# 18th SSBP International Research Symposium
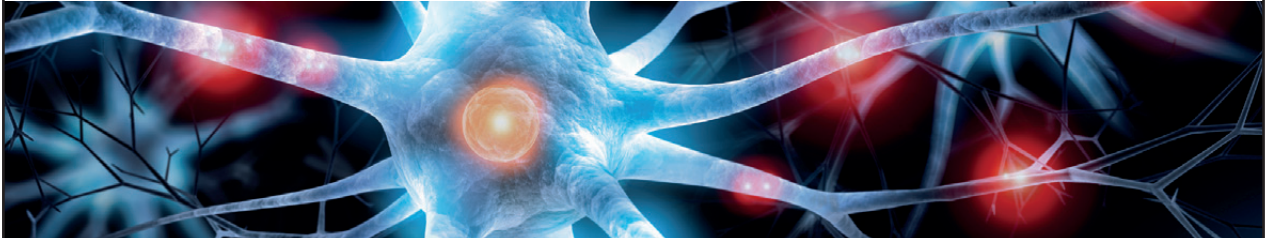
*Behavioural Phenotypes from bench to bedside: translation of basic science to clinical practice*

## Programme Book

3rd – 5th September 2015 • London, UK

**The Society for the Study**

**of Behavioural Phenotypes**

**3rd – 5th September 2015**

# The 18th SSBP International Research Symposium

# Behavioural Phenotypes
# from bench to bedside:
## translation of basic science to clinical practice

## London, UK

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# Welcome to London

We are pleased to welcome you to the 18th Society for the Study of Behavioural Phenotypes International Research Symposium and Continuing Education and Keynote day held in London, one of the strongest medical research sectors in the world.

Dating back over 2000 years, London's history can be traced as far back as Iron Age Trinovantum tribe inhabiting the area around the Thames River. Later the area was to be inhabited by Roman occupiers who gave it its name, before becoming established as a mediaeval capital of England, and it has continued to be the main city in the UK.

University College London was formed in 1826, under the name London University, as a secular alternative to the religious universities of Oxford and Cambridge. Boasting now almost 30 Nobel prize laureates it is one of the centres of excellence for learning in the UK.

The 18th SSBP Research Symposium aims to build on prior meetings by focusing on translation of an increasingly deeper scientific understanding of behavioural phenotypes to clinical practice. The symposium cover animal research and genetic mechanisms and epigenetic modifications while maintaining a focus on clinical phenotypes through neuroimaging and advances in technology in medicine, leading to refinement of diagnostic criteria and intervention updates. Thus we aim to move from the bench to the bedside, and back again, and trust that scientists and clinicians and students will be enriched by a deliberate cross-fertilisation of knowledge and ideas.

**Raja Mukherjee and Andre Strydom**
*Conference Co-ordinators*

# London Conference Organisers

### Dr Raja Mukherjee

**Dr Raja Mukherjee** is an Adult Learning Disability Consultant Psychiatrist for Surrey and Border's Partnership NHS Foundation Trust, with interest in the management of developmental disorders across the lifespan. He is an Honorary Senior Lecturer at St George's. Having worked with Jeremy Turk for 18 Months in his Child and Adolescent LD team, he continues to see and advise local colleagues on the behavioural management of children and adults with Developmental disorders across the lifespan.

In September 2009 he started the first NHS based specialist Fetal Alcohol Spectrum Disorders behavioural clinic and since then has seen over 100 cases for specialist second opinion. The clinic is currently being expanded to offer more comprehensive national opinion on the diagnosis and behaviour management of FASD.

Dr Mukherjee completed his PhD on the subject of Fetal Alcohol Syndrome in 2014. He has also acted as an invited advisor to the BMA board of science, The Department of Health and the World Health Organisation on the subject of FASD. He continues to be an active member of the international scientific panel on FASD for NOFAS UK and for the international conference held biannually in Vancouver and the European meetings related to FASD. Alongside colleagues he has helped set up the first Professional network in the UK for FASD to improve training and knowledge about the subject. Dr Mukherjee is also part of the Royal College of Psychiatrist special interest group on Adult Autism.

### Dr Andre Strydom

**Dr André Strydom (MRCPsych, MSc, PhD)** is a Reader in Intellectual Disabilities at UCL's Faculty of Brain Sciences (Division of Psychiatry) and a Consultant Psychiatrist in Developmental Disabilities. His research is focused on the epidemiology and genetic aetiology of mental disorders in adults with neurodevelopmental conditions, and the development and evaluation of interventions to reduce associated morbidity. He is particularly interested in ageing-related conditions such as dementia in adults with Intellectual Disability and Down syndrome. Dr Strydom is the chief investigator of the LonDownS consortium which is exploring the neurobiological aetiology of Alzheimer's disease in Down syndrome. He is also involved in developing and evaluating complex interventions in adults with ID such as health checks for people with intellectual disabilities in primary care.

# Scientific Committee

**Patricia Howlin**
*Emeritus Professor of Clinical Child Psychology*
Department of Psychology, King's College, London, UK
*Professor of Developmental Disorders*
Brain & Mind Research Institute, University of Sydney, Australia

**Leopold Curfs**
*Director, Governor*
Kremers Centre, Maastricht University Medical Centre,
Department of Genetics, Maastricht University Medical Centre,
The Netherlands

**Kieran O'Malley**
*Child and Adolescent Psychiatrist*
Slievemore Clinic, Dublin, Ireland

**Stephan Huijbregts**
*Assistant Professor*
Leiden Institute for Brain and Cognition/
Department of Clinical Child and Adolescent Studies,
Leiden University, The Netherlands

**Andre Strydom**
*Reader in Intellectual Disabilities*
Division of Psychiatry, Faculty of Brain Sciences,
University College London, London

**Raja Mukherjee**
*Consultant Neurodevelopmental Psychiatrist*
FASD Specialist behaviour Clinic and Adult Autism Service,
Surrey and Borders Partnership NHS Foundation Trust, UK

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# The SSBP

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

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

## The SSBP Executive Committee :

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

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| | *Andre **Strydom*** (UK) (a.strydom@ucl.ac.uk) |
| | *Flora **Tassone*** (USA) (ftassone@ucdavis.edu) |

### Committee : International Representatives

**Europe** – *Leopold Curfs* (Maastricht) (leopold.curfs@maastsrichtuniversity.nl)
**Australia** – *Stewart Einfeld* (Sydney) (s.einfeld@usyd.edu.au)
**USA (East Coast)** – James Harris (Baltimore) (jharrisd@jhmi.edu)
**USA (West Coast)** – Randi Hagerman (Sacramento) (randi.hagerman@ucdmc.ucdavis.edu)
**Africa** –*Lorna Jacklin* (Johannesburg) (jacklin@netactive.co.za)
**Global** –*Pat Howlin* (London) (patricia.howlin@kcl.ac.uk)

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| **Administrator** | *Elizabeth Walmsley* (ssbpliz@gmail.com) |
| **Conference Administrator** | *Rebecca Windram* (conference@ssbp.org.uk) |
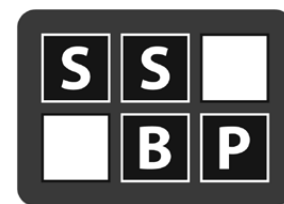
## Meetings of the SSBP

| | | |
|---|---|---|
| 1991 | Kings Fund, London, UK | Workshop |
| 1992 | Welshpool, UK | 2nd International |
| 1993 | Royal Society of Medicine, London, UK | 4th Annual |
| 1994 | Maastricht, The Netherlands | 3rd International |
| 1995 | Edinburgh, UK | 6th Annual |
| 1996 | Dublin, Ireland | 4th International |
| 1997 | Cambridge, UK | 7th Annual |
| 1998 | Baltimore, USA | 5th International |
| 1999 | Birmingham, UK | 8th Annual |
| 2000 | Venice, Italy | 6th International |
| 2001 | Oxford, UK | 9th Annual |
| 2002 | Whistler, Canada | 7th Scientific |
| 2003 | Newcastle, UK | 10th Annual |
| 2004 | Barcelona, Spain | 8th International |
| 2005 | Cairns, Australia | 9th International |
| 2006 | Dublin, Ireland | 11th Annual |
| 2007 | MIND Institute, Sacramento & Lake Tahoe, USA | 10th International |
| 2008 | Cologne, Germany | 11th International |
| 2009 | Cambridge, UK | 12th International |
| 2010 | Pavia, Italy | 13th International |
| 2011 | Brisbane, Australia | 14th International |
| 2012 | Leuven, Belgium | 15th International |
| 2013 | Stellenbosch, South Africa | 16th International |
| 2014 | New York, USA | 17th International |

## Forthcoming Meetings of the SSBP

| | | |
|---|---|---|
| 2015 | London, United Kingdom | 18th International |
| 2016 | Siena, Italy | 19th International |

# Tom Oppé and the Tom Oppé Distinguished Lecture

## Tom Oppé

Tom Ernest Oppé (1925 – 2007) was Professor of Paediatrics at St Mary's Hospital Medical School, University of London, between 1969 and 1990. Over this period he built up a large and respected department. He had a wide range of clinical and research interests, but had a particular passion for the abnormal behaviours associated with genetic syndromes.

Oppé was born in London and was educated at University College School and Guy's Hospital, qualifying with distinction in 1947. He did his national service in the Navy, where a colleague had a child with Williams syndrome. Many believe that this was where Tom's interest in behavioural phenotypes was first stimulated.

After some years at Great Ormond Street, a research fellowship at Harvard and 2 years in Bristol, he returned to St Mary's Hospital (where he had worked as Lecturer in Child Health), and stayed at St Mary's for the rest of

his professional career. He was awarded a CBE in 1984 for services to paediatrics and child health.

Tom was a founder member of the SSBP in 1987 and became Life President of the Society in 2001. He died in 2007 aged 82. This lecture is dedicated to his memory in appreciation for his work for the SSBP and for children with genetic and developmental disorders.

## Tom Oppé Lecturers

| | |
|---|---|
| 2015 | Michael Rutter |
| 2014 | Stewart Einfeld |
| 2013 | Patricia Howlin |
| 2012 | Chris Oliver |
| 2011 | Tony Holland |
| 2010 | Randi Hagerman |
| 2009 | Alcino Silva |
| 2008 | Hans-Christoph Steinhausen |
| 2007 | Petrus J de Vries |

## 2015 Tom Oppé Distinguished Lecturer: Professor Sir Michael Rutter



Michael Rutter has been a consultant psychiatrist at the Maudsley Hospital since 1966. He became the first UK Professor of Child Psychiatry from 1973 –1998 and is now Professor of Developmental Psychopathology. He set up the MRC Child Psychiatry Research Unit and the Social, Genetic and Developmental Psychiatry Centre. His research has included studies of school and family influences on children's behaviour; and the European and Romanian adoptee (ERA) studies on the effects of severe deprivation. He has a special interest in the interplay between genetic and psychosocial risk factors.

He is a Fellow of the Royal Society and a Founding Fellow of the Academia Europaea and the Academy of Medical Sciences. Professor Rutter has published around 500 scientific papers, and over 50 books.

# Patricia Howlin and the Patricia Howlin Prize Lecture

## Patricia Howlin

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

## Pat Howlin Prize Lecture:

### Area of Research:

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

### Eligibility of applicants:

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

## Award Procedure:

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

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

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

## Patricia Howlin Lecturers

| | |
|---|---|
| 2015 | Supriya Malik |
| 2014 | Hayley Crawford |
| 2013 | Mary Heald |
| 2012 | Sheena Grant |
| 2011 | Leah Bull |
| 2010 | Debbie Allen |

## 2015 Pat Howlin Lecturer: Supriya Malik

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

Supriya Malik earned her BA (Hons) in Psychology from University of Delhi, India, and her MSc in Developmental Psychology from Lancaster University, UK. She has trained in several clinical and educational settings and has over 7 years of experience in working with children with neurodevelopmental disorders such as Autism, ADHD, Learning Disability etc. both in Delhi and London. She has keen interest in interventions for children with autism and is a certified consultant for Relationship Development Intervention® (RDI), a comprehensive intervention programme for individuals with autism. Ms. Malik started a centre for children with autism in Delhi, Southend Nurturing Connections, in 2010 and is also currently pursuing her PhD at the University of Birmingham, studying effects of play-based intervention on brain and behavioural functioning in young children with autism.

# Sponsors

**The SSBP is extremely grateful to the Castang Foundation and the Genetics Society for their sponsorship of SSBP 2015 in London.**
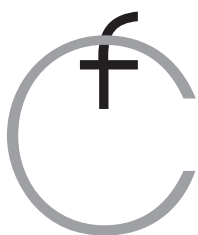
**Castang Foundation**

**the geneticssociety**

**The SSBP is pleased to acknowledge the following journals as media partners for 2015:**

**BBF BEHAVIORAL AND BRAIN FUNCTIONS**

BBF: Behavioral and Brain Functions

*Biology of Mood & Anxiety Disorders*

Biology of Mood & Anxiety Disorder

THE LANCET Psychiatry

The Lancet Psychiatry

*Molecular Autism*
**Brain, Cognition and Behavior**

Molecular Autism
Brain, Cognition and Behavior

# Keynote Speaker Profiles

*(in order of presentation)*

## Professor Mark Good

Mark Good graduated with a Psychology degree from the University of London in 1983 and subsequently studied for a PhD at York University, investigating the cognitive functions of the avian hippocampus. In 1990, Good undertook a postdoctoral position with Prof. Richard Morris FRS (University of Edinburgh) examining the role of the rodent hippocampus in memory. In 1994, Good was appointed as a lecturer at Cardiff University where he continued his work testing theories of hippocampal function in animals and also began evaluating cognitive function in rodent models of human psychological disorders. Good was awarded a personal chair in 2007.

## Professor David Skuse

David Skuse is head of the Behavioural and Brain Sciences Unit at the Institute of Child Health, University College, London and an Honorary Consultant in Developmental Neuropsychiatry to Great Ormond Street Hospital for Children.

He is an academic and clinical child psychiatrist, whose approach to research is quintessentially interdisciplinary, and translational. He has fostered a range of current national and international research collaborations, ranging from basic science (e.g. genetic influences, neuropeptides, and metabolic disorders) through epidemiology (especially with the Avon Longitudinal Study of Parents and Children; ALSPAC), to clinical applications (e.g. assessment procedures for autistic disorders).

## Professor Nessa Carey

Nessa Carey worked for 10 years at the forefront of epigenetic drug discovery, at TopoTarget, CellCentric and Pfizer. She is a former academic at Imperial College, where she is now a Visiting Professor. Nessa has served on a number of committees for UK research councils and is International Director at PraxisUnico, the UK organisation for technology transfer specialists. She is the author of the popular science books The Epigenetics Revolution and Junk DNA: A Journey Through The Dark Matter Of The Genome.

## Dr Paramala Santosh

Dr Paramala Santosh is a Consultant Child & Adolescent Psychiatrist who developed and heads the Centre for Interventional Paediatric Psychopharmacology and Rare Diseases (CIPPRD) at the Maudsley Hospital, London. Dr Santosh is a Visiting Reader at the Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London, and focuses on translational research. He is recognised as an international expert on Autism, developmental psychopharmacology, neuropsychiatry, paediatric neurodegeneration, suicidality, and the use of information technology to improve health delivery. He has conducted research into the overlap of Autism, ADHD, and Bipolar Disorder; psychopharmacology and paediatric neurodegeneration in the context of Hunter syndrome, Hurler syndrome, Sanfillipo disease, Gaucher disease, Neiman-Pick Type C, Rett syndrome, and other diseases. He re-analysed data from the Multimodal Treatment study of ADHD (MTA) using a European perspective, and assisted in improving European guidelines. He is recognised as an expert in the field of assessment and management of complex multiple co-occurring developmental disorders and is currently involved in research of comorbidity in Autism Spectrum Disorders, its assessment and management.

Dr Santosh obtained his MD in Psychiatry from the Post-Graduate Institute of Medical Science and Research (PGIMER), Chandigarh, India; subsequently completed his Psychiatry training at Guy's Hospital; specialised in Child & Adolescent Psychiatry from the Maudsley Hospital, London. He became a Consultant in 2002 at the Maudsley and Guy's Hospitals, moved to Great Ormond Street Hospital for Children, London, in 2004, to set up the Centre for Interventional Paediatric Psychopharmacology (CIPP), and the CIPP moved to the Maudsley Hospital, London in 2012. CIPPRD is involved in assessing and managing children and adolescents with severe and complex treatment-resistant neuropsychiatric disorders including Autism Spectrum Disorders, childhood bipolar disorders, childhood dementias, epilepsy related psychiatric comorbidity, post-head injury syndromes and children with severe physical illness or serious psychotropic induced side-effects. He continues his focus on translational research.

## Professor Annette Karmiloff-Smith

Previously a simultaneous interpreter with United Nations organizations, Annette Karmiloff-Smith has a "Doctorat en Psychologie Génétique et Expérimentale" from the University of Geneva, where she studied with the famous Swiss psychologist, Jean Piaget. She worked for two years in the Palestinian refugee camps of Shatilla and Bourj-el-Barajneh from 1970–1972. She is the author of 13 books and of over 300 chapters and articles in scientific journals, as well as a series of booklets for parents on different aspects of foetal, infant and child development. Until she officially "retired" in 2003, she was Head of the Neurocognitive Development Unit at the Institute of Child Health in London. She currently holds a Professorial Research Fellowship at the Birkbeck Centre for Brain and Cognitive Development, University of London. Her research on neurodevelopmental syndromes focuses on identifying basic-level deficits in early infancy and their cascading effects over developmental time on the resulting neuro-cognitive phenotype. Annette has two grown-up daughters, seven grandchildren and three cats, and lives with her scientist-husband between a studio in Bloomsbury and a large barn in Hertfordshire.

