 1983). The interview used open-ended questions in order to understand fathers' experience of raising a child with an ASD, involvement in caring, sources of support, and coping strategies. **Results:** Survey results indicated that fathers experienced elevated levels of parental stress with 93% scoring in the clinical range on the Parenting Stress Index. In addition, many fathers demonstrated elevated depressive symptoms with 66% scoring in the elevated range on the Depression Anxiety Stress Scale. Fathers' perspectives yielded from interview data augment these findings. **Conclusion:** This study offers insight into the neglected perspective of fathers. Findings from this research provide a foundation to better understand fathers' experiences and to develop appropriate interventions suited to their particular needs and strengths.

ANXIETY DIFFICULTIES AND DISORDERS IN INDIVIDUALS WITH GENETIC SYNDROMES: A SYSTEMATIC REVIEW OF THE LITERATURE 1990-2011

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Background: Increasing research and clinical attention has been paid in recent years in recognizing, assessing, understanding and treating comorbid psychiatric conditions in children, youth and adults with genetic disorders. Anxiety difficulties appear to be particularly prevalent and impairing in Autism Spectrum Disorders and research focusing on anxiety has been emerging for this diagnostic group. Research on anxiety in other genetic disorders, including Fragile X, 22q11.2 deletion, Rett, Cornelia de Lange, Turner and Williams syndromes, is currently limited, but also emerging. **Methods:** PsychInfo and PubMed databases were systematically searched using various combinations of carefully selected search items for relevant empirical studies on anxiety (diagnosis, phenomenology, prevalence or intervention) in individuals with genetic syndromes published between 1990-June 2011 according to predefined criteria. **Results:** This paper will critically summarize and discuss findings from the studies included in the systematic review. In particular, shared and unique characteristics of anxiety in the different syndromes will be considered and factors associated with anxiety in these genetic disorders will also be reviewed,

with a particular focus on ASD. Conclusions: Implications of existing research findings regarding prevalence and phenomenology of anxiety in genetic disorders for research on behavioural phenotypes are discussed. Research and clinical recommendations are made in light of methodological strengths and limitations of the reviewed studies and current gaps in the literature.

NEWBORN SCREENING FOR FRAGILE X: IDENTIFICATION AND EVALUATION

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INTRODUCTION: The University of California Davis M.I.N.D. Institute Fragile X Research and Treatment Center is conducting newborn screening (NBS) for fragile X. **METHODS:** A bloodspot is obtained from each newborn. Parents of each newborn are approached to obtain their consent for participation in the NBS study. When a consented newborn is identified as having the FMR1 mutation, the parents are contacted and informed of the result. The family is seen in clinic. A blood draw is performed on infant and parents to determine parent of origin. Cascade testing of at risk family members follows. The infant is seen every 6 months for developmental assessment. **RESULTS:** At UC Davis, one full mutation male from 5880 analyzed male samples has been identified. Eight premutation carriers; 4 males and 4 females have been identified. In total, 27 other family members have been tested with 17 identified premutation carriers. All identified newborns have had developmental assessments. Infants with the premutation have not shown significant clinical findings. The male infant with the full mutation has an Early Learning Composite of 63 on the Mullen which is consistent with FXS. **CONCLUSION:** The preliminary data from this pilot study demonstrates the importance of NBS and cascade testing for the FMR1 mutation. Infants in this study are being followed to document clinical findings. This ongoing NBS program will provide insights into the clinical and cognitive aspects associated with the FMR1 mutation and provide important information for targeted treatments.

MINOCYCLINE AS A TARGETED TREATMENT FOR FRAGILE X SYNDROME

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Background: Fragile X Syndrome (FXS) is the most common inherited cause of intellectual disability and autism. Deficits in fragile X mental retardation protein are associated with increased levels of matrix metalloproteinase 9 (MMP9) in the brain. Minocycline decreases MMP9 levels and rescues dendritic spine abnormalities in the *Fmr1* knock out mouse. Open label studies in humans suggest benefit.

Methods: Randomized, placebo-controlled, double blinded trial in children with FXS ages 3.5-16 years old. Participants were randomized to either minocycline or placebo and were crossed over at three months. Measures including the Visual Analogue Scale (VAS), Aberrant Behavior Checklist (ABC) and Clinical Global Impression Scale-Improvement (CGI-I) were administered at baseline, 3 months and 6 months. **Results:** This preliminary analysis focuses on data from the first 3 months for 30 individuals. The mean differences between minocycline and placebo in the VAS for the first and second target behaviors showed significant improvement, $p=0.031$ and $p<0.01$ respectively. The mean CGI-I scores of individuals on minocycline was 2.57 (SD 0.94), compared to 3.40 (SD 0.89) for the placebo group, demonstrating greater improvement on minocycline ($p=0.023$). There were no significant changes in the ABC-irritability

scale between the minocycline and placebo groups. The most common side effects included loose stools. Data continues to be gathered. Efficacy and safety data over the full study for a goal of 50 participants will be discussed. **Conclusion:** Over three months, minocycline treatment was well tolerated and appears to be beneficial. Larger, multi-center trials are indicated to further examine these results.