## Professor David Nutt

David Nutt is currently the Edmund J Safra Professor of Neuropsychopharmacology and Head of the Centre for Neuropsychopharmacology in the Division of Brain Science, Dept. of Medicine, Hammersmith Hospital, Imperial College London. He is also visiting professor at the Open University in the UK and Maastricht University in the Netherlands.

After 11+ entry to Bristol Grammar he won an Open Scholarship to Downing College Cambridge, then completed his clinical training at Guy's Hospital London. After a period in neurology to MRCP he moved to Oxford to a research position in psychiatry at the MRC Clinical Pharmacology Unit where he obtained his DM. On completing his psychiatric training in Oxford, he continued there as a lecturer and then later as a Wellcome Senior Fellow in psychiatry. He then spent two years as Chief of the Section of Clinical Science in the National Institute of Alcohol Abuse and Alcoholism in NIH, Bethesda, USA. He returned to England in 1988 to set up the Psychopharmacology Unit in Bristol University, an interdisciplinary research grouping spanning the departments of Psychiatry and Pharmacology before moving to Imperial College London in December 2008 where he leads a similar group with a particular focus on brain imaging especially PET.

He is currently President of the European Brain Council and Chair of the Independent Scientific Committee on Drugs (ISCD) and Past-President of the British Neuroscience Association. In addition he is a Fellow of the Royal Colleges of Physicians, of Psychiatrists and of the Academy of Medical Sciences. He is also the UK Director of the European Certificate and Masters in Affective Disorders Courses and a member of the International Centre for Science in Drug Policy. He has edited the Journal of Psychopharmacology for over fifteen years and acts as the psychiatry drugs advisor to the British National Formulary. He has published over 400 original research papers, a similar number of reviews and books chapters, eight government reports on drugs and 27 books including one for the general public Drugs without the hot air, which won the Transmission book prize in 2014.

Previously he has been member and Chair of the Advisory Committee on the Misuse of Drugs (ACMD – 1998 –2009), President of the British Association of Psychopharmacology (BAP), President of the European College of Neuropsychopharmacology (ECNP), member of the HEFCE/NHS Senior Lecturer Selection Panel and member of the MRC Neuroscience Board. Other previous national contributions include serving as the medical expert on the Independent Inquiry into the Misuse of Drugs Act (2000 Runciman report), and membership of the Committee on Safety of Medicines, the Committee on NHS drugs and the Ministry of Defence Science Advisory Board. He was the clinical scientific lead on the 2004/5 UK Government Foresight initiative "Brain science, addiction and drugs" that provided a 25-year vision for this area of science and public policy and in 2006 he was Director of Bristol Neuroscience.

He broadcasts widely to the general public both on radio and television; highlights include being a subject for The Life Scientific on BBC radio 4, several BBC Horizon programs and the Channel 4 documentary Ecstasy-live. Additionally is much in demand for public affairs programs on therapeutic as well as illicit drugs, their harms and their classification. His also lecturers widely to the public as well as to the scientific and medical communities at the Cheltenham Science and Hay Literary Festivals, Café Scientifiques and Skeptics in the Pub. In 2010 The Times Eureka science magazine voted him one of the 100 most important figures in British Science, and the only psychiatrist in the list. In 2013 he was awarded the John Maddox Prize from Nature/Sense about Science and in 2014 his Book "Drugs: without the hot air" won the Transmission Prize for Communication of Ideas.

## Professor Richard Festenstein

Richard Festenstein is Professor of Molecular Medicine at Imperial College, is an Associate of the MRC Clinical Sciences Centre, Epigenesys Network (FP7) and Honorary consultant in Neurogenetics at Imperial College Health Care Trust and the National Hospital for Neurology and Neurosurgery, Queen Square, London. He undertook his clinical training in London and his PhD at the National Institute for Medical Research where he showed that mammalian Locus Control Regions could overcome position effects by preventing the archetypal epigenetic gene silencing known as position effect variegation. Uncovering a link between epigenetic gene silencing and DNA repeat-expansion diseases, Professor Festenstein has recently provided proof-of-concept in humans for a novel and radical epigenetic approach for the currently incurable and frequently devastating disease Friedreich's ataxia.

## Professor Jaqueline Crawley

Jacqueline N. Crawley, Ph.D., is a Professor in the Department of Psychiatry and Behavioral Sciences and the Robert E. Chason Endowed Chair in Translational Research at the MIND Institute, University of California Davis School of Medicine, in Sacramento, California, USA. Her behavioral neuroscience laboratory employs mouse models of neuropsychiatric and neurodevelopmental disorders to investigate biological mechanisms and evaluate potential treatments. Currently her research program focuses on understanding the consequences of genetic mutations in autism spectrum disorders, and discovering medical therapeutics for the fundamental symptoms of autism. The three-chambered social approach assay for sociability, and the light/dark exploration assay for anxiety-related behaviors, are among the methods developed by the Crawley lab for the behavioral phenotyping of new mouse models with mutations in genes identified in human diseases. Animal models with strong construct validity and high face validity are employed as preclinical tools for testing pharmacological targets implicated by the risk genes. Dr. Crawley received a B.A. in Biology from the University of Pennsylvania, Ph.D. in Zoology from the University of Maryland, conducted postdoctoral research in Neuropsychopharmacology at Yale University School of Medicine, was Chief of the Laboratory of Behavioral Neuroscience at the National Institute of Mental Health Intramural Research Program in Bethesda, Maryland, and moved to the MIND Institute in 2012. She has published over 250 papers and 100 reviews, and serves on 16 editorial boards and numerous scientific advisory committees. Honors include the IBNS Myers Lifetime Achievement Award in Behavioral Neuroscience, IBANGS Distinguished Scientist Award in Behavioural Genetics, NIMH Director's Award, and Gladstone Institute of Neurological Disease Distinguished Scholar Award. Her sole author book, What's Wrong With My Mouse? Behavioral Phenotyping of Transgenic and Knockout Mice, is widely used by the biomedical research community.

## Professor Sébastien Jacquemont

Sébastien Jacquemont is a professor of medical genetics at the University hospital of St. Justine and holds a Swiss national foundation assistant professorship as well as Canadian research chair. SJ was trained as a clinical geneticist and subsequently completed a research fellowship in developmental pediatrics at the University of California, Davis where he developed expertise in FMR1-related disorders. His strong interest in translational research has led him to work, in collaboration with Novartis Pharma, and many other investigators to conduct some of the first targeted clinical trials in patients with Fragile X syndrome. SJ is also investigating the impact of gene dosage on neurodevelopment. In collaboration with a large consortium, he has shown that genomic rearrangements at the 16p11.2 modulate energy imbalance, cognition, brain growth and specific neuroanatomical structures. SJ is currently investigating, gene-dosage effects at other related genomic loci using multimodal approaches integrating cognition, behavior, neuroimaging, transcriptomics and genomics.

## Professor Tony Charman

Prof. Charman holds the Chair in Clinical Child Psychology at the Institute of Psychiatry, Psychology & Neuroscience, King's College London. His main research interest is the investigation of social cognitive development in children with autism and the clinical application of this work via screening, diagnostic, epidemiological, intervention, and 'at risk' studies. He is a Chartered Clinical Psychologist and works in a specialist service for children with autism and complex neurodevelopmental conditions at the South London and Maudsley NHS Foundation Trust. He has published more than 200 peer-reviewed papers and over 30 book chapters. He has served on a number of expert panels for the Medical Research Council and NICE in the UK, NIH in the USA and the WHO. He has worked closely with Ambitious about Autism, the National Autistic Society, Research Autism and Autistica to advocate for services and positive policy development for individuals with autism spectrum disorders and their families.

# Conference Programme

**Venue:** Sir Ambrose Fleming Lecture theatre (G06), Roberts Building, University College London (UCL)

## Continuing Education and Keynote Day

| **Day One:** Thursday 3$^{rd}$ September 2015 | |
|---|---|
| 08:30–09:30 | **Registration and coffee** |
| 09:30–9:40 | **Welcome from the Conference Organisers** |
| **Thursday Morning Session:** (Chair: *Andre Strydom*) | |
| 09:40–10:35 | **Keynote 1:** *Professor Mark Good* – Evaluating Cognitive and Affective Function in Mouse Models of Alzheimer's Disease and Downs Syndrome. |
| 10:35–11:30 | **Keynote 2:** *Professor David Skuse* – Optimizing diagnostic criteria for Autism Spectrum Disorders. |
| 11:30–12:00 | **Morning Refreshments** |
| 12:00–12:55 | **Keynote 3:** *Professor Nessa Carey* – Epigenetic Mechanisms in Developmental Disorders. |
| 13:00–14:00 | **Lunch** |
| **Thursday Afternoon Session:** (Chair: *Raja Mukherjee*) | |
| 14:00–14:55 | **Keynote 4:** *Dr Paramala Santosh* – Behavioural Phenotypes that can be Pharmacologically Targeted in Rare Diseases – The Centre for Interventional Paediatric Psychopharmacology and Rare Diseases (CIPPRD) Model. |
| 15:00–15:55 | **Keynote 5:** *Professor Annette Karmiloff-Smith* – What can babies with Down syndrome possibly tell us about Alzheimer's dementia in adults? |
| 16:00–16:30 | **Afternoon Refreshments** |
| 16:30–17:25 | **Keynote 6:** *Professor David Nutt* – Can we use Neuro-imaging to Develop New Treatments for Developmental Disorders? |
| 19:00–21:00 | **Conference Reception.** Hunterian Museum, 35 - 43 Lincoln's Inn Fields, Royal College Of Surgeons, London WC2A 3PE (See page 167 for map and directions) |

## Research Symposium

| **Day Two:** Friday 4th September 2015 | |
|---|---|
| 08:00–09:00 | **Registration & Coffee** |
| 09:00–09:10 | **Welcome** |

**Session I:** (Chair: *Leopold Curfs*) 4 Research presentations (15 + 5min Q&A)

| | |
|---|---|
| 09:10 –09:50 | **Keynote 7:** *Professor Richard Festenstein* – Overcoming Triplet-repeat Mediated Epigenetic Silencing in Humans |
| 09:50–11:10 | **Talk 1:** *Bassett A.S.* – Fetal Growth and Gestational Factors as Predictors of Schizophrenia in 22q11.2 Deletion Syndrome |
| | **Talk 2:** *Harris J.C.* – Does the Behavioural Phenotype of Lesch-Nyhan Disease/Lesch Nyhan Variant Disorder Correlate best with Hprt or Gprt Enzyme Activity? |
| | **Talk 3:** *Rietman A.B.* – Sensory Processing in Children with Neurocognitive Syndromes |
| | **Talk 4:** *Tassone F.* – Molecular Biomarkers for Targeted Treatments in Fragile X Syndrome |
| 11:10–11:30 | **Morning Refreshments** |

**Session II :** (Chair: *Stephan Huijbregts*) 4 Short research presentations (10 + 2min Q&A)

| | |
|---|---|
| 11:30–12:10 | **Keynote 8:** *Professor David Skuse* – Intellectual Disability and Mental Health: Assessing Genomic Impact on Neurodevelopment |
| 12:10–13:00 | **Talk 5:** *McDonald-McGinn D.M.* – 22q11.2 Duplication Syndrome: Another Important CNV Window into Understanding Behavioural Phenotypes |
| | **Talk 6:** *Rihel J.* – Identifying Small Molecule Regulators of Behavioural Phenotypes in a Zebrafish Model of Autism Spectrum Disorder |
| | **Talk 7:** *Baker K.* – Next-Generation Phenotyping in Intellectual Disability  – What can Gene Function Predict? |
| | **Talk 8:** *Libura M.* – Sense of Coherence, Parental Burnout and Coping with Stress in Mothers of Children with Prader-Willi, Mothers of Children with Intellectual Disabilities and Mothers of Healthy Children |
| 12:40–13:30 | **Lunch** <br><br> **Poster viewing** |

## Day Two: Friday 4th September 2015

**Session III:** (Chair: *Flora Tassone*) 4 Research presentations (15 + 5min Q&A)

| | |
|---|---|
| 14:00–15:20 | **Talk 9:** *Hagerman R.J.*– Can We Reverse Intellectual and Behavioural Problems in Adults with FXS? |
| | **Talk 10:** *Gray K.M.* – N-acetylcysteine in Children with Autism: a Randomised, Double-Blind, Placebo Controlled Trial |
| | **Talk 11:** *McAlonan G.* – Pharmacological Modulation of Brain Excitatory/ Inhibitory Balance in Autism Spectrum Disorder |
| | **Talk 12:** *de Vries P.J.* – TSC-Associated Neuropsychiatric Disorders (TAND): Baseline Data from the TOSCA International Disease Registry |
| 15:25–15:45 | **Afternoon Refreshments** |

**Session IV:** (Chair: *Petrus de Vries*) 5 Rapid-fire oral presentations (5+1min Q&A)

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|---|---|
| 15:40–16:00 | **Talk 13: Pat Howlin Prize Lecture:** *Malik S.* – Pilot Randomised Controlled Trial of the Effects of Reciprocal Imitation Training on Children with Autism |
| 16:00–16:40 | **Talk 14:** *Eddey G.E.* – Dosing Allopurinol in Patients with Classic Lesch-Nyhan Disease/ Syndrome to Eliminate Uric Acid and Xanthine Nephrolithiasis |
| | **Talk 15:** *Fiksinski A.M.* – Autism Spectrum and Psychosis Risk in the 22q11.2 Deletion Syndrome. Findings from a Prospective Longitudinal Study |
| | **Talk 16:** *Hall J.H.*– The Tc1 Mouse Model of Trisomy-21 Dissociates Properties of Object Recognition Memory |
| | **Talk 17:** *Leonard H.* – Need for a New International Rare Disease Database: The MECP2 Duplication Syndrome |
| | **Talk 18:** *Adams D.* – Challenging Behaviour, Chronic Health Problems and Health Related Quality of Life in Cornelia de Lange, Cri du Chat and Angelman Syndrome |
| 16:40–17:40 | **Talk 19: Tom Oppé Lecture:** *Professor Sir Michael Rutter* – What Genetics has Taught Us about Developmental Disabilities |
| 17:40–18:40 | **Poster Viewing** |
| 20:00 – 23:00 *19:30 for 20:00* | **Gala Dinner:** Royal College of General Practitioners, 30 Euston Square, NW1 2FB (See page 168 for map and directions) |

## Day Three: Saturday 5th September 2015

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| 08:30–09:00 | **Registration and coffee** |

**Session V :** (Chair: *Randi Hagerman*) 4 Research presentations (15 + 5min Q&A)

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|---|---|
| 09:00–09:40 | **Keynote 9:** *Professor Jacqueline Crawley* – Mouse Models of Autism to Understand Causes and to Discover Treatments |
| 09:40–11:00 | **Talk 20:** *Raznahan A.* – Parallel Neuroimaging-Genomics of Sex Chromosome Aneuploidy in Humans and Mice |
| | **Talk 21:** *McQuillin A.* – The Influence of Copy Number Variation Burden on Behavioural and Psychiatric Symptoms in ID |
| | **Talk 22:** *Goh P.* – Modelling Neural Pathology and Dementia in Down Syndrome using Induced Pluripotent Stem Cells |
| | **Talk 23:** *Trickett J.* – Sleep in Children with Neurodevelopmental Disorders |
| 11:00–11:30 | **Morning Refreshments** |
| 11:30–12:30 | **SSBP AGM and Award Ceremony** |
| 12:30–13:30 | **LUNCH** |

**Session VI :** (Chair: *Patricia Howlin*) 5 Short research presentations (10 + 2min Q&A)

| | |
|---|---|
| 13:30–14:10 | **Keynote 10:** Professor Sébastien Jacquemont - Gene Dosage Effects at the 16p11.2 Genomic Region |
| 14:10–15:10 | **Talk 24:** *McKenna R.* – Informing the Structure of Executive Function in Children: A Meta-Analysis of Functional Neuroimaging Data |
| | **Talk 25:** *McEwen F.S.* – Psychiatric Outcomes in Tuberous Sclerosis Complex (TSC): Autistic Traits and Autism Spectrum Disorder (ASD) in the TS2000 Cohort Study |
| | **Talk 26:** *Moss J.* – Changes in Autism Spectrum Disorder Characteristics in Cornelia de Lange and Cri du Chat Syndromes: Results from a Seven Year Follow-Up |
| | **Talk 27:** *Von Gontard A.* – Incontinence in Persons with Down Syndrome |
| | **Talk 28:** *Courtenay K.* – Mental Health Care in Smith Magenis Syndrome: Case Series |
| 15:10–15:30 | **Afternoon Refreshments** |
| 15:30–16:30 | **Keynote 11:** *Professor Tony Charman* – Getting Answers from Babies about Autism |
| 16:30 | **Close of Research Symposium** |

# Abstracts for Continuing Education and Keynote day: *(in order of presentation)*

## KEYNOTE 1: Evaluating Cognitive and Affective Function in Mouse Models of Alzheimer's Disease and Downs Syndrome.

*Good M.*

*School of Psychology, Cardiff University*

Mouse models of human cognitive disorders are an important tool in efforts to understand the mechanisms of both cognitive and non-cognitive impairments and their potential treatments in human disorders. The ability to link genetic alterations in mice to behavioural changes requires careful consideration of the brain systems likely influenced by the disorders and the nature of the psychological changes under investigation. In this presentation, I will consider behavioural methods for interrogating different aspects of memory function and affective processes in mouse models of amyloid pathology and Downs syndrome. The nature of the memory and hedonic brain systems will be considered and examples provided of behavioural tests that can be used to assess, e.g., episodic-like memory and recognition memory and changes in affective or hedonic processes in mice.

**Keywords:** Memory, hedonic, episodic, Downs syndrome, Alzheimer's

## KEYNOTE 2: Optimizing diagnostic criteria for Autism Spectrum Disorders

*Skuse D.*

*Head of Behavioural and Brain Sciences, Institute of Child Health, University College, London*
*Honorary Consultant in Developmental Neuropsychiatry, Great Ormond Street Hospital for Children.*

In the 70 years since the condition of autism was first formally described, there has been an exponential rise in its apparent prevalence, from <4 per 10,000 to 200+ per 10,000 children in the latest US surveys. Neuroscientists, and more recently geneticists, have sought evidence for an underlying dysfunctional developmental process, a unifying aetiology to explain the collection of symptoms conventionally used to describe the autism phenotype. That very phenotype has recently been redefined by DSM-5 (as Autism Spectrum Disorder) and ICD-11's definition will be closely similar. Neither diagnostic system adequately addresses the potential bias against ascertainment in females, in part because of the inevitable reliance upon a search for historical and observational material derived from a male stereotype. We do not have diagnostically useful biomarkers for ASD.

Increasing pressure on clinical services has led to major changes in the assessment of ASD in the UK. No longer regarded as a 'mental health disorder' by psychiatrists, community paediatricians are nowadays tasked with evaluating suspected cases. Unwilling to engage in a lengthy structured interview, they increasingly employ brief questionnaires and the ADOS. Lack of adequate training, and inherent biases in the instruments employed, has led to widespread under- and over-diagnosis. How do we optimise the diagnostic process, given these practical and policy-related constraints?

## KEYNOTE 3: Epigenetic Mechanisms in Developmental Disorders

*Carey N.*

*PraxisUnico; Visiting Professor at Imperial College*

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The establishment of the appropriate epigenetic modifications is an essential requirement during development. Drawing on a range of human conditions and experimental findings, this presentation will focus on how defects in the establishment of appropriate epigenomes can lead to a range of developmental disorders from severe Mendelian learning disabilities to more subtle adult conditions influenced by foetal programming.

**Keywords:** epigenetics; development; retardation; chromatin; delay

# KEYNOTE 4: Behavioural Phenotypes That Can Be Pharmacologically Targeted In Rare Diseases – The Centre For Interventional Paediatric Psychopharmacology And Rare Diseases (CIPPRD) Model

*Santosh P.J.*

*Head and Consultant Child & Adolescent Psychiatrist, Centre for Interventional Paediatric Psychopharmacology and Rare Diseases (CIPPRD), Child and Adolescent Mental Health Services, Michael Rutter Centre, Maudsley Hospital, South London and Maudsley NHS Foundation Trust*

*Visiting Reader in Developmental Neuropsychiatry & Psychopharmacology, Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London*

*Honorary Consultant Child & Adolescent Psychiatrist, Great Ormond Street Hospital for Children, London*

*Honorary Consultant Child & Adolescent Psychiatrist, Tadworth Children's Trust for Neurorehabilitation, Tadworth, Surrey*

Many rare diseases with neurological involvement present with co-occurring overactivity, irritability, aggression, inattention, oppositional and defiant behaviour, anxiety, perseveration, autonomic dysfunction, disinhibition and mood lability. The presentation will focus on Rett Syndrome and Mucopolysaccharidoses and discuss strategies that are currently used in CIPPRD.

A careful assessment to identify the role of bio-psycho-social factors that influence psychopharmacological outcomes is essential before prescribing. Baseline target symptom monitoring and target setting for the response expected is essential to ensure optimized response. Symptoms such as inattention, impulsivity, hyperactivity, tics, obsessions and psychosis may respond largely to medication alone. Symptoms such as aggression, rituals, self-injury, anxiety and depression are likely to require both medication and other forms of management. Symptoms that are unlikely to respond to medication and need specific remediation include skill deficits in academic or social domains, though there are experimental drugs showing some promise. The aim is to choose and adjust medication that achieves maximum benefit with minimum adverse effects. Detailed Profile of Treatment Response (POTR) ratings longitudinally allow for individualized pharmacological decision-making.

The presentation will discuss symptom- and disorder-based prescribing and will discuss long-term consequences of prescribing as well as not prescribing. Cumulative side-effect morbidity-based decision-making will be discussed. Severity and type of symptoms, developmental stage, multi-system involvement, and the profile of past treatment response will be used in the model to individualize treatment. Apart from symptom management using typical psychotropic medications, the emerging research on disease-modifying biological agents and their potential will be discussed.

**Keywords:** Rett Syndrome, Mucopolysaccharidoses, Sanfilippo, Pharmacotherapy, Rare Diseases, POTR

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## KEYNOTE 5: What can babies with Down syndrome possibly tell us about Alzheimer's dementia in adults?

*Karmiloff-Smith A.*

*Professorial Research Fellow, Centre for Brain & Cognitive Development, Birkbeck, University of London*

It may seem paradoxical to focus on babies when attempting to understand a disease only apparent in adulthood, but I have always argued that the only way to understand a phenotypic endpoint at the neural, cognitive, behavioural or environmental levels is to trace its developmental trajectory from infancy onwards. By age 30, 100% of individuals with Down syndrome (DS) present with the amyloid-beta plaque brain pathology of Alzheimer's disease, because of the trisomy of the APP gene on chromosome 21. Yet not all of them go on to develop the clinical symptoms of dementia, despite life expectancy having increased significantly in recent decades. What protects those who don't? The aim of the project that I will present during this talk is to identify, already in infancy, individual differences in DS that might explain the protective and risk factors for subsequent dementia, by comparing the study of infants with DS, over a very broad genetic, cellular, neural, cognitive, behavioural and environmental protocol, with the study of adults with DS who do or do not have Alzheimer's disease.

**Keywords:** Down syndrome; infants/toddlers; Alzheimer's disease; risk/protective factors; cognition; biomarkers

## KEYNOTE 6: Can We Use Neuro-Imaging to Develop New Treatments for Developmental Disorders?

*Nutt, D.*

*Imperial College, London, UK*

Neuro-imaging using PET and fMRI is revolutionising our understanding of brain disorders, but has not been applied with similar efforts to study developmental disorders. Currently PET tracers allow the identification of over twenty neurotransmitter receptor systems in the brain and this research has thrown light on the brain mechanisms of dementia, addiction, schizophrenia, depression and anxiety to name just a few disorders. FMRI techniques have identified the brain circuits involved in many cognitive processes, particularly memory and executive function and also the impact of drug treatments on these.

Many of the developmental disorders are thought to involve similar neurotransmitter systems. For example, Down's syndrome is believed to be due to Alzheimer's disease like changes in amyloid deposition that can now be imaged with PET tracers such as PIB. Alterations in serotonin and dopamine function are theoretically possible in autism and related disorders yet have still to be studied with the range of serotonin PET tracers available. Molecular preclinical research in rodent models of other developmental disorders, such as Fragile X, have identified glutamate and GABA targets for possible interventions and some trials have been conducted.

The most exciting data at present relates to Down's Syndrome where credible rodent models of this trisomy syndrome have shown that the memory impairment is due to excessive inhibition in the hippocampus. Moreover this excess inhibition can be reversed by a GABA receptor inverse agonist that is selective for the a5 subtype which is highly localised in the hippocampus. This has led to trials of one such compound in adults with Down's and the result of these studies should be available soon.

**Keywords:** PET; fMRI; Down's syndrome; GABA

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

## KEYNOTE 7: Overcoming Triplet-Repeat Mediated Epigenetic Silencing in Humans

*Festenstein, R.*

*Professor of Molecular Medicine, Division of Brain Sciences, MRC Clinical Sciences Centre Associate, Imperial College, London W12 0NN*

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A growing number of currently incurable neurodegenerative diseases are being shown to be caused by the pathological expansion of repetitive DNA sequences. Our basic research on the mechanism whereby such repetitive DNA sequences can epigenetically silence genes in vivo, opened up the possibility that diseases caused by such a mechanism may be sensitive to epigenetic modifiers which has subsequently spawned a whole new field of research. Focusing on Friedreich's ataxia as a prototypic example we showed that the pathological epigenetic silencing of the Frataxin gene could be partially restored to asymptomatic carrier levels firstly in primary cells from patients and most recently in a proof-of-concept study in patients using high doses of the histone deacetylase inhibitor, nicotinamide (Vitamin B3), where we also established safety. The potential impact of this finding is that nicotinamide or other histone deacetylase inhibitors, by ameliorating the deficiency of Frataxin, may provide a radical epigenetic therapy for this currently incurable and frequently devastating progressive disease by halting its progression and that other diseases caused by a similar mechanism such as Fragile X may also be amenable to a similar approach.

**Keywords:** Epigenetic gene silencing, triplet repeat diseases, histone deacetylase inhibitors, Friedreich's ataxia, Fragile X

## TALK 1: Fetal Growth and Gestational Factors as Predictors of Schizophrenia in 22q11.2 Deletion Syndrome

*Van L.1, Butcher N.J.[1], Costain G.[1], Ogura L.[1], Chow E.W.C.[1,2] and* **Bassett A.S.**[1,2,3]

[1] *Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, Canada.*

[2] *Department of Psychiatry, University of Toronto.*

[3] *Dalglish Family Hearts and Minds Clinic, and Toronto General Research Institute, University Health Network, Toronto, Canada.*

**Background:** Schizophrenia occurs in 20 to 25% of adults with 22q11.2 deletion syndrome (22q11.2DS). General population studies of schizophrenia report associations with perinatal complications, although effect sizes are generally low. We aimed to determine whether such factors are associated with expression of schizophrenia in individuals with 22q11.2DS.

**Methods:** We investigated the relationship of small for gestational age (SGA) birth weight (<3rd percentile for sex and gestational age) and prematurity (<37 weeks gestation) to expression of schizophrenia in a well-characterized cohort of 123 adults with 22q11.2DS. Outcome measures included adjusted odds ratios and positive and negative predictive values for schizophrenia.

**Results:** SGA birth weight (odds ratio = 3.52, 95% confidence interval = 1.34, 9.22) and prematurity (odds ratio = 5.38, 95% confidence interval = 1.63, 17.75), but not maternal factors, were significant risk factors for schizophrenia in 22q11.2DS. Being born SGA or premature resulted in a positive predictive value of 46% for schizophrenia; negative predictive value in the absence of both features was 83%. Post hoc analyses suggested these perinatal complications were also associated with factors indicative of increased severity of schizophrenia.

**Conclusion:** In 22q11.2DS, fetal growth and gestation may have a clinically significant impact on future risk for schizophrenia. These data advance our understanding of determinants of disease-specific expression in 22q11.2DS, with implications for other genomic disorders.

**Keywords:** copy-number variation; 22q11 deletion; genetic counselling; intrauterine growth restriction; prematurity; schizophrenia.

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## TALK 2 : Does the Behavioural Phenotype of Lesch-Nyhan Disease/Lesch Nyhan Variant Disorder Correlate Best with Hprt or Gprt Enzyme Activity?

*Harris J.C.[1], Ward R.[1], Callon W.[1], Fu R.[2], Jinnah H.[2] and Schretlen D.[1]*
*[1] The Johns Hopkins University School of Medicine, Baltimore, MD 21287 USA.*
*[2] Emory University School of Medicine. Atlanta, Georgia 30322 USA.*

**Background:** Lesch-Nyhan disease (LND) is a rare, X-linked recessive neurogenetic syndrome caused by deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGprt), an important enzyme in the purine salvage pathway. HGprt recycles both hypoxanthine and guanine. There is a distinct behavioural phenotype. The respective roles of Hypoxanthine phosphoribosyltransferase (Hprt) versus Guanine phosphoribosyltransferase (Gprt) in producing the behavioural phenotype is unclear with some evidence pointing to hypoxanthine recycling and other evidence pointing to guanine recycling.

**Methods:** To clarify the respective roles of these enzymes we selectively assayed hypoxanthine (Hprt) and guanine (Gprt) recycling in both LND and in attenuated variants (LNV) cases. We assayed skin fibroblasts from 17 persons with LND, 11 with an attenuated variant of the disease (LNV), and 19 age-, sex-, and race-matched healthy controls (HC). Thirty-six participants (76.6%) are Caucasian, 7 (14.9%) are African-American, 2 (4.3%) are Hispanic, and the other 2 did not state their race. The sample includes only males.

**Results:** Activity levels of both enzymes differed across groups ($p<0.0001$), however, only Gprt distinguished patients with LND from those with LNV ($p<0.05$). Moreover, Gprt showed higher correlations than Hprt based on 13 of 14 measures of the clinical behavioural phenotype. These included severity of the dystonic movement disorder, patterns of neurocognitive impairment, and behavioural features measured on standardized rating scales.

**Conclusion:** These findings suggest that loss of guanine recycling may be more closely linked to the LND/LNV phenotype than loss of hypoxanthine recycling. These finding are consistent with possible links of Guanosine Triphosphate. (GTP) depletion to impaired G-protein function. GTP depletion resulting from Gprt loss may affect dopamine synthesis pathways. Moreover dystonia is found in both LND and autosomal dominant GTP cyclohydrolase I deficiency (Segawa disease).

**Keywords:** Lesch Nyhan Disease, Lesch Nyhan Variant, behavioural phenotype, dystonia, Gprt, Hprt.

## TALK 3: Sensory Processing in Children with Neurocognitive Syndromes

*Rietman A.B.[1], Oostenbrink R.[1], Nicholson B.A.[1], Plasschaert E.[2], Descheemaeker M.J.[2], Legius E.[2] and De Wit M.C.Y.[1]*

[1] Erasmus MC Sophia Children's Hospital ENCORE, Rotterdam, the Netherlands.
[2] Catholic University Leuven, Centre for Human Genetics, Leuven, Belgium.

**Background:** Sensory processing (SP) refers to the processing of, and reaction to, sensory information from body and environment. Impairments in this neurological process lead to maladaptive behaviours, including being over-excitable or under-responsive to sensory stimuli. The purpose of the current study was to investigate the prevalence and nature of SP problems in children with Neurofibromatosis type 1 (NF1), Tuberous Sclerosis Complex (TSC), and Angelman Syndrome (AS).

**Methods:** In a cross-sectional retrospective design, data were collected on children with NF1, TSC, or AS participating in clinical trials or visiting outpatient clinics of expertise centres for genetic neurocognitive developmental syndromes in the Netherlands and Belgium between 2011 and 2014. Primary outcome measure was parent-rated SP problems, as measured by the Dutch version of the Short Sensory Profile (SSP-NL) (Dunn, 2006). Additionally, data were collected on disease characteristics, intelligence, emotional and behavioural problems.

**Results:** In total, 142 children were included (age 6y 10mo; 71 boys and 71 girls): 86 with NF1, 32 with TSC, and 24 with AS. Serious problems in sensory processing were found in 27% of children with NF1, 34% of children with TSC, and 67% of children with AS, compared to 5% of a normative sample. Children with NF1 had more problems processing auditory stimuli; children with TSC with auditory and tactile stimuli; children with AS with movement sensitivity. Lower intelligence and epilepsy were associated with more SP problems. Problems with auditory filtering or tactile sensitivity predicted internalizing emotional and behavioural problems. Problems with auditory filtering and visual/auditory sensitivity, and fewer problems with movement sensitivity, were associated with externalizing problems.

**Conclusion:** There is a high prevalence of sensory processing problems in these children with neurocognitive syndromes, which are partly similar between syndromes, but there are also syndrome-specific SP problems. Some of these problems clearly contribute to emotional and behavioural problems.

**Keywords:** Sensory processing; Neurofibromatosis type 1 (NF1); Tuberous Sclerosis Complex (TSC); Angelman Syndrome (AS); Sensory profile; Behavioural problems.

## TALK 4: Molecular Biomarkers For Targeted Treatments In Fragile X Syndrome

*Tassone F.[1, 2], Pretto D.[1], Yrigollen C.[1], Durbin-Johnson B.[3] and Hagerman R.J.[2, 4]*

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[3] *Department of Public Health Sciences University of California Davis, California, USA.*

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**Background:** An important goal in the research of neurodevelopmental disorders is the development of biomarker profiles to be used for prediction of disease and for monitoring response to a treatment. One of the well-studied neurodevelopmental disorders is Fragile X syndrome (FXS) caused by the lack of expression of the *FMR1* protein (FMRP). Increased knowledge about the role of FMRP, particularly from recent advances in animal models of FXS, has paved the way to target treatments for FXS. The results of several studies have demonstrated that the lack of FMRP leads to dramatic altered protein production in the CNS with up-regulation of the mGluR5 and down-regulation of the GABA$^A$ pathways in addition to dysregulation of a number of other molecular pathways influenced by FMRP, including the Serotonin Receptor Signaling. However, results from several targeted treatment controlled trials for FXS in humans have suggested some positive but also mixed signals due to a large variability in treatment response but also partly to the lack of validated outcome measures.