UNDERSTANDING THE PROVOCATIONS FOR TEMPER TANTRUMS IN PEOPLE WITH PRADER-WILLI SYNDROME

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Background: The behavioural phenotype of Prader-Willi syndrome (PWS) includes: excessive eating, temper tantrums, skin picking, mood fluctuations, compulsive behaviours and difficulty with changes in routine. Hyperphagia and behavioural problems such as temper tantrums are the two leading causes of stress for individuals with PWS and their families. As temper tantrums are typical of this syndrome it is possible that people with PWS share common motives for this behaviour. Identifying common motives may allow for better management of temper tantrums and provide a better understanding of the cognitive processes of this syndrome. The only known study to investigate the phenomenology of temper tantrums in PWS focused on only one possible motive and is limited in generalisability due to a small sample size. The aim of this study is to determine the precipitating or palliating factors for tantrums for people with PWS. **Methods:** 100 people with Prader-Willi syndrome (8 to 30 yrs) and their main carer will be asked to complete a semi-structured questionnaire. Participants will be sought from Australia and overseas. Analysis of the data will provide a description of the common precursor behaviours, individual and environmental factors and a secondary analysis will identify any common themes. **Future Studies:** (1) If common motives are identified in experiment one a second experiment will determine the validity of these motives. If the motives are specific to PWS it is hypothesised that an experimental setting designed to elicit these motives should provoke temper tantrums in people with PWS. The design of this experiment will be determined by the findings from the former study. (2) A third experiment will test the validity and reliability of an inventory/questionnaire developed from the findings of the former two studies. The inventory/questionnaire will be a user-friendly clinical method for assessing the specific motives of temper tantrums in individuals with Prader-Willi syndrome. Such a tool will allow for clinicians to effectively identify the causes for upset in their patients and provide a direction for intervention.

PRADER-WILLI SYNDROME [PWS] IS BEHAVIOURAL MODIFICATION POSSIBLE?

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Background: There is a distinct behavioural phenotype in PWS, encompassing temper tantrums, perseveration, obsessive compulsive, manipulative conduct, sudden aggression and abnormal food seeking with pica. It is the behavioural aspects which are of most concern for carers. Post mortem studies on brain tissue have shown a deficiency of oxytocin producing cells in the hypothalamus in PWS. A priori administration of oxytocin could alleviate behavioural problems, which would be worthwhile in terms of management. **Methods:** A clinical trial was set up with DNA proven subjects with PWS, administering oxytocin as a nasal spray (24IU for participants aged 16 years and over; 18IU for those under 16 years). The study comprises enrolment of 30 PWS subjects, aged 12 – 30 years, in a randomised controlled crossover within-subjects double blind trial (each subject is its own control) with OT (or placebo)

administered for 8 weeks (1st arm), followed by a wash out period of 2 weeks, and then a further 8 weeks of OT nasal spray (or placebo) (2nd arm), with assessments made at standard time points. The modules used for testing include well validated items from the Developmental Behaviour Checklist, Yale Brown Obsessive Compulsive Scale, the Dykens Hyperphagia Questionnaire, Epworth Sleepiness Scale and Reading the Mind in the Eye test (RMET) **Results:** To date, 6 clients have completed both arms of the trial, 3 have completed 1st arm, and 11 are ready to start. Codes have not yet been broken, but anecdotally, some have noticed a change in behaviour while others have not. Conclusion – it is too early to say whether or not the trial is successful. New evidence suggests that administration of OT alters innate OT production, so that increasing the dose of OT may be more efficient to track alteration of behaviour.

PRADER WILLI SYNDROME- THE RELATIONSHIP OF GENETICS TO SLEEP PARAMETERS

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Background:Prader-Willi syndrome (PWS) is a contiguous gene syndrome characterised by interstitial deletions, uniparental disomy and imprinting errors of chromosome 15q11-q13 region. Central and obstructive sleep apnea and hypersomnolence are more common in children with PWS than typically developing children. In people with PWS, obesity, hypotonia, craniofacial features and hypothalamic dysfunction may contribute to the sleep phenotype as may underlying molecular abnormalities.

Methods:A retrospective analysis of polysomnograms for individuals with PWS was conducted. A total of 178 studies from 56 patients over 5 years were analysed. Sleep parameters were correlated with individual genotypes. Longitudinal analysis of the sleep phenotype is pending. **Results:**51% of studies were done in children 5 years and under. BMI ranged from 11.5-36.8 in the under 5 year olds to 14.7-54 in the older children. Genotype was classified according to the presence of UPD(n=16), Deletion (Class I or II)(n=87) or imprinting centre defect (n=1). The genotype (UPD) correlated with the presence of significant central hypoventilation especially in the children less than 5 years(p<0.005). BMI had strong correlations with Obstructive events(p<0.001). This correlation was not seen in children >5 years. **Conclusion:** The genotype has a small correlation with sleep phenotype. We postulate that this relationship is due in part to genes in the region of 15q11-q13, including gamma-aminobutyric acid receptor, beta3 known to be associated with insomnia.

CHW SCHOOL-LINK: A NEEDS ANALYSIS FOR IMPROVING MENTAL HEALTH OF CHILDREN AND ADOLESCENTS WITH AN INTELLECTUAL DISABILITY IN SPECIAL SCHOOLS

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Background: School-Link is a partnership between NSW health and education addressing the mental health (MH) of students since 1999. School-Link recently expanded its' activities through CHW School-Link project to focus on the MH of children and adolescents (C&A) with an intellectual disability (ID) in Schools for Special Purposes that cater for ID (SSPs). A needs analysis was completed in 2009 under the key themes of: 1) The improving pathways to care. 2) Training and education for school counsellors

and other professional staff. 3) School based MH promotion, prevention or early intervention programs (PPEI). **Methods:**Data was collected for the needs analysis through a literature review, an online survey of school counsellors of SSPs (35/58), and telephone interview (11/35). **Results:**The needs analysis highlighted areas of improvement: school counsellors found MH of C&A with ID to be complex and in need of a collaborative interdisciplinary interagency approach. PPEI for mainstream populations are not suitable and need special development. School counsellors and other professionals require ongoing specialty training. **Conclusion:** The needs analysis has led to a number of initiatives including: Advocacy through a website (www.schoolink.chw.edu.au) and quarterly newsletter. Education through a pilot of cross agency interdisciplinary supervision with school counsellors; developing and implementing interdisciplinary training and publishing a book on MH for C&A with ID; running regular cross agency conferences. Promoting Pathways to Care through enhanced interagency collaboration/networking and an interagency specialist tertiary developmental psychiatry clinic. PPEI: Pilot of Stepping Stones Triple P Group parent training in 4 SSPs; promoting a specialised emotional literacy program, Emotion based Social Skills Training for Autism and mild ID.