**Methods:** We have carried out a blinded controlled trial of low-dose sertraline, for a six-month period, in young children with FXS and investigated candidate blood biomarkers. These included matrix metalloproteinase 9, amyloid-beta, brain-derived neurotrophic factor (BDNF), and genetic variants of genes involved in the serotonin pathway that could predict treatment response to sertraline, providing a foundation for individualized treatment based on the biomarker profile.

**Results:** Preliminary data demonstrates a significant effect of sertraline treatment on the Clinical Global Impressions-Improvement scale. In addition, they indicates that the response to sertraline differed significantly by BDNF genotype (P = 0.020) and 2D6 genotype (P = 0.011).

**Conclusion:** The identification of biomarkers in peripheral blood is of importance as it can provide new insights potentially leading to the development of new therapies for neurodevelopmental disorders.

**Keywords:** clinical trial, molecular biomarker, SSRI.

## KEYNOTE 8: Intellectual Disability and Mental Health: Assessing Genomic Impact on Neurodevelopment

*Skuse D.*

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*Honorary Consultant in Developmental Neuropsychiatry, Great Ormond Street Hospital for Children.*

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To date, we know little about the specific behavioural and emotional difficulties associated with intellectual disabilities caused by minor structural anomalies of the genome (copy number variants – CNV). The IMAGINE programme of research, funded by the MRC and MRF, aims to identify genomic, environmental and developmental factors that are predictive of mental health outcomes in childhood and, subsequently, in early adulthood, within a large sample of this population (up to 10,000 subjects).

The programme involves the pragmatic but systematic NHS-based ascertainment and online parent-reported phenotyping of a national representative sample of individuals with CNV-associated ID (~10–15% of the ID population overall), and deep phenotyping of selected subsets of individuals with high-risk CNVs based on existing literature and online results. The IMAGINE cohort and datasets will generate extensive opportunities for future collaborative translational research. The study began in April 2014 and has proved to be highly successful in recruitment of both volunteers and families identified through Regional Genetic Centres. Online phenotyping is a realistic and efficient methodology for identifying patterns of behaviour that are associated with specific CNVs.

## TALK 5: 22Q11.2 Duplication Syndrome: Another Important CNV Window into Understanding Behavioural Phenotypes

*McDonald-McGinn D.M.*[1,2], *Wenger T.*[3], *Dicairano L.*[1], *Schlechtweg K.*[1], *Grand K.*[1], *Krajewski A.*[1], *McGinn D.E.*[1], *Schultz R.*[1,2], *Emanuel B.S.*[1,2] *and Zackai E.H.*[1,2]

[1] The Children's Hospital of Philadelphia.
[2] The Perelman School of Medicine of the University of Pennsylvania.
[3] Seattle Children's Hospital.

**Background:** Chromosome 22q11.2 copy number variants (CNV) are well-described entities involving deletions and duplications as the result of unequal meiotic crossovers causing aberrant interchromosomal exchanges due to the presence of low copy repeats which flank the deletion/duplication defining the breakpoints. Although expected to occur with equal frequency due to this common underlying mechanism, 22q11.2 deletions purportedly occur twice as often as duplications. However, a 2015 prenatal report examining 10,000 pregnancies using BACS-on Beads technology, identified 22q11.2 deletions and duplications in <1/1000 foetuses. Suggesting under-ascertainment for both CNV but in particular the duplication. This is noteworthy in light of the high prevalence of associated behavioural phenotypes, in particular autism spectrum disorder (ASD), and the lower overall prevalence of congenital anomalies.

**Methods:** Here we present 97 subjects with 22q11.2 duplications identified using FISH, MLPA or microarrays, specifically cataloguing duplication size; clinical findings; and familial variability.

**Results:** In addition to identifying developmental delay/cognitive deficits (62%) and associated medical problems such as congenital heart disease (33%) and seizures (17%), we observed an elevated prevalence of ASD in males (52%) versus females (20%), often with macrocephaly.

**Conclusion:** 22q11.2 duplication syndrome is similar to 22q11.2 deletion syndrome in many ways: the etiologic mechanism; CNV size (A-D in 83% dup v. 85% del); and associated medical features, albeit less common. However, until the recent survey study, the 22q11.2 duplication has been identified half as frequently as the deletion. Perhaps signifying that patients with duplications are less likely to come to CNV diagnosis as their features frequently mirror those seen in the general ASD population, specifically macrocephalic males without concomitant medical issues, as our data suggests. Thus, 22q11.2 duplication syndrome is an important and perhaps under-diagnosed cause of ASD in the general population that may well provide a larger window towards understanding behavioural phenotypes in general.

**Keywords:** 22q11.2 Duplication CNV Anticipatory Guidance.

## TALK 6: Identifying Small Molecule Regulators of Behavioural Phenotypes in a Zebrafish Model of Autism Spectrum Disorder

*Hoffman E.J.[1,2], Turner K.J.[3], Fernandez J.M.[1,2], Ghosh M.[3], Wilson S.W.[3], **Rihel J.**[3], State M.W.[1,4,5] and Giraldez A.J.[4]*

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[2] *Program on Neurogenetics, Yale School of Medicine, New Haven, CT 06510, USA.*

[3] *Department of Cell and Developmental Biology, University College London, Gower St., London WC1E 6BT, UK.*

[4] *Department of Genetics, Yale University School of Medicine, New Haven, CT 06510, USA.*

[5] *Department of Psychiatry, University of California San Francisco, San Francisco, CA 94143, USA.*

**Background:** Autism spectrum disorders (ASD) are a collection of often devastating neurodevelopmental syndromes that affect 1 in 68 children. Despite rapid advances in the ability to identify ASD risk genes, the underlying pathophysiological mechanisms remain uncertain, limiting the development of targeted pharmacotherapies. To establish a phenotyping pipeline for rapid behaviour and small molecule screening, we have developed zebrafish mutants in ASD risk genes. Here we report the generation and characterization of zebrafish mutants of Contactin Associated Protein-like 2 (Cntnap2), a member of the neurexin family of cell adhesion molecules linked to ASD in humans.

**Methods:** Using zinc finger nucleases, targeted deletions were generated in the zebrafish *cntnap2a* and *cntnap2b* genes, and homozygous mutants were generated by breeding. These mutants were subjected to a battery of high-throughput behavioural tests for seizure and sleep/wake phenotypes using automated tracking software in a 96-well plate format. To test the effect of small molecules on wild type and mutant behaviours, compounds (1nM to 50 µM) were diluted directly in the fish water.

**Results:** Zebrafish *cntnap2* paralogs are highly expressed in the CNS during early development, particularly in the forebrain. Analysis of *cntnap2* mutants reveals GABAergic deficits in the ventral telencephalon. We observed that cntnap2 mutants are hypersensitive to drug-induced seizures and identified night-time hyperactivity as a key sleep/wake phenotype in mutants. Comparing this phenotype by cluster analysis to wild type drug-induced phenotypes, we found that estrogenic compounds significantly anti-correlate with the behavioural fingerprint of *cntnap2* mutants. In particular, this screen identified the phytoestrogen, biochanin A, as a strong and specific rescuer of the *cntnap2* mutant hyperactivity phenotype, with no sedation during the day.

**Conclusion:** Together, these results demonstrate how brain structural, behavioural and pharmacological analysis of zebrafish mutants of ASD risk genes can rapidly identify novel pathways for further pre-clinical investigation in ASD.

**Keywords:** autism spectrum disorder, zebrafish, chemical genetics, behavioural analysis, sleep.

## TALK 7: Next-Generation Phenotyping in Intellectual Disability – What can Gene Function Predict?

*Baker K.[1,3], Scerif G.[2], Astle D.A.[3] and Raymond F.L.[1]*

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[2] *Department of Experimental Psychology, University of Oxford.*
[3] *MRC Cognition and Brain Sciences Unit.*

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**Background:** It is increasingly possible to identify a genetic cause of intellectual disability (ID). However very little is yet known about the specific behavioural and cognitive problems associated with each rare cause. This presentation will illustrate the challenges and opportunities of phenotyping in newly-discovered rare causes of ID, focusing on a post-synaptic gene functional network. Pathogenic variants in Membrane-Associated Guanylate Kinase (MAGUK) genes cause ID and have been associated with neuropsychiatric risk in the non-ID population. Our study aimed to determine whether risk for psychiatric symptoms is elevated amongst individuals with ID due to MAGUK gene mutations, and whether specific cognitive differences are associated with disruption to this gene functional network.

**Methods:** This study addresses these two questions via behavioural questionnaires and cognitive testing, applying quantitative methods previously validated in populations with ID. We compared males with X-linked ID caused by mutations in three MAGUK genes (PAK3, DLG3, OPHN1; n=9) to males with ID caused by mutations in other X chromosome genes (n=17).

**Results:** Groups did not differ in age, global cognitive impairment, adaptive function, or epilepsy prevalence. However, individuals with MAGUK gene mutations demonstrated significantly higher psychopathology risks, comprising elevated total problem behaviours, prominent hyperactivity, and elevated scores on an autism screening checklist. Despite these overt difficulties, individuals in the MAGUK group performed more accurately than expected for age and IQ on computerised tests of visual attention, convergent with mouse models of MAGUK loss-of-function.

**Conclusions:** Our findings support a role for MAGUK genes and post-synaptic actin dynamics in influencing cognitive parameters relevant to psychiatric risk. In addition to establishing clear patterns of impairment for this group, our findings highlight the importance of careful phenotyping after genetic diagnosis, showing that gene functional network disruptions can be associated with specific psychopathological risks and cognitive differences within the context of ID.

**Keywords:** Intellectual disability, genetics, cognition, psychiatric disorders.

## TALK 8: Sense of Coherence, Parental Burnout and Coping with Stress in Mothers of Children with Prader-Willi, Mothers of Children with Intellectual Disabilities and Mothers of Healthy Children

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**Background:** The aim of this study was to examine differences in the sense of coherence, stress coping and parental burnout between mothers of children: with Prader-Willi syndrome (PWS), with intellectual disabilities (ID) and healthy controls (HC) and to examine correlations between these variables.

**Methods:** The study involved 97 women aged 32 to 75. Mothers of children with PWS were members of the Prader-Willi Syndrome Association, mothers of children with ID were recruited from participants of occupational therapy workshops in Warsaw, while mothers of HC worked in various companies in Warsaw. The following questionnaires were used: SOC-29, CISS and Parental Burnout.

**Results:** Mothers of children with PWS and HC had a higher sense of manageability than comprehensibility and meaningfulness while in mothers of children with ID the levels of comprehensibility and manageability were the same or higher than the sense of meaningfulness. All mothers exhibited similar patterns of coping with stress, scoring significantly higher on task oriented style. The study revealed significant differences in parental burnout. Mothers of children with developmental disorders had higher levels of emotional exhaustion and cynicism than mothers of healthy children, the two groups did not differ, though, on parental incompetence scale. In addition, mothers of HC had significantly lower levels of emotional exhaustion than mothers of children with PWS and a lower level of cynicism than mothers of children with intellectual disabilities. As expected, there was a significant positive correlations between overall coherence and task-oriented style and a significant negative correlation between coherence and emotion- oriented style.

**Conclusion:** The study did not confirm the hypotheses that significant differences exist in the sense of coherence and stress coping styles between mothers of children with developmental disorders and mothers of healthy children. However, the study revealed specific profiles of coherence dimensions, differentiating the compared groups.

**Keywords:** Prader-Willi syndrome, mental retardation, sense of coherence, parental burnout syndrome, coping with stress.

## TALK 9: Can We Reverse Intellectual and Behavioral Problems in Adults with FXS?

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**Background:** Although the short-term controlled trials with the mGluR5 antagonist AFQ056 were not efficacious in adult and adolescent patients with fragile X syndrome (FXS), researchers were hopeful that improvements could be seen in long-term open-label studies.

**Methods:** Adults with FXS who underwent a controlled trial of AFQ056 were offered enrolment in an open-label trial with flexible dosing from 25 mg up to 100 mg twice a day.

**Results:** 148 adults (10 females) with a mean age of 26.6 (SD 6.85) were enrolled in this open-label trial (91% of the patients having completed the earlier controlled trial). The median exposure was 546.5 days per patient (overall: 218 patient years). Gradual improvements were seen over time in Aberrant Behavior Checklist-Community (ABC-C) and Clinical Global Impressions-Improvement (CGI-I) scores, although patient numbers decreased over time (1/4 dropped) causing a retention bias. By 52 weeks, there were 100 patients on the study, and 5% were very much improved, 34% much improved, 43% minimally improved, 15% no change, and 3% minimally worse in terms of CGI-I scores. AFQ056 was generally safe, although 58.8% had an adverse event (AE) possibly related to AFQ056 (41.5% in 100 mg bid vs 20% or less in other doses). The most common AEs were insomnia (15.5%), aggression (8.8%), dizziness (6.8%), and headache (6.8%). Serious AEs occurred in 7 patients (4.7%).

**Conclusion:** AFQ056 was generally well tolerated and safe. Gradual improvements were seen in ABC and CGI scores. In CGI-I scores, 30–40% of patients were showing *much improved* or *very much improved* outcomes over time. However, we do not know if cognitive improvements were seen, because cognitive measures were not utilized. It is recommended that future studies combine a targeted treatment to strengthen synaptic connections with a learning/cognitive intervention and cognitive/brain-based outcome measures so both behavioural and cognitive benefits can be seen in long-term clinical trials.

**Keywords:** Fragile X syndrome, open-label trial, AFQ056, neurodevelopmental, mGluR5, intellectual disabilities.

## TALK 10: N-acetylcysteine in Children with Autism: A Randomised, Double-Blind, Placebo Controlled Trial

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**Background:** The underlying genetic, environmental, and biochemical factors have latterly been an increasing focus in autism spectrum disorder. Oxidative stress, inflammation and heavy metal chelation have been implicated in the aetiology of autism. N-acetylcysteine (NAC) has been shown to modulate these pathways, providing a rational to trial NAC as a treatment for autism. There are two published pilot studies suggesting efficacy, particularly in symptoms of irritability. This study aimed to test if NAC is a useful treatment for autism in children.

**Methods:** This was a placebo-controlled, randomised clinical trial of 500 mg/day oral NAC for 6 months, in addition to treatment as usual, in children with a DSM-IV-TR diagnosis of Autistic Disorder. The primary outcomes were communication skills (Children's Communication Checklist; CCC-2), social interaction skills (Social Responsiveness Scale; SRS), and repetitive behaviours (Repetitive Behavior Scale; RBS-R). Secondary outcomes were behaviour and emotional problems (Developmental Behaviour Checklist), and parent/clinical global impressions (Parent Global Impression – Improvement scale, Clinical Global Impression – Improvement scale, Clinical Global Impression – Severity scale). Additionally, demographic data, the parent-completed Vineland Adaptive Behavior Scales, Social Communication Questionnaire and clinician-administered Autism Diagnostic Observation Schedule were completed. The trial was registered in the Australian New Zealand Clinical Trials Registry (ACTRN12610000635066).

**Results:** A total of 102 children with autism were randomised into the study, and 98 (79 male, 19 female; age range: 37–119 months) attended the baseline appointment with their parent/guardian. Assessments were conducted at 4, 12, and 24 weeks. The results of the intention to treat analyses will be reported, evaluating the impact of NAC on the primary and secondary outcomes.

**Conclusion:** The results of this clinical trial will be discussed, relative to the other existing trials of NAC in young people with autism, alongside the strengths and limitations of the study.

**Keywords:** autism, randomised clinical trial, N-acetylcysteine (NAC).

## TALK 11: Pharmacological Modulation of Brain Excitatory/ Inhibitory Balance in Autism Spectrum Disorder

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**Background:** There are no pharmacological treatments for the core symptoms of Autism Spectrum Disorder (ASD). However, accumulating evidence suggests an imbalance between excitatory (E) glutamate and inhibitory (I) GABA in ASD; and may explain the early promise of proGABA and anti-glutamate drugs such as riluzole. Here we tested the hypothesis that, compared to unaffected controls, individuals with ASD have differences in the E/I response to a riluzole drug challenge.

**Methods:** 50mg of riluzole or matched placebo was administered orally in a randomised, double blind, crossover design, 1 hour before scanning. MEGAPRESS proton magnetic resonance spectroscopy ([1H]-MRS) was used to measure concentrations of Glx (glutamate + glutamine) and GABA in the frontal lobe and subcortex of men with and without ASD. An inhibitory index was calculated as GABA/(GABA+Glx). Whole brain resting-state fMRI (rs-fMRI) data was acquired as an indirect measure of E/I influence on widespread brain networks. A significance threshold of $p < 0.05$ was adopted for all analyses.

**Results:** Subcortical GluX was significantly lower in men with ASD compared to controls at baseline (placebo); Riluzole significantly increased the inhibitory index in the subcortex of both groups ($p = 0.02$). However, in the prefrontal cortex, riluzole increased the inhibitory index in the ASD group only ($p=0.04$). Post-hoc testing suggested that increases in inhibitory indices in both groups were driven by increased GABA. Differences in frontal lobe connectivity in ASD appeared normalized by riluzole.