EXAMINING BEHAVIOUR AND EMOTIONAL PROBLEMS IN PRESCHOOL CHILDREN WITH DEVELOPMENTAL DELAY

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Background: Research has established that behaviour and emotional problems occur at a significantly high rate young people with intellectual disability and decline slowly over time. Comparatively less is known about the nature and presentation of such difficulties in preschool children with developmental delay. This study aimed to examine behaviour and emotional problems in preschool children and associations with maternal and paternal psychosocial distress. **Methods:** The first stage of this study involved the development of a measure designed specifically to examine behaviour and emotional problems in preschool children with developmental delay. This measure, the Developmental Behaviour Checklist-Under 4, was then used to examine behaviour problems in a community sample of children aged 18-48 months, with or suspected of developmental delay. **Results:** Data will be presented on the rate and presentation of behaviour problems, along with associations with age, gender and developmental level. The relationship between child behaviour problems and maternal and paternal psychosocial distress will also be explored. **Conclusion:** Greater understanding of the presentation of behaviour and emotional problems in early childhood will facilitate the development of specific early interventions. This may also provide insight into the origins of severe behaviour and emotional problems that can be observed in later childhood and adolescence.

PSYCHOPATHOLOGY IN ADULTS WITH 22Q11 DELETION SYNDROME AND MODERATE TO PROFOUND LEARNING DISABILITY

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Background: 22q11 deletion syndrome (22q11DS) is caused by a microdeletion on chromosome 22q11.2. Although several studies reported that 22q11DS is associated with mild or borderline learning disability, a more severe learning disability is also seen in clinical practice. Within the latter group a subgroup of 22q11DS subjects suffer from cognitive deterioration. There is also a subgroup of 22q11DS with an already pre-existing moderate to profound learning disability. There are no studies to date who report on the psychopathological characteristics of these subgroups. **Methods:** 22q11DS adults with a cognitive deterioration (n = 21) and adults with a pre-existing low intelligence (n= 12) were included. The Adult Behavior Check List (ABCL), the Vineland-Screener and the Mini PAS-ADD were administered to assess for psychopathology. **Results:** Remarkable high scores on psychopathology subscales were found for both subgroups. In both subgroups high scores on autistic symptoms, mainly on social and communication symptoms were found. Significant differences between these subgroups were found for symptoms of depression, anxiety, psychosis and unspecified disorders, all with higher scores for the deterioration subgroup, as well for ADHD symptoms on the ABCL. **Conclusion:** Although moderate, severe and profound intellectual disabilities are thought to be rare in VCFS, we were able to identify 33 patients with an FSIQ below 55. Our findings also suggest that VCFS subjects with a cognitive deterioration in adulthood show higher rates of comorbid psychopathology than adults with pre-existing moderate to profound learning disability.

AN INVESTIGATION INTO THE COGNITIVE PROFILE OF CHILDREN WITH AUTISTIC SPECTRUM DISORDER ON THE "BEHAVIOURAL ASSESSMENT OF DYSEXECUTIVE SYNDROME IN CHILDREN" (BADS-C)

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Children with Autistic Spectrum Disorder (ASD) have been found to have deficits of executive functioning, specifically cognitive flexibility, verbal reasoning, self-monitoring and planning. The Executive Control theory suggests that deficits in understanding the mental states of others in ASD are a result of executive dysfunction. Clinical applications of findings from previous research of executive dysfunctioning in children with ASD have been limited as the effects of intellectual disability have not been accounted for and only isolated executive functioning subtests were administered. The aims of the present study were (1) to investigate executive functioning in children with ASD while taking intellectual ability into account by administering a complete battery of intellectual and executive functioning tests which have been designed and normed specifically for the child population, and, (2) for the first time, to identify the cognitive profile for children with ASD on the Behavioural Assessment of Dysexecutive Syndrome for Children (BADS-C). The BADS-C was administered to 19 children with ASD or Aspergers Disorder. Scores were normed for age and IQ. Results were compared with a physical health control group. On the majority of BADS-C subtests the children with ASD performed within normal limits and consistent with their mean Full Scale IQ scores. However, results from two of the six BADS-C subtests, the Playing Cards Test and the Six Part Test, revealed significant impairment for children with ASD when compared with controls. The results indicate deficits in cognitive flexibility, complex planning and self-monitoring although there was no evidence of a global dysexecutive profile for children with ASD. Deficits with processing speed, perseveration, and cognitive workload are implicated. The study suggests that a generalisable neuropsychological profile for children with ASD remains elusive. Strengths and limitations of the study are discussed including clinical implications.

Exploring the cognitive-motor phenotype in Williams syndrome

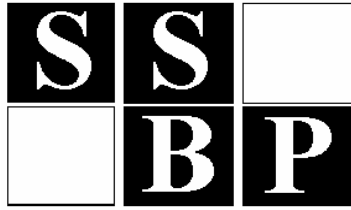
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Background: Recent evidence indicates that children with Williams syndrome (WS), a rare genetically based developmental disorder, show specific weaknesses in executive functions and response inhibition within the visual/motor domain. Here we examined the extent to which impairments in attentional control impact on motor inhibition using game-based assessments of cognitive inattention and stepping performance. Embedding experimental paradigms within a game-based context provided a novel approach to examine atypical development of attention using both age- and ability-appropriate measures in a genetic disorder with specific attentional weaknesses. **Methods:** Participants were adolescents and adults with WS who were compared to both chronological- and mental-age (MA) matched controls. We examined the relationship between motor inhibition using a novel dance mat measure of choice stepping reaction time (CSRT) and performance on a well-documented attentional control paradigm (Visearch). The effects of cognitive dual-task paradigms (semantic fluency) on reaction time (RT) during performance on the CSRT dance mat were explored to examine dual task processing as a component of executive function. **Results:** Preliminary results showed marked delays in selective attention under greater attentional demands and slower RT during dual task stepping performance in the WS group when compared to chronological age and MA. The WS group also showed specific weaknesses in response inhibition during the inhibitory component of the dance mat measure of CSRT. **Conclusion:** These findings emphasise the need to examine the cognitive-motor phenotype in WS across the full developmental trajectory into adulthood using intrinsically motivating and engaging game-based behavioural paradigms.

22Q11MICRODUPLICATION: CLINICAL AND BEHAVIORAL PHENOTYPE

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Background: The 22q11 region is susceptible to chromosomal rearrangements, leading to various types of congenital malformations and intellectual disability. The most common anomaly is 22q11.2 microdeletion. The frequency of the microduplication 22q11 is approximately half that of the deletions. The 22q11 microduplication syndrome is an extremely variable disorder with a variable phenotype. **Methods:** We present the results of the longitudinal observation of a 24 yrs old male affected by tetrasomy of chromosome 22q11. Laboratory studies included conventional cytogenetic, FISH testing, and CGH- microarray. **Results:** The patient was born from nonconsanguineous parents after a morbid pregnancy. Weight at birth: 2450 g. Motor developmental milestones were delayed: upright station at 18 months, first steps without help at 2 years. He attended the Secondary School and now he has supported employment. At clinical examination he presents facial dysmorphic features, bilateral fourth nerve palsy, oculo- rhinitis and atopic dermatitis. The patient has hypospadias and bilateral vesicoureteral reflux. Brain MRI documented a thinning of the posterior third of the corpus callosum. The cognitive phenotype is characterized by mild learning disability and specific language impairment. IQ level is borderline at WAIS (QI tot= 72; QIv=78; QIp= 68). Behavioural phenotype is characterized by an exaggerated response to threatening stimuli, presence of stereotyped behaviours and interests, motor stereotypes. High levels of anxiety and an enduring fearfulness of painful situations are also frequent. CGH microarray detected the tetrasomy of about 4Mb on chromosome 22q11 (first amplified oligo:15.471 Mb; last amplified oligo :19.707 Mb, first normal oligo:20.123 Mb) **Conclusion:** Our case report contributes to the characterization of 22q11 tetrasomy behavioural phenotype.



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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 electro-encephalography and cytogenetic testing could greatly contribute to identifying affected patients. Clinical diagnostic criteria rest on physical and behavioural features (Williams *et al.* 1995).

Genetic aspects: Angelman syndrome is caused by a disruption of the maternally inherited proportion of chromosome 15q 11-13 (Clayton-Smith & Laan, 2003; Knoll, Nicholls & Lalande, 1989) via four known genetic mechanisms (Jiang, *et al.*, 1999; Louise *et al.*, 2001). Williams, Lossie and Driscoll's (2001) review suggests that approximately 68-75% of individuals with Angelman syndrome have a deletion on the maternally derived chromosome 15q 11-13; 2-7% have uniparental disomy (where both copies of chromosome 15 are paternally inherited); 2-5% have an imprinting defect and 8-11% have a mutation in the UBE3A gene (which lies at the 15q 11-13 locus; Jiang *et al.*, 1999). Between 5-20% (dependent upon sample and extent of molecular investigations) of individuals with the physical and behavioural features of Angelman syndrome show no identifiable abnormalities in the 15q 11-13 region (Clayton-Smith *et al.*, 2003; Laan *et al.*, 1998; Lossie *et al.*, 2001; Williams *et al.*, 2001). The genetic association between Angelman syndrome and Prader-Willi syndrome has evoked interest in genomic imprinting and within these individuals (see Brown & Consedine, 2004; Haig & Wharton, 2003 for an excellent discussion). Many of the features of the syndrome are thought to result from impaired expression of UBE3A. This gene is found throughout the brain and has a role in proteic scavenging 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 microbathycephaly, 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).

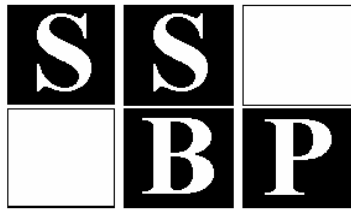
Cognitive aspects: Cognitive functions are severely to profoundly impaired in all cases. Early social interaction is usually not delayed, but vocalisation is poor or absent. Attention span is short. Patients exceptionally acquire more than 5 words and one third of individuals have no words. Speech impairment 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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C Oliver, 2009



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Autism and Asperger Syndrome

Classification:

Autism and Asperger Syndrome are the two principal conditions included by DSM-IV & ICD-10 in the category of Pervasive Developmental Disorders (PDD). The others include atypical autism and PDD Not Otherwise Specified (PDD NOS). There has been continuing debate as to whether autism and Asperger syndrome are distinct conditions and lack of consistency in differentiating between Asperger syndrome and high functioning autism, or between PDD-NOS and atypical autism have resulted in the draft proposals for DSM-V suggesting an over-arching classification of Autism Spectrum Disorder in which there will be no differentiation between these categories. In addition, whereas current diagnostic criteria require specific impairments in 3 domains (Social, Communication, and Restricted, Repetitive and Stereotyped behaviours/interests [RRSB]) the proposed criteria will be based on just 2 domains, Social – Communication impairment and RRSB. Additionally, a dimensional rating of severity of disorder is also proposed.