**Conclusion:** Individuals with ASD have differences in E/I balance and responsivity, at regional and whole-brain levels. Thus, the glutamate-GABA system may be a tractable treatment target in ASD. This MRS/rs-fMRI approach may provide a safe means to fractionate the ASD sample into more biologically homogeneous sub-groups, for example prior to clinical trial. It may also help predict who will be responsive to glutamate-GABA treatments (such as riluzole).

**Keywords:** Autism Spectrum Disorder; Glutamate; GABA; Riluzole; MRS; rs-fMRI.

## TALK 12: TSC-Associated Neuropsychiatric Disorders (TAND): Baseline Data from the Tosca International Disease Registry

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**Background:** Even though Tuberous Sclerosis Associated Neuropsychiatric Disorders (TAND) is of great concern in tuberous sclerosis complex (TSC), and constitutes a major burden of the disease, there are limited large-scale data on TAND. Here we report the baseline TAND data from the TuberOus SClerosis registry to increase disease Awareness (TOSCA) study.

**Methods:** TOSCA is a multicentre, international disease registry. Participants from 170 centres in 31 countries were recruited over a 2-year period. A follow-up observational period of 5 years is ongoing. Data collection includes a core section (general information on patients' backgrounds) and research projects (additional data on specific disease manifestations).

**Results:** As of September 30, 2014, baseline core data were available on 2093 patients. Intellectual quotient data were available on 822 patients (39.2% of the overall cohort). Of those, 371 (45.1%) patients had normal intellectual ability, while mild, moderate, severe, and profound degrees of intellectual disability was observed in 232 (28.2%), 123 (15.0%), 75 (9.1%), and 21 (2.6%) patients respectively. Psychiatric disorders included autism spectrum disorder (291 [20.7%]*), attention deficit hyperactivity disorder (260 [19.6%]*), anxiety (118 [9.1%]*, and depression (80 [6.1%]*) (*percentages calculated excluding the unknown data/data not available). Neuropsychological deficits (performance <5th percentile on formal measures) were reported in 281 (55.1%) out of 510 patients assessed and academic difficulties in 332 (48.7%) out of 682 patients assessed. Overall, 1868 (89.2%) patients reported a lifetime history of at least one behavioural problem. In contrast to physical manifestation data and epilepsy data, TAND was not evaluated in a 30 –50% of cases.

**Conclusion:** TOSCA represents the largest clinical collection of TSC data to date. Baseline data confirmed the high rates of TAND, but also highlighted the fact that, even in specialist centres, TAND is often not evaluated, and therefore not treated. Results suggest the need for further and more systematic evaluation for TAND. Here we present frequencies of TAND data, age- and gender distributions, and will outline the more detailed TAND research project within TOSCA.

**Keywords:** TSC, TOSCA, TAND, intellectual disability.

## PAT HOWLIN PRIZE LECTURE – TALK 13: Pilot Randomised Controlled Trial of the Effects of Reciprocal Imitation Training on Children with Autism

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**Background:** Reciprocal Imitation Training (RIT) is a play-based naturalistic behavioural intervention focused on increasing imitation skills and gesture use in individuals with autism. Previous research has demonstrated RIT to be effective for increasing spontaneous object and gesture-based imitation. The current study is therefore an attempted replication of these previous behavioural effects to add to the evidence-base for RIT.

**Methods:** Participants to date are 21 children with autism aged 2- to 6-years. Stratified randomisation is conducted (matched on chronological age & verbal mental age) after first set of assessments into – Treatment & Wait-list control groups. Participants in the treatment group receive 20 hours of RIT over a period of 12 weeks. Pre- and post-intervention assessments include a battery of standardised assessments and two experimental-behavioural change measures: Unstructured Imitation Assessment (UIA) and Structured Imitation Assessment (SIA), administered by experimenters who are blinded to intervention status.

**Results:** Intervention effects on spontaneous and elicited imitation were of interest. Repeated-measures ANOVA indicated a significant Condition by Time effect where children in the Treatment group made significantly more gains in spontaneous imitation, measured on UIA, compared with children in the Wait-List group, $F_{(1,19)} = 7.73$, $p = .01$, $\eta_p^2 = .29$. Follow-up t-tests on the treatment group also supported this finding, where a significant difference between pre- and post-intervention imitation skills was observed, $t_{(11)} = 3.09$, $p = .01$. However, there was no significant difference between the groups on the elicited imitation scale, $F_{(1,19)} = 3.72$, $p = .07$, $\eta_p^2 = .16$.

**Conclusion:** These findings provide further support for RIT as an effective intervention for teaching critical social imitation skills to this population. Because reciprocal imitation of the actions of others in unstructured contexts is considered to be a core deficit that impacts negatively upon socialisation and learning in this population, the results of this study are very encouraging.

**Keywords:** Autism, Early Intervention.

## TALK 14: Dosing Allopurinol in Patients with Classic Lesch-Nyhan Disease/Syndrome to Eliminate Uric Acid and Xanthine Nephrolithiasis.

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**Background:** Patients with Lesch-Nyhan disease (LND) have historically been treated with allopurinol to maintain serum Uric Acid in the 4.0 to 6.0 mg% range to decrease (but not eliminate) Uric Acid crystals/stone formation a*s well as* minimize Xanthine nephrolithiasis. We attempted to eliminate Uric Acid excretion from the urine as well decrease Xanthine excretion with allopurinol by lowering serum uric acid to less than 1.0 mg/%. This review of four cases began when gout developed in a 36 yo patient; treatment suggested by W. Nyhan resolved the clinical situation. The surprise finding of a change in behaviour, a qualitative finding of comfort, had not previously been reported.

**Methods:** Using the protocol of WN four patients with LND were treated with allopurinol to lower serum uric acid below 1.0 mg%, although quantification of urine purine salvage pathway metabolites (mmol/mol Cr) were used to determine optimal allopurinol dosing. The dose of allopurinol was determined when urine Hypoxanthine levels were twice that of Xanthine levels and urine uric acid was not detectable.

**Results:** The results suggest elimination of uric acid crystals/stones can be achieved when the dose of allopurinol is between 800 and 1200 mg/day, without side effects. Early data suggest elimination of Xanthine stones is also possible. And the important surprise finding of an improvement in the overall "state" of the four patients based on qualitative data, previously unreported, was identified.

**Conclusion:** Allopurinol doses in the 800 to 1200 mg/day range can eliminate Uric Acid and Xanthine crystals in the urine when Hypoxanthine excretion is approximately twice that of Xanthine; therefore, serum uric acid has limited usefulness. Also these data suggest the behavioural phenotype of LND can be modified by lowering serum uric acid – either from a direct effect of allopurinol or a decrease in total body purine salvage pathway metabolites.

**Keywords:** Lesch-Nyhan, allopurinol, xanthine, hypoxanthine, behavioural phenotype.

## TALK 15: Autism Spectrum and Psychosis Risk in the 22q11.2 Deletion Syndrome. Findings from a Prospective Longitudinal Study

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**Background:** Individuals with 22q11.2 deletion syndrome (22q11DS) have a 25-fold increased risk for psychotic disorders, in particular schizophrenia. Several studies in children with 22q11DS also report increased rates of Autism Spectrum Disorders (ASD). However, a diagnosis of ASD in 22q11DS may be a clinical misinterpretation of the observed social and communicative defects, if those would actually represent an early stage of schizophrenia. If true, one would expect that an ASD diagnosis predicts the emergence of psychosis later in life in individuals with 22q11DS. Here, we investigate whether in children with 22q11DS, those with an ASD diagnosis are more likely to develop psychosis compared to those without ASD.

**Methods:** 80 children with 22q11DS were assessed twice in a prospective longitudinal study; the average ages (±SD) were 14.3±1,9 and 19.3±3.0 years at first and second measurement respectively. Both measurements were performed by the same research team using standardized clinical interviews. Diagnoses of ASD and/or psychosis were made in accordance to Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria. The rates of individuals who developed psychotic disorders were compared between those with and those without ASD.

**Results:** A total of 21.3% of children developed a psychotic disorder. No significant difference was found in the proportion of children who developed a psychotic disorder at follow-up between those with and those without ASD at baseline (14,9% and 30,3% respectively; $p=0.097$).

**Conclusion:** These findings indicate that a diagnosis of ASD is not associated with an increased risk for the subsequent development of psychotic disorders. If any, our data suggest that those with ASD may be less likely to develop psychotic disorders later in life, which replicates a retrospective study in adults with 22q11DS. The early deficits in social and communicative skills, observed in a subgroup of patients with 22q11DS, cannot be considered as prodromal symptoms of schizophrenia.

**Keywords:** Psychosis, comorbidity, autism, 22q11DS.

## TALK 16: The Tc1 Mouse Model of Trisomy-21 Dissociates Properties of Object Recognition Memory

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**Background:** The Tc1 mouse is a model of trisomy 21, which manifests as Down syndrome (DS) in humans. Previous work has suggested a specific deficit in short-term but not long-term recognition memory in Tc1 mice. Studies have revealed impaired novelty detection following a short (10 min) but not long (24 hr) delay using an object recognition task. Tc1 mice were able to detect a novel cue only after a 24 hour delay between sample and test trial. Intriguingly however, further research used a similar object recognition procedure except that mice received two sample phases separated by 24 hours before a novelty test conducted shortly after the last sample trial. Despite the 24 hour interval between sample phases, Tc1 were impaired following a short delay.

**Methods:** Given the theoretical importance of alerted short-term but not long-term memory in Tc1 mice, the present study was designed to establish the effect of short and long-term retention intervals on object recognition memory in Tc1 mice using novel object recognition, object in place and object location tasks.

**Results:** The results confirm and extend the observation that recognition memory in Tc1 mice is sensitive to the interval between the sample and test trial. There is a clear dissociation between immediate, short term, and long term recognition memory in the Tc1 mouse model of trisomy-21, confirming a delay dependent deficit in object recognition memory. This pattern of results is generalizable across sensory domains.

**Conclusion:** The results indicate disparity in the deficits of the Tc1 mouse with regards to spatial recognition memory and object recognition memory. This may reflect differential impact of the mutation on perirhinal vs. hippocampal/parahippocampal regions, enhancing understanding of the potential brain systems disrupted by the Tc1 mutation.

**Keywords:** Tc1 mouse, recognition, short term memory, long term memory.

## TALK 17: Need for a New International Rare Disease Database: The MECP2 Duplication Syndrome

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**Background:** Individuals who have two or more copies of the MECP2 gene, located at Xq28, have been found to share clinical features and a distinct facial phenotype known as MECP2 duplication syndrome (MDS). The aims of this study are provide a preliminary snapshot of MDS to inform the development of a new international database.

**Methods:** The International Rett Syndrome Database (InterRett), first established in 2002, collects data on Rett syndrome and Rett-related disorders including MDS.

**Results:** Data are available on 57 cases (49 males and 8 females) with MDS. Median age at ascertainment was 7.9yrs (range 1.2–37.6yrs) and at diagnosis 3yrs (range 3wks –37yrs). Only 10% had an initial diagnosis of MDS. Less than a third (30%) learned to walk (median age 30 months), while 70% learned to use babble or words (median age 15 months). Speech deterioration was reported in 37% and only 20% were able to use word approximations or better at ascertainment. The majority (85%) had been hospitalised in the first two years of life often because of respiratory infections. Just under half (45%) had seizures, occurring daily in half (56%) of this group. Scoliosis affected a quarter of those aged over 7 years. The majority (90%) had gastrointestinal problems and a third had a gastrostomy. Respiratory infections and sleep apnoea were common.

**Conclusion:** Parents and clinicians alike need to know more about this disorder, particularly the occurrence of comorbidities and their management. These data supported by consumer consultation will inform the development of a new MDS-specific international database.

**Keywords:** Rare disorder; international database; phenotype; familial recurrence; natural history; intellectual disability

## TALK 18 : Challenging Behaviour, Chronic Health Problems and Health Related Quality of Life in Cornelia De Lange, Cri Du Chat and Angelman Syndromes

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**Background: Background:** Individuals with Intellectual Disabilities experience higher levels of health difficulties, including elevated levels of epilepsy in Angelman Syndrome and gastrointestinal reflux in Cornelia de Lange. Despite this, there are no published studies exploring the association between such health difficulties and Health Related Quality of Life (both physical and psychosocial) in this population.

**Method:** 43 carers of individuals with Angelman (n=18), Cri du Chat (n=12), Cornelia de Lange (n=13) syndromes completed questionnaires at two time points, approximately seven years apart. Measures collected information on challenging behaviour, health problems, adaptive behaviour and health related quality of life (HRQoL at T2 only). The group was divided into those showing chronic challenging behaviour between the two data points (n=17) and those showing low or no challenging behaviour (n=26).

**Results:** The most frequently reported health problems were dental and skin, with over half the sample reporting these as chronic (i.e. present at T1 and T2). HRQoL in the total sample was significantly lower than published norms for healthy, acutely ill and chronically ill individuals. HRQoL is were significantly associated with the number and severity of health problems. Challenging behaviour was not associated with the number or severity of health problems. Those with chronic challenging behaviour had lower physical but not psychosocial QoL scores.

**Conclusions:** Individuals with Angelman, Cri du Chat and Cornelia de Lange experience a range of health problems, many of which remain unresolved seven years later. Different aspects of HRQoL are associated with Challenging Behaviour, emphasising the need for careful measurement and targeted intervention. The small sample does not allow for exploration of health or HRQoL scores at the individual syndrome level, highlighting the need for replication with larger samples.

**Keywords:** Challenging behaviour, health, quality of life, syndrome.

## TOM OPPÉ DISTINGUISHED LECTURE – TALK 19: What Genetics Has Taught Us About Developmental Disabilities

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The concept of a behavioural phenotype has been helpful in providing a healthy corrective to the view that all genetic or brain damage effects are diagnostically non-specific; it has focused attention on the immense gains that can come from the rigorous study of specific patterns; it has led to an appreciation that there are numerous syndromes that have some degree of specificity despite huge heterogeneity. The lessons with respect to genetics more broadly are rather similar. These are reviewed with respect to: epigenetics; copy-number variations; genome-wide association studies; conceptual findings on diagnosis; rare genes and common polymorphic variations; epistasis; the discovery of new genetic mechanisms; the role of gene-environment correlations; the role of gene-environment interactions; polygenic risk scores; and "junk" DNA.

In summary, there have been huge advances in the field of genetics but the practical clinical utility of most genetic findings remains quite limited.

**Keywords:** behavioural phenotype, epigenetics, copy number variations, gene-environment interaction, rare genes, diagnosis

## KEYNOTE 9: Mouse Models of Autism to Understand Causes and to Discover Treatments

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Autism is a neurodevelopmental disorder diagnosed by two classes of behavioral criteria: (a) social interaction and communication deficits and (b) repetitive behaviors with restricted interests. Over 100 risk genes for autism spectrum disorder have been identified over the past decade. Mice with targeted mutations in many of these risk genes are increasingly available to test hypotheses about genetic causes of autism. Our laboratory designed mouse behavioral paradigms with conceptual analogies to the diagnostic and associated symptoms of autism. Reciprocal social interactions are assayed longitudinally across developmental stages with simple automated measures of sociability, and with in-depth scoring of reciprocal social interactions. Communication in mice is assessed by the emission, detection, and responses to olfactory and auditory social cues. Repetitive behaviors are assayed for spontaneous motor stereotypies, repetitive self-grooming, marble burying and perseveration during the reversal phase of water maze spatial navigation. Mouse behavioral assays relevant to associated symptoms of autism, including anxiety, hyperactivity, cognitive impairments, and reactivity to sensory stimuli provide further insights into genetic substrates of additional phenotypes. Forward and reverse genetic models will be presented, including BTBR T+ Itpr3tf/J, an inbred strain that displays abnormalities on multiple autism-relevant behavioral tasks, *Engrailed2*, a knockout mouse with a haplotype variant associated with autism in multiple independent cohorts, and 16p11.2 deletion, a human syndrome associated with autism. Mouse models further offer preclinical translational tools to discover therapeutic targets and to evaluate treatment efficacy. We employ lines of mice with the most robust autism-relevant traits for the discovery of effective therapeutic targets. Proof-of-principle results will be presented on hypothesis-driven pharmacological interventions that reversed components of autism-relevant behavioral phenotypes in mouse models.

**Keywords:** autism, mouse models, social behaviors, repetitive, anxiety, cognitive

# TALK 20: Parallel Neuroimaging-Genomics of Sex Chromosome Aneuploidy in Humans and Mice

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**Background:** Sex chromosome aneuploidies (SCAs) increase risk for multiple neurodevelopmental morbidities. Better understanding this elevated risk requires clarifying (i) which brain systems are sensitive to changes in X- and Y-chromosome dosage, and (ii) which gene-sets are most likely to mediate effects of SCA on brain development.

**Methods:** We specify brain systems that are anatomically altered by varying X and Y-chromosome dosage through high-resolution structural neuroimaging in humans (n:300, karyotypes: XO, XX, XXX, XY, XXY, XYY, XXYY) and mice (n:90, karyotypes: XO, XX, XY, XXY) with assorted SCAs. We study candidate transcriptomic drivers of SCA phenotypes by (i) modelling gene dosage effects in beadarray measures of gene expression from human SCA lymphoblastoid cell-lines (LCLs), and (ii) merging maps of altered brain anatomy in murine SCA with publically-available atlases of brain gene-expression.