First described: Autism by Kanner in 1943 and Asperger syndrome by Asperger in 1944. Both accounts note the abnormal patterns of communication and social development and the presence of ritualistic and stereotyped behaviours that are now recognised as the core symptoms of Autism Spectrum Disorders (ASD) (van Engeland & Buitelaar, 2008). Both Kanner and Asperger also described a variety of other behavioural difficulties and they included individuals of normal/above average IQ, as well as those with more severe cognitive impairments.

Associated conditions:

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

Genetics:

The risk of ASD in siblings of probands is significantly increased and there is an exceptionally high concordance rate in monozygotic twins. Family studies indicate that the “Broader Autism Phenotype” (i.e. having problems related to social, language and/or cognitive functioning) occurs in up to 20% of first degree family members. However, although ASDs are clearly highly heritable, attempts to identify specific susceptibility genes have thus far met with limited success. Genome-wide association studies have

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

Prevalence:

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

Physical Phenotype:

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

Life expectancy/natural history:

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

Behavioural and cognitive characteristics:

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

Outcome:

Functioning in adulthood is determined both by innate cognitive abilities and the levels of educational and post- school support provided. Mental health problems, especially related to anxiety and depression often emerge in late adolescence/ early adulthood (Hutton et al., 2008).

Websites:

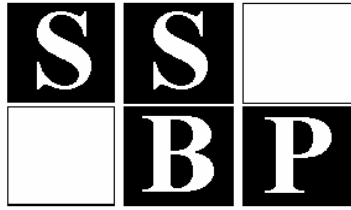
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Patricia Howlin, April 2010



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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.

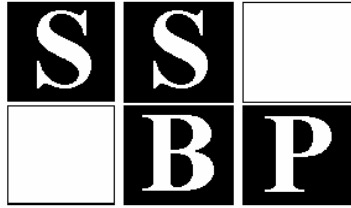
Useful websites/associations for more information:

- 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



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Coffin-Lowry Syndrome

First description:

The Coffin–Lowry syndrome (CLS) (MIM 303600) is a syndromic form of X-linked severe intellectual disability characterized in male patients by psychomotor impairment, 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 severely intellectually disabled. 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 severe learning disability (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 learning disabilities. 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:

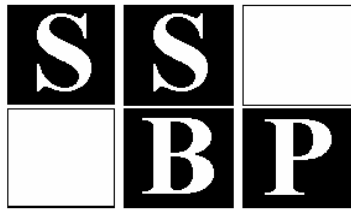
There is no specific treatment. Sensorineural hearing deficit should be addressed very early to improve the development and quality of life of the patients. Treatment for individuals with CLS who experience drop attacks includes medications such as valporate and clonazepam or selective serotonin uptake 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



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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-Onychodysplasia”, “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:

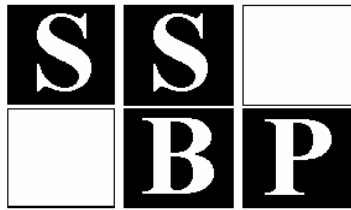
Frequent infections have been reported for individuals diagnosed with Coffin Siris syndrome. Respiratory infections may be related to hypotonia, poor sucking, and aspiration besides increased susceptibility. Consultation with feeding clinics, G tube placement, fundoplication, thickened infant feedings, 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



SOCIETY FOR THE STUDY OF BEHAVIOURAL PHENOTYPES

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Cornelia de Lange syndrome

First description and alternative names:

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

Incidence/prevalence:

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

Genetics:

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

Physical features and natural history:

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

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

Behavioural characteristics:

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

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

An association between CdLS and autism spectrum like characteristics has recently been recognised (Basile *et al.*, 2007; Berney *et al.*, 1999; Bhyuian *et al.*, 2006; Moss *et al.*, 2008). This association with ASD is not solely accounted for by associated intellectual disability (Moss *et al.*, 2008). Extreme shyness and social anxiety are characteristic of many individuals with CdLS and an unusually high number of individuals with CdLS are reported to show characteristics of selective mutism. These difficulties may become more prominent with age (Collis *et al.*, 2006)

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

Neuropsychological characteristics:

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

Available guidelines for behavioural assessment/treatment/management:

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Useful websites/associations for more information:

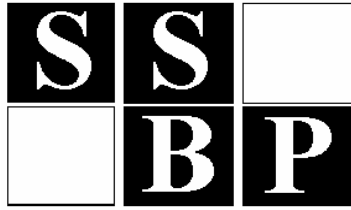
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J Moss & C Oliver, July 2010.



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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/

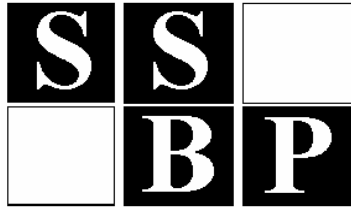
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P Tunnicliffe, J Moss, & C Oliver, July 2010.



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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:

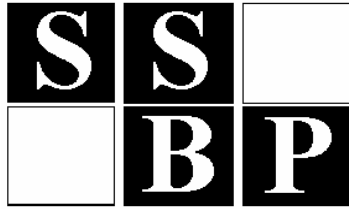
- www.fasdaware.co.uk
- www.fasdtrust.co.uk
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Kieran D O'Malley, Raja Mukharjee, July 2010



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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 hypermethylation 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

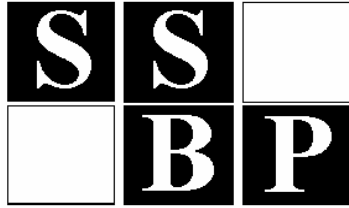
- **The Fragile X Society**, 53 Winchelsea Lane, Hastings, East Sussex, TN35 4LG. 01424 813 147
- **The National Fragile X Foundation**, P.O. Box 37, Walnut Creek, California, 94597, USA. 800-688-8765
- **FRAXA Research Foundation**, 45 Pleasant St., Newburyport, MA 01950, USA. 978-462-1866

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Randi Hagerman, September 2010



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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.

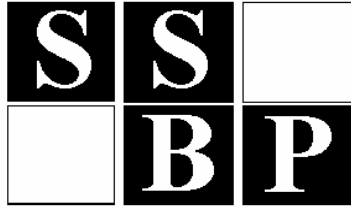
Useful websites/associations for more information

- 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



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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 learning disability 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 injury him or herself using external surfaces, this pattern tends to continue throughout the life-span. If the self-injury involves oral cavity or biting, then this pattern will reoccur throughout the life-span. Forms of self-injury include eye-poking, head banging, fingers in wheelchair spokes, and extension of arms in doorways. Emotional self injury, or outwardly directed aggressive behaviors, include hitting, kicking, head-butting, biting others, spitting, swearing, ethnic slurs, inappropriate remarks to the opposite sex, frequently changing opinions, and/or lying.

Treatment:

Treatment for the behavioral manifestations of LND is multi-modal and should include: 1) judicious use of protective devices, 2) utilization of a behavioral technique commonly referred to as selective ignoring with redirection of activities, and 3) occasional use of medications. The use of medications for treating the behavioral component of this disorder is controversial yet most children and adults with LND are treated with different medications. No medication has been found to reverse the so-called 'Lesch-Nyhan behaviors', either motor or behavioral. Selective ignoring is a methodology that is designed to extinguish self-destructive emotional or physical behavior in the LND patient. It requires the caretaker to ignore such behavior by the LND patient towards said caretaker so that the behavior decreases or ceases. Along with selective ignoring, the use of redirection is also found to be helpful. At times controversial, the use of protective devices is essential, yet often problematic for patients and institutions not familiar with the care of LND patients. Professionals unfamiliar with LND may perceive the use of these protective devices from a traditional paradigm of restraints – which is to say, the use of these devices against a patient's will. When protective devices are requested by the patient -- and used to safeguard the patient from him or herself -- the outcome is an extraordinary feeling of comfort and safety. Not allowing the use of protective devices would violate the autonomous rights of the patient. In Lesch-Nyhan Disease self-injury far exceeds that associated with other developmental disabilities and is a consequence of the neurotransmitter abnormality characterizing the disorder. Although not all individuals with this condition

demonstrate severe behavioral manifestations, it is reasonable to say that all benefit from the use of protective devices at some point during their lifetime.

Recently, Deep Brain Stimulation (DBS) has been tried with several patients with LND in Japan, Switzerland/France, India and the United States. In this procedure neurosurgeons place two stimulators in the basal ganglia, similar to the stimulators used in other movement disorders such as Parkinson's disease. The results suggest a decrease in dystonic movements as well as a decrease in self-injurious behavior. This procedure may very well be an ideal treatment for this disorder.

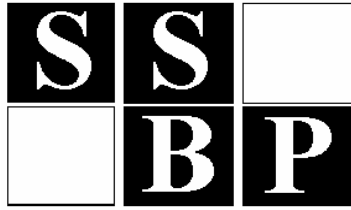
Life expectancy:

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

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Gary E. Edey, 2010



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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:

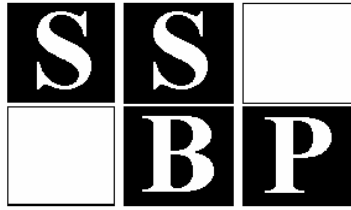
Many patients experience social and behavioural difficulties (Barton & North, 2004). These include communication difficulties and difficulties forming and maintaining friendships. More than half of children with NF1 show significant scholastic difficulties and more than 30% meet criteria for ADHD. NF1 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 intellectual disability (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 dysmorphism (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 intellectual disability is found (Allanson, 2005). Verbal and performatory capacities are divided more or less equally. Language and motor development are often delayed, but are in general no longer dysfunctional in adulthood. Mild attention problems have been found, as well as problems in executive functioning (i.e. slightly diminished organization skills and compromised abilities to structure complex information). As a result, learning difficulties may be present, requiring special educational attention. As described above, social cognitive functions (recognizing and expressing emotions) may be impaired as well (Wingbermühle et al, 2010).

Available management guidelines:

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

More information

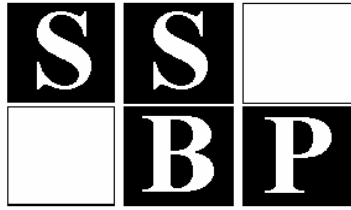
- **www.dyscerne.org**. For the 2010 NS guideline PDF-document as developed by the Dyscerne Network of Centres of Expertise for Dysmorphology.
- **www.ncbi.nlm.nih.gov/omim/163950**. For the information on NS in OMIM, an online database of human genes and genetic disorders.
- **www.noonansyndrome.org**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

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



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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

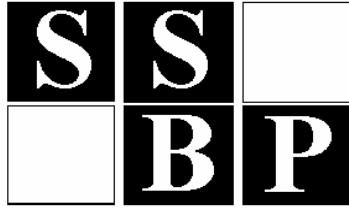
- PWS Association UK <http://pwsa.co.uk/main.php>
- PWS Association USA: <http://www.pwsausa.org/>
- Online Mendelian Inheritance in Man (OMIM):
<http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=176270>

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Sarita Soni, April 2010



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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.