**Results:** Both humans and mice show replicable evidence for regionally-specific X-chromosome aneuploidy effects on brain anatomy, which involve systems that are critical for adaptive social functioning in each species. In humans, we identify strong cortical and subcortical overlaps between X- and Y- chromosome supernumeracy effects – suggesting a role for dosage-sensitive X-Y chromosome homologous gene pairs. Our transcriptomic analyses in human SCA LCLs prioritize sex chromosome genes by dosage sensitivity, and reveal order-of-magnitude differences amongst SCAs in the degree of autosomal gene dysregulation. In mice, distributed brain regions with differing profiles of anatomical change across XO, XX, XY and XXY groups show distinct patterns of gene-expression which point towards a striking interplay between sex-chromosome and sex-steroid effects on brain development.

**Conclusion:** Our multimodal cross-species approach provides a set of highly articulated and falsifiable hypotheses regarding specific pairings of gene-sets and brain-regions which may mediate the neurodevelopmental impairments that can accompany altered X and Y chromosome dosage. Testing these hypotheses in model systems will further advance the translational science of SCA.

**Keywords:** Sex Chromosome Aneuploidy, Brain Anatomy, Gene Expression, Systems Biology.

## TALK 21: The Influence of Copy Number Variation Burden on Behavioural and Psychiatric Symptoms in Intellectual Disability

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**Background:** Psychiatric disorders such as autism and psychosis are highly comorbid with idiopathic intellectual disability (ID). Previous studies have identified an increased burden of Copy Number Variation (CNVs) in individuals presenting with ID and severe psychiatric disorders. We aimed to explore if in a population of patients with ID and comorbid psychiatric/behavioural problems the burden of CNVs varies according to the severity of the psychiatric presentation.

**Methods:** We recruited a UK wide sample of 200 adults with idiopathic ID and comorbid psychiatric conditions/ behavioural issues. CNV detection was performed by the NHS North Thames Regional Genetics Service. Participants were assessed using the British Picture Vocabulary Scale, the Mini Psychiatric Assessments Schedules for Adults with Developmental Disabilities (PAS-ADD) and the Behaviour Problems Inventory. The sample was dichotomised by psychiatric disorder severity and by behaviour severity. CNVs were stratified by the clinical genetics service designation of being pathogenic, of having unknown significance (VOUS) and of being benign; by copy number size and state; and by presence of brain expressed genes.

**Results:** When the total CNV burden was filtered excluding CNVs that did not contain genes, the total number of common CNV was overrepresented in participants with severe mental illness (p=0.024) even when including VOUS CNVs (p=0.032). Total length of CNV was larger in participants with severe behaviours (p=0.039). Analyses that included VOUS CNVs and/or benign CNVs were able to predict the level of ID, the severity of behavioural problems and the severity of psychiatric illness.

**Conclusion:** The results from our study suggest that the inclusion of CNVs that are not considered to be pathogenic may provide important information regarding the severity of symptoms that an individual may develop. However, the modest size of the sample analysed means that the results presented should be considered to be exploratory and require replication in independent cohorts.

**Keywords:** Copy Number Variation, Deletion, Duplication, CNV, Psychiatric, Psychosis, Autism, Behavioural.

## TALK 22: Modelling Neural Pathology and Dementia in Down Syndrome Using Induced Pluripotent Stem Cells

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**Background:** Down Syndrome (DS) is the most common genetic cause of intellectual disability and is associated with an increased risk of Alzheimer's disease (AD). Triplication of a chromosome 21 (HSA21) gene, amyloid precursor protein (APP) is the main cause of this pathology. Non-DS individuals with inherited duplication of APP (dupAPP) present with a build-up of amyloid plaques caused by over production of β-amyloid, intra-cerebral haemorrhages and 100% penetrant early dementia. At age 35, all DS individuals show build-up of amyloid plaques but not all will go on to develop AD, suggesting roles for other HSA21 genes in modulating severity and age of onset of AD. The LonDowns Consortium aims to draw correlations between dementia, cognitive defects, mouse models and genetics with *in vitro* neurons derived from DS induced pluripotent stem cells (iPSCs).

**Methods:** For iPSCs, our strategies are: (i) isogenic DS iPSC models, (ii) dupAPP iPSCs and (iii) iPSCs from adults and infants, at extremes of the DS spectrum for intensity of pathology.

**Results:** For (i) we developed an isogenic iPSC model from a DS adult with constitutional mosaicism. These isogenic trisomy 21 and euploid iPSC lines reproduced several cellular pathologies seen in primary DS cells. Neuronal differentiation showed increased β-amyloid, abnormal mitochondria number/size, and increased DNA double strand breaks indicating accelerated ageing. While differentiated 3D cerebral organoids recapitulated aspects of human brain structure/layering. As for (ii) iPSCs have been generated from 1 dupAPP patient and for (iii) hair follicles/blood samples are collected from participants clinically stratified for cognitive ability and dementia. So far, 120 DS adults have been recruited with 85 keratinocyte lines isolated (10 extremes). iPSC lines have been established from 4 extremes: 2 with early, and 2 late/no onset of dementia.

**Conclusion:** Future studies include 2D and 3D differentiation of neuronal subtypes and evaluation of defects using methods established in our lab.

**Keywords:** Down Syndrome, induced pluripotent stem cells, neuronal differentiation, 3D cerebral organoids.

## TALK 23: Sleep in Children with Neurodevelopmental Disorders

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**Background:** High frequency of sleep disturbance has been reported for children with neurodevelopmental disorders. However, these data are limited by the lack of standardisation of measures used across groups. The present study delineates the nature of sleep disturbance across children with different neurodevelopmental disorders in order to refine the behavioural phenotype associated with these disorders and identify risk markers for poor sleep quality in these children.

**Methods:** Parents of children with Angelman syndrome (AS; N= 32), Tuberous Sclerosis Complex (TSC; 20), Autism Spectrum Disorder (ASD; N= 20) Prader-Willi syndrome (PWS= 16) and Smith-Magenis syndrome (SMS; N=13) completed the Modified Simonds and Parraga Sleep Questionnaire, The Gastric Reflux Questionnaire (GRQ), the Wessex and the Social Communication Questionnaire (SCQ).

**Results:** Preliminary results suggest that children with SMS had the highest frequency of severe sleep problems (92%), followed by children with ASD (70%), AS (50%), TSC (45%) and PWS (25%). Children with SMS had a significantly higher prevalence of severe early morning waking compared with all other disorders (76.9%, p<.001). Children with ASD had significantly higher prevalence rates of severe settling problems (40%, p<.001) compared with all other disorders. For the total sample of children, the presence of behaviours indicative of gastrointestinal reflux contributed significantly to the variance in night-waking (p<.001), bedtime resistance (p<.001), sleep onset latency (p<.001), daytime sleepiness (p<.01), sleep-disordered breathing (p<.01) and parasomnia scores (p<.01). Poorer self-help ability contributed significantly to variance in night-time waking (p<.05); and greater self-help ability significantly contributed to bedtime resistance scores (p<.05).).Neither ASD phenomenology nor night-time seizures significantly predicted variance in any of the sleep quality domains.

**Conclusion:** Specific patterns of sleep disturbance are experienced by children with SMS and ASD relative to children with other neurodevelopmental disorders. Gastrointestinal reflux may be an important predictor of sleep disturbance in children with neurodevelopmental disorders.

**Keywords:** Neurodevelopmental disorders, sleep.

## KEYNOTE 10: Gene Dosage Effects at the 16P11.2 Genomic Region

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Copy Number Variants (CNVs) have been recognized as major contributors to neurodevelopemental disorders (NDs) but the effects of these variants on cognition and behaviour and how they lead to neuropsychiatric disorders remain largely unknown. Because some CNVs (such as those at the 16p11.2 locus) occur recurrently at a specific locus as either a loss or reciprocal gain of genomic copies, they allow beyond a simple case-control study, to investigate relationships between gene dosage and clinical as well as intermediate traits. Our group has studied the 16p11.2 genomic region and characterized the effect of gene dosage on cognitive, behavioural and structural neuroimaging phenotypes as well as medical comorbidities (obesity in particular). We are extending this systematic study to all major recurrent genomic variants associated with autism and schizophrenia to understand how multiple genomic loci may converge on key mechanisms leading to these two neuropsychiatric disorders.

**Keywords:** 16p11.2 deletion; 16p11.2 duplication; autism; schizophrenia; obesity; gene dosage

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## TALK 24: Informing the Structure of Executive Function in Children: A Meta-Analysis of Functional Neuroimaging Data

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**Background:** Executive function deficits have been examined in genetic syndromes, such as Prader-Willi, Fragile X and Williams Syndromes and Tuberous Sclerosis. In some cases specific impairments in executive function have been linked to particular aspects of the behavioural phenotypes associated with these syndromes. However, problems inherent in measurement and a lack of understanding of the structural development of executive function have contributed to limitations of exploration in this area. As the first study of its kind, this meta-analysis aims to contribute to a better understanding of the structure of executive function in children.

**Methods:** A coordinate-based meta-analysis was conducted (using BrainMap GingerALE 2.3), which incorporated studies administering functional magnetic resonance imaging during inhibition, switching and working memory updating tasks in typical children (aged 6 –18 years). The neural activation common across all executive tasks was compared to that shared by tasks pertaining only to inhibition, switching or updating, which are commonly considered to be fundamental executive processes.

**Results:** Results support  – for the first time at a neural level  – the existence of partially separable but partially overlapping inhibition, switching and updating executive processes in children over 6 years. Further, the shared neural activation across all tasks (associated with a proposed "unitary" component of executive function) overlapped to different degrees with the activation associated with each individual executive process.

**Conclusion:** These findings provide some evidence to support the suggestion that one of the most influential structural models of executive functioning in adults can also be applied to children. However, they also highlight the need for a new systematic developmental model, which captures the integrative nature of executive function in children. Importantly, when examining the association between executive functioning and aspects of behavioural phenotypes, the results call for careful consideration and measurement of both specific executive processes, and unitary executive function.

**Keywords:** behavioural phenotypes; executive function; fMRI; meta-analysis

# TALK 25: Psychiatric Outcomes in Tuberous Sclerosis Complex (TSC): Autistic Traits and Autism Spectrum Disorder (ASD) in the TS2000 Cohort Study

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**Background:** Tuberous Sclerosis (TSC) increases the risk for autism spectrum disorder (ASD), though there is marked variability between individuals. Various risk factors may be important, such as mutation type, number and location of brain cortical tubers, and epilepsy. Risk for ASD may be dichotomous (ASD vs. unaffected) or there could be a general increase in risk for autistic traits, even in those not meeting criteria for ASD. Aims were to establish: (1) the prevalence of ASD in a population-representative sample of children and young adults with TSC; (2) whether autistic traits have a bimodal (ASD vs. unaffected) or continuous distribution; (3) which risk factors predict autistic traits, including mutation (TSC1 vs. TSC2), cortical tuber load, and type and severity of epilepsy.

**Methods:** TS2000 is the first UK population-representative, prospective longitudinal study to chart the development of TSC throughout childhood. All cases identified as newly diagnosed during 2001–2006 were recruited (N=125) and followed for up to 14 years. In-depth assessments for ASD have been carried out, and medical and genetic data have been collected.

**Results:** Fifty-two percent of participants met criteria for ASD (on parent-report Autism Diagnostic Interview-Revised; AGRE criteria); a further 23% showed subthreshold autistic traits; a minority (24%) had low levels of autistic traits. Autistic traits were continuously distributed. Mutation was not associated with ASD (31% of TSC1 vs. 53% of TSC2 with ASD; p>.20). Higher levels of autistic traits were associated with higher cortical tuber load (rho=.30; p=.024); epilepsy severity in the 1st (rho=.33; p=.003), 2nd (rho=.44; p<.001), and subsequent (rho=.46, p<.001) years of life, and infantile spasms (d=0.91, p<.001).

**Conclusion:** Children with TSC are at high risk for ASD, as well as social/communication difficulties that fall short of diagnosis of ASD but might nonetheless be clinically important. More severe epilepsy – particularly infantile spasms – carries a poorer prognosis.

**Keywords:** Tuberous sclerosis complex (TSC); autism spectrum disorder (ASD); autistic traits; epilepsy; infantile spasms.

## TALK 26: Changes in Autism Spectrum Disorder Characteristics in Cornelia De Lange and Cri Du Chat Syndromes: Results from a Seven Year Follow-Up

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**Background:** Previous studies indicate an age-related decline in behaviour and mood in Cornelia de Lange syndrome (CdLS), alongside early onset of physical ageing characteristics. In this study we evaluated the trajectory of autism spectrum disorder (ASD) characteristics in CdLS and Cri du Chat syndrome (CdCS) over a seven year follow-up period.

**Methods:** Participants were individuals with CdLS (N=30; T1 Mage=12.24, SD=3.90; T2 Mage=19.20, SD=3.91) and CdCS (N= 18; T1 Mage=9.64, SD=2.72; T2 Mage=16.58, SD=2.81). The Social Communication Questionnaire (SCQ) and the Autism Diagnostic Observation Schedule (ADOS) were completed at Time 1 (T1) and seven years later at Time 2 (T2). No significant group differences were identified at T1 with regard to gender, adaptive behaviour skills, verbal ability and mobility ($p>.05$).

**Results:** There was a significant time by group interaction for reciprocal social interaction (ADOS and SCQ) and communication (SCQ only); indicating increasing levels of impairment in social and communication skills between T1 and T2 in the CdLS group, while scores remained stable in the CdCS group (ADOS RSI: $F_{(1,45)} = 5.69$, $p =.02$; SCQ RSI: $F_{(1,41)} = 5.65$, $p =.02$; SCQ Communication: $F_{(1,40)} = 6.39$, $p =.02$). No significant group by time interaction and no significant main effects were identified with regard to repetitive behaviour.

**Conclusion:** Individuals with CdLS show increased levels of impairment in some (but not all) aspects of ASD symptomatology over time. Specifically, impairments in social interaction and communication become more pronounced while repetitive behaviour remains relatively stable. This is consistent with previous reports of a decline in behaviour and mood in CdLS and may be linked to causal mutations within the cohesin pathway.

**Keywords:** Cornelia de Lange syndrome, Cri du Chat syndrome, longitudinal, behavioural phenotypes, autism spectrum disorder, follow-up.

## TALK 27: Incontinence in Persons with Down Syndrome

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**Background:** Down Syndrome (DS), characterized by typical facial features and a physical growth delay, is caused by the presence of partial or complete triplication (trisomy) of chromosome 21. It is the most common genetic cause for intellectual disability, which is in the mild and moderate range. The aim of this study was to assess the rates of incontinence and associated psychological problems in persons with DS.

**Methods:** 122 children (4 –18 years) and 160 adults (18 –51 years) with DS were recruited through a German parent support group (59.6% male, mean age 19.2 years). The Parental Questionnaire: Enuresis/Urinary Incontinence, the Incontinence Questionnaire-Pediatric Lower Urinary Tract Symptoms (ICIQ-CLUTS), as well as the Developmental Behavior Checklist for parents (DBC-P) or for adults (DBC-A) were filled out by parents or care-givers.

**Results:** 17.2% of the sample had nocturnal enuresis (NE), 15.9% had daytime urinary incontinence (DUI) and 14.2% had faecal incontinence (FI). Incontinence was present in 64.0% of young children (4 –12 years), 10.3% of teens (13 –17y), 12.8% of young adults (18 –30y) and in 22.4% of older adults (>30y). 13.6% of children and 8.4% of adults had a DBC score in the clinical range. 19.5% of children and 27.8% of adults with incontinence had behavioural problems. There was a significant association between NE/DUI and clinical DBC score in adults.

**Conclusion:** Incontinence in DS is mainly present in young children, but adults are affected, as well. Behavioural comorbidity is associated with incontinence only in adults with DS. Screening and treatment of incontinence in children with DS is recommended.

**Keywords:** Down syndrome, incontinence, enuresis, encopresis, behavioural problems.

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## TALK 28: Mental Health Care in Smith Magenis Syndrome: Case Series

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**Background:** Smith Magenis Syndrome (SMS) is a genetic disorder associated with mild to severe intellectual disability due to a micro-deletion of chromosome 17p11.2. Its prevalence is 1:25,000 and people with SMS have a well-described behavioural phenotype that includes abnormally aggressive behaviour, self-injurious behaviour such as head-banging and skin-picking, and tantrums. Mental disorders include Attention Deficit Hyperactivity Disorder in children, mood disorders and anxiety disorders in adults. The behaviour challenges services to meet their needs. People with SMS may often use psychotropic medication to manage mental disorders and challenging behaviour. On account of their behaviour some individuals are at risk of spending long periods in mental health institutions because of the extreme nature of their behaviour.

**Methods:** In this case series we present a review of the literature of mental health difficulties in people with SMS and explore the management strategies.

**Results:** The associated mental health diagnoses in this case series included: anxiety, hypomania, and childhood ADHD. Complex drug regimens were required that included mood stabilisers and antipsychotics to manage their behaviour and mental disorders. Cases presented here have spent from one to five years as involuntary in-patients in psychiatric hospitals to manage their behaviour and in the absence of appropriate community placement, but several currently live in the community.

**Conclusion:** Behavioural difficulties associated with SMS can lead to extended in-patient care in psychiatric hospitals. Management strategies include using psychotropic medication for behaviour and to treat co-morbid mental disorders. Experience of in-patient care is common but living in the community is possible that depends on the severity of the behaviour and the availability of effective support to the person.

**Keywords:** Smith Magenis Syndrome; mental disorder; challenging behaviour.

## KEYNOTE 11: Getting Answers from Babies about Autism

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Until recently, most of what we knew about the emergence of autism in infancy relied on retrospective accounts. A new approach, the study of infants at familial risk, aims to identify the earliest "pure" manifestations of autism, before subsequent years of atypical development exacerbate, or compensate for, initial atypical development. An emerging picture from these studies is that early impairments in one or more of several functional cognitive systems are associated, respectively, with familial risk and with a later autism diagnosis. Understanding the temporal associations between these impairments over time will reveal the underlying mechanisms of atypical development in autism and inform approaches to early intervention. I will describe the latest findings from the UK BASIS 'sibs' study (http://www.basisnetwork.org/) and other groups conducting similar research worldwide. Some of the findings are unexpected and are changing how we view and understand the emergence of autism. I will also outline our latest work on testing a parenting intervention with infants at risk in the first year of life.

**Keywords:** autism, infancy, risk, mechanisms, early intervention

# Abstracts for Poster Presentations

*(in alphabetical order of primary author)*

## POSTER 1: How Epilepsy is Related to the Behavioural Phenotype of Angelman Syndrome

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**Background:** Epilepsy in Angelman syndrome (AS) typically begins in early childhood and appears to improve around puberty. Age of first seizure is reported to be related to autism spectrum disorders (ASD) in other clinical groups. Animal models have indicated possible mechanisms for behavioural changes after early epileptic seizures. In the present study, we want to explore the relationship between seizure history and behavioural phenotype of AS.

**Methods:** This ongoing study combines data from questionnaires (SCQ, SDQ) with somatic information obtained from medical records such as age at epilepsy onset, seizure types and frequency, anti-epileptic drugs, EEG and type of genetic aberration. The parents/guardians of 115 individuals with AS were contacted, 52 surveys have been returned (45% response rate). 46 individuals (32 male 14 female) had genetic verified AS. Age 1 –58 (mean 16.8). 32 (69%) had epilepsy. Mean age was 20.3 years in the epilepsy population and 8.8 years in those without epilepsy (p=0.003). SCQ and SDQ data from individuals >= 4 years was used (*n*=37).

**Results:** There was no significant difference in SCQ or SDQ-scores between individuals with, and without epilepsy. Mean age at epilepsy onset was 32 months (range 3 –80, SD 24). Age at epilepsy onset was highly correlated with total SCQ score. *r* -.55, *p*.022). It is the communication subscale of the SCQ that is most related to debut of seizures. The hyperactivity/inattention dimension of SDQ is also significantly related to age of epilepsy onset.

**Conclusion:** Age of first seizure is related to ASD and hyperactivity/inattention in AS. More information about seizures types, seizure frequency, effect of medication and genetic source and its impact on the behavioural phenotype of AS will be presented at the time of the meeting. Possible mechanisms will also be discussed.

**Keywords:** Angelman syndrome, epilepsy, Autism spectrum disorder, attention, hyperactivity.

## POSTER 2: Profiling the Behavioural Phenotype of Potocki-Lupski Syndrome

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**Background:** Potocki-Lupski syndrome (PTLS; dup 17p11.2) is the reciprocal disorder to Smith-Magenis syndrome (SMS; del 17p11.2). SMS is characterised by a striking behavioural phenotype, including high rates of self-injury. However, the behavioural profile of PTLS is currently less well defined; for example, reported prevalence of behaviours associated with autism spectrum disorder (ASD) is highly variable. This study investigated the behavioural phenotype of PTLS, in contrast to SMS and idiopathic ASD.

**Methods:** Caregivers of individuals with PTLS ($n = 34$; $M$ age = 12.43, $SD$ = 6.78) completed online measures of behaviour, including challenging behaviour, ASD symptomatology, and repetitive behaviour. Individuals with PTLS were matched on age and adaptive functioning to individuals with SMS ($n = 31$; $M$ age = 13.61, $SD$ = 6.85) and idiopathic ASD ($n = 33$; $M$ age = 12.04, $SD$ = 5.85) from an existing dataset.

**Results:** Self-injury and destruction of property were less common in both individuals with PTLS and ASD than SMS (rates did not differ between individuals with PTLS and ASD). In terms of ASD symptomatology, individuals with PTLS and SMS were both less impaired than individuals with ASD in *communication* and *reciprocal social interaction*. However, neither individuals with PTLS or SMS differed from individuals with ASD on *restricted, repetitive and stereotyped behaviours*. Individuals with PTLS and SMS did not differ on these three subscales. Specific examination of repetitive behaviour indicated that both individuals with PTLS and ASD had higher scores than individuals with SMS on the *compulsive behaviour* subscale (scores did not differ between individuals with PTLS and ASD).

**Conclusion:** PTLS does not appear to be characterised by challenging behaviour, or deficits in communication or reciprocal social interaction. However, restricted, repetitive and stereotyped behaviours, evident in both PTLS and SMS, may be characterised by compulsive behaviours in particular in individuals with PTLS.

**Keywords:** Potocki-Lupski syndrome, Smith-Magenis syndrome, autism spectrum disorder, behavioural phenotype, challenging behaviour, repetitive behaviour.

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## POSTER 3: Challenging Behaviours in Adults with Intellectual Disabilities and Autism: Baseline data from a Cluster Randomised Control Trial of Positive Behavioural Support.

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**Background:** Individuals with Intellectual Disabilities (ID) are more likely to display Challenging Behaviours compared to the general population. This seems to be further exacerbated when individuals have a comorbid diagnosis of Autism. The ensuing negative consequences include decreased levels of engagement in daily activities, the need for long-term drug treatment and the need for external help from carers to perform daily tasks.

**Methods:** A comparison between Service Users with ID and autism traits and Service Users with ID but with no autism traits is made. We have reviewed baseline data from an ongoing randomised controlled trial which aims to investigate the clinical and cost effectiveness of Positive Behaviour Support for treating challenging behaviour in people with intellectual disabilities to explore a subgroup of participants with reported autism features in their behaviour. The Psychiatric Assessment Schedule for Adults with Developmental Disabilities (Mini PAS-ADD) has been used to assess Autism Spectrum Disorder traits. The study assessments are carried out at Baseline, 6 months and 12 months and they include validated measures of challenging behaviour, mental health, carer burden and health economics data.

**Results:** In our sample of 246 participants around 24% of participants display symptoms of Autism Spectrum Disorder. We will present data from baseline assessments, and compare this against participants with ID who do not have symptoms of autism traits.

**Conclusions:** Detailed results and conclusions will be available in September.

**Keywords:** Challenging Behaviour, Intellectual Disability, Autism Spectrum Disorder, Randomised Controlled Trial

## POSTER 4: Well-Being of Biological Mothers of Children with Fragile X Syndrome

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**Background:** This study was designed to characterize the mental health status of biological mothers of children with fragile X syndrome (FXS). These women are at risk of mental health challenges because (a) they are raising children with significant intellectual and behavioural challenges and (b) they themselves carry the FMR1 mutation or premutation. We addressed four research questions: (1) What is the mental health status of the mothers of children with FXS? (2) Which disorders most commonly occur and do mothers meet criteria for more than one diagnosis? (3) What child characteristics relate to mental health status? (4) What mother characteristics relate to mental health status?

**Methods:** The Structured Clinical Interview for Disorders (SCID) was completed with 33 mothers of children with FXS to assess mental health status. Additionally, maternal IQ was assessed, blood samples analysed to determine carrier status and activation ratio, and information collected regarding number of affected children in the family, child challenging behaviours, and child autism symptoms.

**Results:** Of the 33 mothers, 85% met criteria for a psychiatric disorder during their lifetime. For primary diagnoses, 15 mothers met criteria for depression and 13 for anxiety. Of those with depression, 13 had a comorbid diagnosis of anxiety. One-way ANOVAs were computed to assess child and mother characteristics associated with maternal mental health status (diagnosis vs. no diagnosis). There was a trend for higher levels of autism symptoms in children of mothers who had a diagnosis. There were no differences in maternal characteristics between those with and without a diagnosis. There was a positive correlation between maternal global psychiatric symptom severity and activation ratio, $r(30)=.349, p<.05$ (one-tailed).

**Conclusion:** Our findings indicate that mothers of children with FXS have high rates of psychiatric disorders, especially anxiety and depression. These symptoms are related to both child factors and maternal genetic factors.

**Keywords:** fragile X syndrome, maternal well-being, mental health, intellectual disabilities.

## POSTER 5: Case Presentation of a Patient with 22q11.2 Deletion Presenting with Mental Illness

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**Background:** Microdeletions of 22q11.2 occur in approximately 1:4000 live births. The exact prevalence is unknown due to variable penetrance and differing levels of awareness amongst clinicians.

**Methods:** Miss LE is a 24 year old woman with a mild intellectual disability admitted to a specialist inpatient psychiatric unit, having been discharged from a psychiatric hospital the previous month. She had become selectively mute, was not carrying out personal care and hygiene and would only leave the house to go to one particular shop. She was refusing food other than quiches and pizzas bought from the particular shop, and would only eat half of them, often trying to eat them uncooked. Antidepressants were not effective and her self-neglect was such that she was admitted to hospital under the Mental Health Act.

**Results:** In hospital, psychosis was suspected and she was commenced on Olanzapine 10mg. She started to improve, eating and carrying out personal care and started to participate in activities on the ward (including karaoke). Once she started communicating again, she was able to express a range of paranoid delusions and hallucinations and the diagnosis of paranoid psychosis was made. Phenotypically, her features suggested a microdeletion of chromosome 22q11.2 and a review of her developmental and medical history revealed features consistent with the diagnosis. Array CGH was undertaken and confirmed the diagnosis.

**Conclusion:** Deletion of 22q11.2 is associated with both physical and behavioural phenotypes. Variable penetrance means that the diagnosis is often missed. Prevalence of schizophrenia in this group is estimated at 25%, and an accurate genetic diagnosis assists clinicians in being vigilant to the possibility of psychotic phenomena causing a change in functioning.

**Keywords:** psychosis, 22q11.2 deletion, schizophrenia, Di George

## POSTER 6: Visual Preference for Social versus Non-Social Stimuli in Children and Adults with Neurodevelopmental Disorders

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**Background:** Recent research has identified differences in relative attention to competing social versus non-social video stimuli as a putative diagnostic marker for autism spectrum disorders (ASD). However, it is yet to be investigated whether the extent to which the stimuli move towards participants, influences attentional allocation. In addition, existing research has highlighted distinct patterns of visual attention to social stimuli in individuals with other neurodevelopmental disorders, such as Williams syndrome, which appear consistent with the profiles of social behaviour displayed in this group. Whether such patterns exist for individuals with other neurodevelopmental disorders associated with subtle differences in social behaviour has yet to be investigated.

**Methods:** In Study 1, adolescents with ASD (n = 16) and control participants (n = 16) were presented with social and non-social video stimuli in directed and non-directed formats whilst their eye movements were recorded. In Study 2, this same paradigm was employed with individuals with Fragile X (n = 15), Cornelia de Lange (n = 14), and Rubinstein-Taybi syndromes (n = 19). Total looking time for directed versus non-directed social and non-social video stimuli (attention maintenance), and time taken to fixate on each stimulus type (attention priority), were analysed in each study.

**Results:** Consistent with previous studies, children with ASD demonstrated reduced attention maintenance for social versus non-social videos during the directed condition but this did not extend to the non-directed condition. Individuals in the three genetic syndrome groups showed similar attention maintenance, but differences in attentional priority, for directed social stimuli.

**Conclusion:** Taken together, these results provide evidence to suggest that visual attention to competing social versus non-social video stimuli may provide a robust marker for clinically-relevant, genetically mediated differences in social phenotypes.

**Keywords:** eye-tracking, autism, fragile X syndrome, Cornelia de Lange syndrome, Rubinstein-Taybi syndrome.

## POSTER 7: Neuropsychology of Older Individuals with Down Syndrome

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**Background:** Individuals with Down syndrome (DS) have an increased risk to develop Alzheimer's disease (AD) as they become older. It is not clear whether the cognitive decline in DS individuals follow a similar course as in the general population. The aim of the present study was to assess memory and executive abilities as a function of cognitive-impairment status in a sample of 94 elder voluntary participants with DS.

**Methods:** A multicentric, longitudinal study (L0-1–2) was designed to investigate cognitive, psychiatric, anatomical and functional patterns (MRI, fMRI, spectroscopy, magnetoencephalograph). The present results concern the cognitive data at L0. Neuropsychological functioning was assessed by the Barcelona Test for Intellectual Disability, the CAMCOG-DS, the Tower of London (ToL), the Weigl's Colour-Form Sorting Test, and the Behaviour Rating Inventory of Executive Function. Cognitive impairment status was determined by the CAMDEX-DS and three groups were formed: no cognitive impairment (No CI; n = 65), mild cognitive impairment (MCI; n = 22) and AD (n = 7).

**Results:** When compared to the No CI group, the MCI group showed difficulties in a wide range of memory subtests (e.g., related to word-list learning or requiring natural access to memory storage; clues are less useful) but only in two executive tasks (inhibition difficulties and verbal semantic fluency). Conversely, the AD group showed a severe memory decline (worse scores in eight memory subtest) and a stronger disexecutive pattern when they were compared to the MCI group (e.g.,ToL total score p=.017; total move score p=.043).

**Conclusion:** 1) Although none of the participants had requested specialised consultation, MCI and AD rates were considerably high (44%). 2) Together with the previous literature, our results show that the pattern of neurocognitive decline in DS population with MCI or AD is similar to the pattern exhibited by the general population.

**Keywords:** Down syndrome, Mild Cognitive Impairment, Alzheimer Disease, neuropsychology.

## POSTER 8: Deletion Size in Patients with 22q11 Deletion Syndrome and Low Intellectual Functioning.

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**Background:** 22q11 deletion syndrome (22q11DS) is caused by a microdeletion in chromosome band 22q11.2. It is believed that deletion size has no influence on the phenotype. 22q11DS is associated with mild or borderline learning disability. Moderate or severe learning disabilities seem less common. It is not clear if intelligence is associated with different deletion sizes.

**Methods:** 33 22q11DS subjects with an IQ < 55 were included and 31 22q11DS subjects with an IQ > 55. Multiplex ligation-dependent probe amplification (MLPA) was performed in both groups with the P250-A1 22q11 MLPA mix. An alternative MLPA mix (P324-A2) was also performed on the group IQ < 55.

**Results.** In the low IQ group, 29 out of 33 patients had the typical deletion size (CLTCL1 – LZTR1) compared to 25 out of the 31 patients of the higher IQ group. In the low IQ group one patient had a longer deletion ranging from CLTCL1-HIC2, one subject had the common deletion, but also a distal duplication (SMARCB1 – SNRPD3). One subject had a shorter deletion (CTLC1 – DGCR8) and one subject group had a short deletion (CTLC1 – PCQAP). In the higher IQ group one patient had a shorter deletion (CLTCL1 – PCQAP) and five patients had the shorter deletion (CLTCL1 – DGCR8). The deletion in two subjects in the low IQ group were described as typical with the P250-A1 kit, but the deletion in these two patients could be characterised with the P324 kit to be smaller compared to the other 27 "typical" deletions.

**Conclusion.** Length of deletion can be easily performed with MLPA techniques. In the low IQ group one patient had a longer deletion, in the higher IQ group there were no longer deletions. Adding alternative MLPA mixes gives extra information about deletion size.

**Keywords:** 22q11 deletion syndrome, MLPA, deletion size, intelligence

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## POSTER 9: Behavioural Features within Adaptive Behaviour Profiles: VABS Subdomain Profiles in Subtelomeric Disorders

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**Background:** Previously, we found significant differences in adaptive behaviour profiles in children with subtelomeric deletions. The aim of this study was to determine if there were significant profile differences among subtelomeric disorders within the subdomains of the Vineland Adaptive Behavior Scale [VABS].

**Methods:** Forty-nine children diagnosed with WHS, JBS, 2q37 or 8p21invdupdel were recruited. Ages ranged 4 – 20 years. M:F ratio was ~ 1:1 (25:24). Children were with the SBFE and VABS.

**Results:** Mean IQs differ significantly from among the genetic disorders. VABS Domain raw scores were converted into Age-Equivalent [AE] years. Despite their lower raw scores, AEs in the Written subdomain were markedly higher than Receptive or Expressive subdomain AEs in Communication. Community subdomain AEs from the DLS were somewhat higher than Personal or Domestic subdomains, but subdomain AEs in the Socialization Domain did not differ noticeably from one another. A MANOVA of the 3 Domain AEs as a function of Genetic Disorder and Gender showed significant differences in AEs for Communication and DLS as a function of Genetic Disorder but not Gender. Neither predictor variable had a significant effect on Socialization AE. Not surprisingly, given their respective IQ scores, highest AEs were recorded among children with JBS; lowest among children with WHS (Scheffe corrected $p<0.05$). To correct for the effect of IQ, AEs for the 4 genotypes were analysed using an ANCOVA model with IQ as covariate. As expected, IQ contributed significantly to AEs in all 3 adaptive behaviour Domains ($p<0.03$). Interestingly, when AE was adjusted for by IQ, genotype did not contribute significantly to AE in any adaptive behaviour domain.