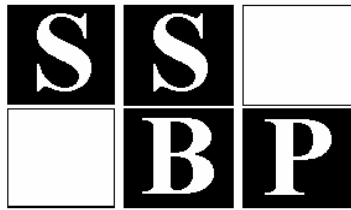
Due to their complex physical and psychological needs these people require careful periodic multidisciplinary assessment and monitoring throughout life. The family or carers also require emotional and physical support. Adequate provision for an individual with Rett Disorder is likely to involve specialist 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



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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:

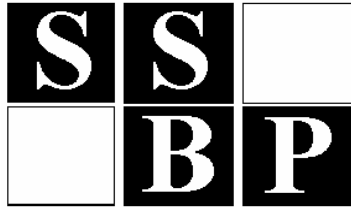
- The Dutch parents' support website: <http://triple-x-syndroom.nl/> . This website shows many links to scientific papers and useful links, e.g. links to international chat pages for parents and triple-X girls/women. Scientific papers and syndrome sheets are available in English, French, Spanish, German 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



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Tuberous Sclerosis Complex (TSC)

First description and alternative names:

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

There is a wide variability of expression. The previously used "diagnostic triad" (of epilepsy, intellectual disability and characteristic facial skin lesions) is seen in only about 30% of people with the disorder. TSC is multi-system and can include hamartomatous growths affecting the brain, skin, kidneys, heart, eyes, teeth, bones, lungs and other organs. About 80% of affected people have a lifetime history of epilepsy. Diagnosis is based on meeting clinical criteria for the disorder (Roach et al., 1998). Mutations are identified in ~80% of individuals with clinically confirmed TSC.

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

Behavioural and psychiatric characteristics:

Tuberous sclerosis complex is associated with high rates of various disruptive behaviours, sleep problems and occasionally self-injurious behaviours. Developmental disorders including autism and autism spectrum disorders (ASD) (40-50%), ADHD and attention-related disorders (30-50%) are seen at high rates. TSC is one of the medical conditions most commonly associated with ASD. In adolescents and adults, very high rates of anxiety and mood-related disorders are reported. Psychotic disorders

should raise the possibility of seizure-related psychopathology (Prather & de Vries, 2004; Kwiatkowski et al., 2010).

Neuropsychological characteristics:

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

Available guidelines for behavioural assessment/treatment/management:

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

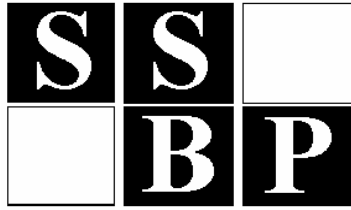
Useful websites/associations for more information:

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

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Petrus de Vries, August 2010



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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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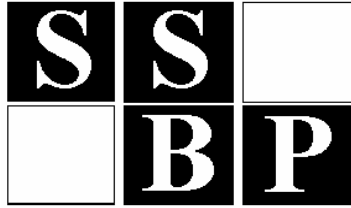
Useful websites/Associations for more information:

- 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



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Velo-Cardio-Facial Syndrome/22q11.2 Deletion 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:

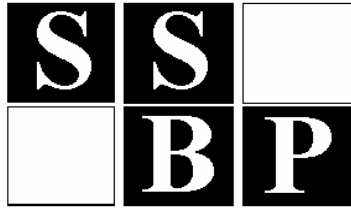
Neuroanatomical differences reported in people with VCFS include an increased incidence of white matter hyperintensities and developmental midline abnormalities (e.g. septum pellucidum defects) (19-20) and a significant reduction in volume of posterior brain structures (especially in the cerebellum, 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



SOCIETY FOR THE STUDY OF BEHAVIOURAL PHENOTYPES

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Wolf- Hirschhorn Syndrome

First description:

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

Genetics and Molecular Biology:

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

Prevalence and Mortality:

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

Physical Features:

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

Behavioral and Neuropsychological characteristics:

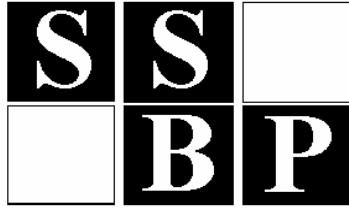
Attention deficits are observed in all subjects and adaptive behavior levels are extremely limited. Children with WHS are more severely impacted (~ 65% are profoundly ID) in both general cognitive ability and overall adaptive behavior skills compared to children with other microdeletions. Among less severely affected children, i.e., those who have expressive language, the profile of mean cognitive abilities and deficits is relatively flat and extends to all cognitive areas tested: verbal, quantitative, and abstract / visual reasoning, and short-term memory. Interestingly, and despite their limitations in cognitive ability and

overall adaptive behavior, children with WHS exhibit relative competence in socialization skills compared to their abilities in other adaptive behavior domains. On the other hand, they often have significant social problems, as assessed by the Conners Parent Rating Scale and Child Behavior Checklist. Limited attention span among children with WHS likely has a negative impact on their short-term memory skills. To that extent, these difficulties are not unique to the WHS phenotype. The proportion of children with WHS with autism or autistic-like features is significantly lower than the rates of autism found in the other subtelomeric disorders such as 2q37, 8p23 and 11q22-25 (Jacobsen syndrome).

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Gene S Fisch, March 2011



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XYY Syndrome

First description and alternative names:

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

Genetics and molecular biology:

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

Incidence/prevalence:

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

Physical features and natural history:

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

Behavioural and psychiatric characteristics:

Individuals with XYY syndrome are at increased risk for behavioural problems and psychiatric disorders. There is a high rate of diagnosis of Attention Deficit Disorder, and increased risk of problems with distractibility, impulsivity and difficulties with temper management. Problems with social relatedness are also common. Individuals with XYY have been reported as having increased scores on measures of autistic spectrum symptoms, although these were within clinically referred populations and may not be indicative of individuals with XYY syndrome overall.

Neuropsychological characteristics:

XYY syndrome is usually associated with normal to slightly diminished cognitive function as measured with IQ; verbal IQ may be more affected than performance IQ. Speech delay is common and many boys require speech therapy and special education. Reading may be particularly affected. Delayed motor development and impaired fine and gross motor function have been reported. Educational performance may be more adversely affected than what would be expected based on IQ measures alone. Difficulties with attention and impulse control are frequently reported.

Available guidelines for behavioural assessment/treatment/management:

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

Useful websites/associations for more information

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

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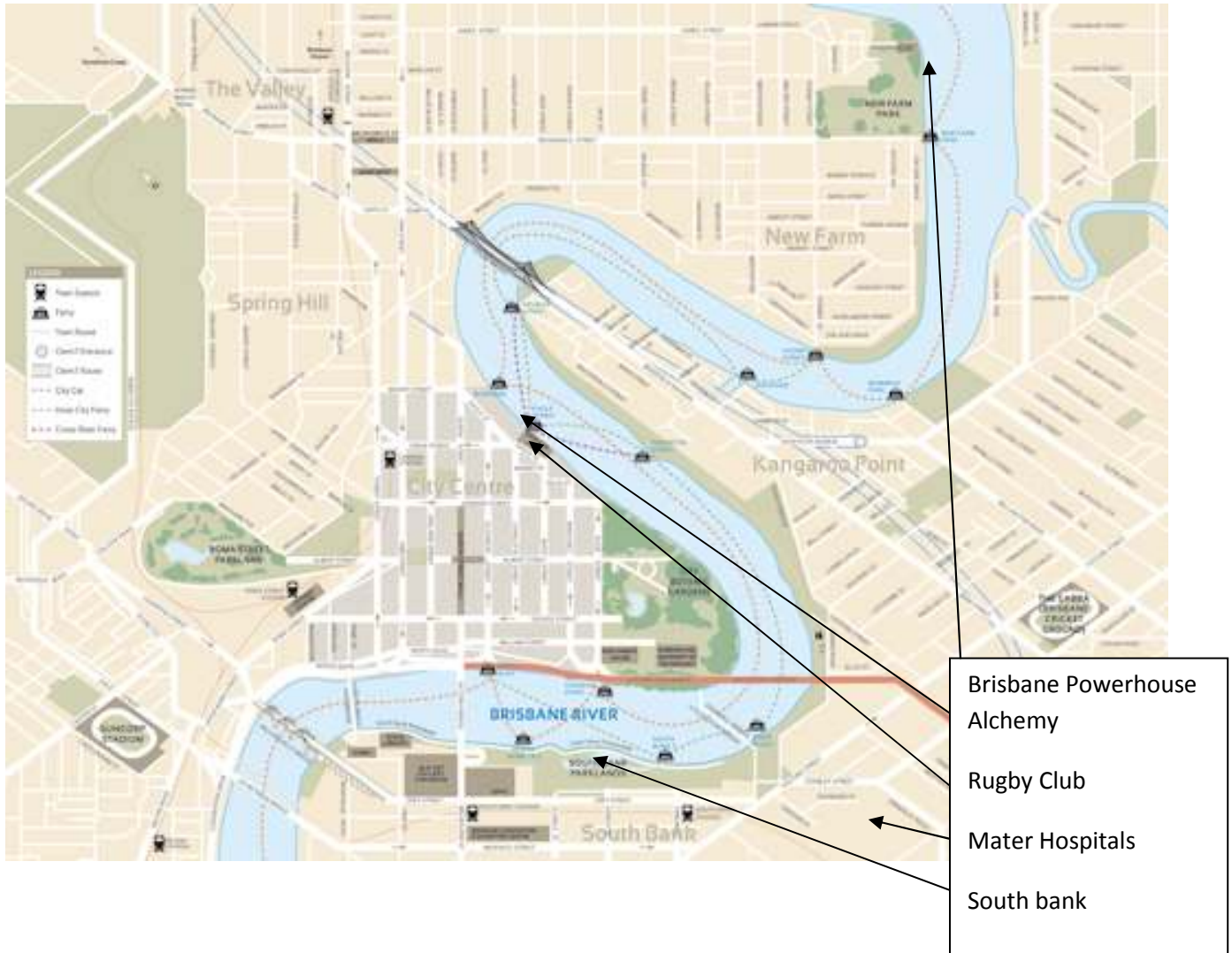
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Rhoshel K Lenroot, 2010

The Strand at Rugby Quay is conveniently located in the heart of Brisbane's CBD on Eagle Street. Positioned directly adjacent to the Riverside Centre, this stylish event centre is located in the city's newest landmark riverside redevelopment known as Rugby Quay.

LOCATION

The Strand at Rugby Quay
Plaza Level, Rugby Quay
123 Eagle Street
Brisbane Queensland 4000



ACCESS BY RIVER

Conveniently located next to the Riverside Centre, adjacent to Brisbane CBD's main CityCat ferry terminal, access by river provides another unique experience for event arrival and departures. For ferry transfer information or private group charters, please contact the following -

Brisbane CityCat

<http://www.translink.qld.gov.au/>

Ph: 07 3229 7778 - Riverside Terminal

Brisbane Cruises

<http://www.brisbanecruises.com.au/>

Ph: 07 3630 2666 - Private Charters available

ACCESS BY RAIL.

Brisbane main railway station, Central Station, is located within an easy 10 minute walk from The Strand at Rugby Quay. Simply turn right into Creek Street (off Ann Street) and follow for three blocks. Turn left into Eagle Street and The Strand at Rugby Quay is approx 100 metres on the right. For the latest Brisbane train timetables, please contact the following -

Qld Rail - Citytrain

<http://www.citytrain.com.au/>

Ph: 07 3606 5555 - General Enquiries

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The Strand at Rugby Quay is conveniently surrounded by numerous public car parks providing hundreds of paid parking bays, all within a few minutes walk of the centre. For parking locations and fees, please contact the following -

Wilson Car Parking

<http://www.wilsonparking.com.au/>

Ph: 07 3233 0700 - Brisbane Head Office

Kings Car Parking

<http://www.kingsparking.com.au>

Ph: 07 3232 2800