**Conclusion:** Although it has been well documented that IQ is strongly correlated DQ, the extent to which IQ accounts for various activities associated with adaptive behaviour in genetic disorders that produce ID should probably be reconsidered.

**Keywords:** Intellectual Disability, Cognitive Profiles, Adaptive Behaviour Profiles, Genetic Disorders, Subtelomeric Deletions.

## POSTER 10: Extended Brief Intervention to Address Alcohol Misuse in People with Mild to Moderate Intellectual Disabilities Living in the Community (EBI-ID): Study Protocol for a Randomised Controlled Trial

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**Background:** There is some evidence that people with intellectual disabilities (ID) who live in the community are exposed to the same risks of alcohol use as the general population. Various interventions have been evaluated in the general population to tackle hazardous or harmful drinking, but the literature evaluating interventions is limited regarding ID. The National Institute for Health and Clinical Excellence recommends that brief and extended brief interventions be used to help young people and adults who have screened as positive for hazardous or harmful drinking. The objective of this trial is to investigate the feasibility of adapting and delivering an extended brief intervention (EBI) to persons with mild/moderate ID who live in the community and whose level of drinking is harmful or hazardous.

**Methods:** The study has three stages, which include the adaptation of the EBI for people with ID, a single blind, randomised controlled trial of an individual EBI to test the feasibility of the intervention, and a qualitative study to assess the perceived acceptability and usefulness of the intervention. Fifty participants in total will be recruited from community ID services and social care or third sector organisations.

**Results:** The main outcome will be changes in alcohol consumption as measured by the Alcohol Use Disorders Identification Test. Recruitment rate and loss to follow up will also be used to inform the sample size calculation for a multicentre clinical trial.

**Conclusion:** Alcohol misuse is a relatively under-researched mental health problem in people with ID. Therefore, the study addresses both diagnostic issues and the delivery of a simple first stage intervention, which is available to the population of average intelligence and young persons in particular. The findings from the study will guide the preparation of a large-scale study to test whether this treatment is clinically and cost-effective in this population.

**Keywords:** Alcohol misuse, intellectual disabilities, brief intervention, AUDIT, RCT.

## POSTER 11: Validation of the Tower of London-Drexel University: 2nd Edition Test for Intellectual Disability in People with Down Syndrome

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**Background:** Despite the importance of assessing the executive function in people with intellectual disability (ID), there are not enough tools adapted and validated for this population. The aim of the present study was to assess the validity of the adapted version of TOLDXtm for people with Down Syndrome (DS).

**Methods:** This is a multicentric study that was conducted in La Princesa University Hospital (Madrid, Spain) and the Specialised Service for ID (Girona, Spain). Sixty-three participants with DS aged > 40 years were divided in mild (n = 39) and moderate (n = 24) ID groups. All participants were assessed with a neuropsychological examination that includes TOLDXtm adapted version for ID, Kaufman Brief Intelligence Test, 2nd ed (K-BIT II), CAMCOG-DS, Barcelona Test for Intellectual Disability (TB-DI, the Weigl's Colour-Form Sorting Test (WCFST), the Color Trails Test (CTT), and the Behaviour Rating Inventory of Executive Function (BRIEF).

**Results:** The TOLDXtm for ID has a robust structure, shows significant associations with related neuropsychological tests, and exhibits significant differences between mild and moderate ID. E.g., two variables in TOLDXtm related to the movements made by the subject (Movements to zero –MovZero- and Number of movements –NumMov-) have different values between mild and moderate ID: MovZero (mild ID = 0.3, moderate ID = 0.17) and NumMov (mild ID = 0,03; moderate ID = 2,79). Internal consistency of MovZero (mild ID, α = 0.63, moderate ID, α = 0.81). The contrast to observe alpha equality between mild and moderate ID MovZero (p = 0.066). This value indicates that MovZero consistency is the same in both groups.

**Conclusion:** The adapted TOLDXtm for ID is a valid test for use with people with DS and has a high sensitivity to discriminate between mild and moderate ID.

**Keywords:** Tower of London, Down Syndrome, Intellectual Disability, Executive Functions.

## POSTER 12: "The Only One in the World": Experiences of Families of Children with Very Rare Chromosome Disorders and Implications for Clinical Practice

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**Background:** Translating science into clinical practice is challenging in cases where there is no existing documentation of even a single person with that particular diagnosis. An increasing number of individuals are now being identified with very rare chromosome disorders and, in some cases, the diagnosis is not only rare, but also apparently unique.

**Methods:** Families were invited to participate in this study if they had been told that their child was the only one in the world with a particular chromosome abnormality. Parents provided information about their child's development, the diagnostic process, and their experiences since diagnosis.

**Results:** Although the sample contained a range of reportedly unique chromosome disorders, the experiences of families were not unique. A number of common themes were identified. Following diagnosis, parents reported feeling shocked, confused, and frustrated by the lack of available information. The most striking similarities among the families were the aloneness they experienced as a result of being told their child was unique and the frustration they felt when professionals could provide little information and uncertain prognoses. Few parents reported receiving sensitive support from professionals, and some described being dismissed as too difficult or too complex.

**Conclusion:** The aim of this research was to increase awareness of the issues that are shared by families whose child is diagnosed with a rare, and apparently unique, chromosome disorder. Such awareness will have benefits for the professional understanding and support that is offered to these families. The findings may stimulate researchers and practitioners to publish more case reports of very rare disorders. In particular, descriptions of cognitive, behavioural and social phenotypes are much needed as the basis for more effective clinical practice.

**Keywords:** rare chromosome disorders; unique diagnosis; behavioural phenotype; family perspectives; clinical practice.

## POSTER 13: Psychological Growth, Family-Centred Care, and Social Support in Parents of Children with Developmental Disability

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**Background:** Parents who have a child with a developmental disability are at an increased risk of psychological issues, such as depressive symptoms. However, these features can be reduced through family-centred services and strong social support. We aimed to examine whether these same elements are also implicated in promoting positive psychological outcomes; for example, psychological growth. That is, experiencing positive change or finding new meaning in life.

**Methods:** Four hundred and twenty-four parents and caregivers completed an online survey that included standardised measures of social support (Significant Others Scale), family-centred services (Measure of Processes of Care), and perceived changes as a result of their child (Psychological Well-Being – Post-Traumatic Changes Questionnaire). The children's developmental conditions included 22q11.2 deletion syndrome and Down syndrome.

**Results:** The results indicated that receiving more general information from medical professionals was related to greater parental psychological growth. Receiving more general information was also associated with higher satisfaction with social (emotional) support, as indicated by a smaller discrepancy between ideal and actual emotional support. Participants who reported a higher level of satisfaction with emotional support experienced more growth, even after controlling for satisfaction with provision of general information. A bootstrapping analysis was carried out to explore the mediating role of emotional support on the relationship between general information and psychological growth. The technique suggested a weak but non-significant mediating effect of emotional support.

**Conclusion:** Although the relationships were quite weak, they suggest that provision of general information can facilitate satisfaction with emotional support, promoting psychological growth. Parents may be empowered to seek the emotional support they desire when they have an understanding of their child's disability. Healthcare services provide an optimal setting for reducing psychological difficulties and enhancing positive outcomes.

**Keywords:** Psychological growth, family-centred services, social support, disability.

## POSTER 14: Association of Young Simpson Syndrome with Autistic Spectrum Disorder: A Case Report

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**Background:** Young-Simpson syndrome is a rare congenital disorder which has been reported in the scientific literature to present clinically with learning difficulties, hypothyroidism, facial dysmorphia, heart defects and cryptorchidism. There are no case reports of associated Autistic Spectrum Disorder Diagnoses (ASD). We present the case of a man who attended our ASD diagnostic service with Young-Simpson syndrome.

**Methods:** The ASD diagnostic service is a NICE compliant diagnostic service that assesses an individual for DSM V ASD as a well as for some, their underlying cognitive profile. This assessment was completed by the team ASD specialist and psychologist and further assessment by speech therapist was recommended, but not complete at the time of submission.

**Results:** The individual met diagnostic criteria for ASD. Underlying cognitive and communicatory findings as well as sensory profile are currently being analysed. They will be presented at the conference.

**Conclusion:** This is the first case report we have been able to find regarding Young-Simpson Syndrome and its association with ASD. As a rare disorder it is important that these features are not overlooked in affected individuals.

**Keywords:** Young Simpson syndrome, Autistic spectrum disorder, Cognitive function, Communication.

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## POSTER 15: Baseline Brain Activity in Young Adults with Down Syndrome: Preliminary Analysis of Individual Alpha Peak Frequency

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**Background:** Brain activity measured with electroencephalography (EEG) in the alpha band is associated with IQ performance as well as specific learning and memory processes in the general population. It has been suggested that impaired cognitive abilities in individuals with Down syndrome (DS) may be related to atypical alpha band activity (including power, frequency and topographical properties); however conflicting results have been reported, particularly in relation to younger adults with DS.

**Methods:** We aimed to explore the relationship of Individual Alpha Peak Frequency (IAPF; extended alpha band approach) and cognitive ability in young adults with DS using eyes-open baseline EEG. We report cross-sectional data from 34 adults aged 16 –35.

**Results:** There was a significant negative relationship between IAPF (M=7.84, SD=.61 Hz) and estimated general cognitive ability (M=49.52, SD=22.76), r = -.41, p<.05. This contrasts with findings in the general population.

**Conclusion:** Reasons for this relationship are as yet unclear but may be elucidated by subsequent analyses involving a larger sample, additional electrophysiological (e.g. eyes-closed baseline data) and cognitive measures. EEGs in DS require further study to establish typical patterns in this population.

**Keywords:** Down syndrome, Cognitive abilities, EEG, Alpha, Individual Alpha Peak Frequency.

## POSTER 16: What Do We Currently Know About Resting State EEG Biomarkers For Autism Spectrum Disorder?

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**Background:** Electroencephalography (EEG) is a non-invasive technique that captures the underlying electrical changes in brain activity at the scalp surface. Resting state EEG (rsEEG) biomarkers may be useful in the early detection of risk of autism spectrum disorder (ASD). These biomarkers extract measures such as spectral power, coherence and complexity of the EEG signal, which may be helpful to identify individuals at risk for neurodevelopmental disorders, to stratify clinically meaningful subgroups, and to track the response of targeted intervention strategies.

**Methods:** A critical review of the current state of rsEEG biomarkers in ASD was conducted to draw attention to clinical and methodological considerations that need to be addressed in future work. Relevant literature was identified by conducting a systematic review using the terms "resting state", "EEG", "biomarker", and "autism", contained in the title, keywords or abstracts of papers in *BioMed Central*, *PubMed*, *Scopus*, *ScienceDirect* and *IEEE Xplore* journals. Primary papers identified were used to identify secondary literature sources regarding strengths and weaknesses of identified methods.

**Results:** Three primary next-generation biomarkers were identified: modified multiscale entropy, coherence analysis, and recurrence quantification analysis. These methods appear to be useful in the binary categorical classification of ASD versus typical development, but many analytical and clinical questions remain unanswered. Potential confounders in rsEEG biomarker development that require rigorous evaluation include age, gender, socio-economic status, comorbidity, medication use, eyes-open versus eyes-closed condition, the number and location of electrodes, and test-retest reliability.

**Conclusion:** With ongoing advances in experimental design, equipment specifications, and signal processing techniques, it may be possible to develop biomarkers and computer-based screening tools to read, interpret, and extract diagnostically relevant information from the unique EEG signature of individuals. There is, however, a clear need for rigorous electrophysiological studies that investigate the heterogeneous nature of ASD and potential confounders of next-generation rsEEG biomarkers.

**Keywords:** autism spectrum disorder, electroencephalography, biomarker.

## POSTER 17: Recurrence Quantification Analysis (RQA) of Resting State EEG as Risk Biomarker for Autism Spectrum Disorder

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**Background:** Autism Spectrum Disorder (ASD) is one of the most common neurodevelopmental disorders (NDD), with a global prevalence of 1 to 2%. 90% of people with ASD live in low- and middle-income countries where there is a significant demand for screening tools that do not require highly trained professionals. There has been growing interest in electroencephalography (EEG) as an investigational tool for biomarker development in NDD. However, one of the key challenges lies in the identification of appropriate multivariate, next-generation analytical methodologies that can characterise the complex, nonlinear dynamics of neural networks in the brain.

**Methods:** We developed a recurrence quantification analysis (RQA) biomarker by extracting RQA features from recurrence plots of multivariate embedded EEG signals and using linear discriminant analysis to classify these features as ASD or typically developing (TD). We tested the ability of the biomarker to classify 12 subjects (7 ASD, 5 TD, aged 8–17 years) in a proof-of-concept study.

**Results:** An accuracy of 83.3% (10/12 subjects correctly identified), a sensitivity of 85.7% (6/7 ASD subjects correctly identified), and a specificity of 80% (4/5 TD subjects correctly identified) was achieved. The positive proof of principle has led to replication of the method in an independent, larger dataset of 16 ASD and 46 TD individuals, aged 0 –18 years. Here we will present the results from the larger replication dataset.

**Conclusion:** The results suggest that recurrence analysis may be a potentially reliable approach to the binary categorical classification of ASD and TD. There are, however, various methodological and clinical questions that remain unanswered. Given the heterogeneous nature of ASD, it will be important to show not only differentiation between ASD and TD, but also differentiation of ASD from other NDD, particularly in genetic syndromes associated with ASD and intellectual disability, which may be significantly more challenging.

**Keywords:** autism, electroencephalography, biomarker, recurrence quantification analysis.

## POSTER 18: Understanding the Cognitive Phenotype of Down Syndrome – the London Down Syndrome Consortium (LonDownS) Adult Cognitive Test Battery

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**Background:** The London Down Syndrome Consortium (LonDownS) is a large, multi-disciplinary project investigating cognition and risk for Alzheimer's disease in Down syndrome. Our aim is to examine cognitive and behavioural phenotypes (including dementia status) in relation to genetic and cellular data. The adult cognition workstream focusses on individual differences in abilities in people with Down syndrome both with and without dementia. Here we will present data on our adult cognitive test battery, including floor and ceiling effects.

**Methods:** The first stage of the project is cross-sectional and includes people with Down syndrome aged 16 years and above, both with and without dementia. Younger adults (N=75) are considered those aged less than 35 years and older adults (N=130) those 36 years and above. Participants complete a comprehensive range of cognitive tests based on the Arizona cognitive test battery. The LonDownS adult cognitive test battery includes measures of general cognitive function, executive function, memory, language and motor skills. Saliva, hair and blood samples are taken where possible.

**Results:** We will present results showing that we have been successful in recruiting adults with a broad range of cognitive abilities. The majority are able to engage with our cognitive tests, however we have identified floor effects, particularly in measures of executive function and one of our memory measures for paired associate learning.

**Conclusion:** Individuals with Down syndrome show broad diversity in their cognitive abilities. Our cognitive test battery is accessible to the majority of our participants and is capable of identifying individual differences. However, floor effects in some tests highlight the need for more reliable measures for those with lower levels of functioning or visual impairment.

**Keywords:** 'Down syndrome", cognition, "cognitive phenotype", "Alzheimer's disease".

## POSTER 19: Behavioural Abnormalities as a Clue to Diagnosis in a Child with Ataxia

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**Background:** The differential diagnosis of childhood-onset ataxia may be challenging, especially in the absence of brain MRI or lab abnormalities. We present a child with ataxia in whom the findings of intra-axonal spheroids on muscle biopsy in combination with subtle behavioural abnormalities led to the diagnosis of atypical neuraxonal dystrophy (NAD).

**Methods and Results:** The proband was referred for frequent falls at age 4 years. Acquisition of early developmental milestones was normal. Concerns were first expressed at age 3 years, when she developed an unsteady gait. Eye movements were slightly saccadic, gait ataxic, balance poor, ankle jerks were absent, and there was proximal muscle weakness in the lower limbs. Formal evaluation of development showed normal intelligence, normal speech and language development except for intermittent whispering, and confirmed poor coordination and balance. Behaviour was at times introverted or over-familiar. Brain MRI was normal and remained so after 3 years. EMG and nerve conduction studies, fundoscopy, and metabolic work-up were normal. Friedreich ataxia and Pompe disease were excluded. Muscle biopsy showed a predominance of type1 fibres and normal immunohistochemistry. Electron microscopy revealed intra-axonal spheroids in the peri- and endomysial myelinated nerve bundles as well as in the motor endplates. Neuroaxonal spheroids are present in >80% of cases with PLA2G6-associated neurodegeneration (PLAN), which most frequently presents as infantile neuroaxonal dystrophy (INAD). Although the clinical phenotype was very different from INAD, the socially inappropriate behaviour oriented the differential diagnosis towards atypical NAD. Mutation analysis of PLA2G6 confirmed the presence of the compound heterozygous c.1021G>A (p.Ala341Thr) and c.2036G>T (p.Gly679Val) mutations in the patient, while both parents were heterozygous carriers.

**Conclusion:** This report highlights that subtle behavioural abnormalities may be helpful clues in the work-up of ataxia and of movement disorders in general.

**Keywords:** Behavioural abnormalities, ataxia, neurodegeneration, PLA2G6.

# POSTER 20: Understanding Behaviour in Mucopolysaccharide Disorders (II And III)

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**Background:** Mucopolysaccharidosis (MPS) types II and III are multi-systemic genetic disorders with a broad spectrum of clinical presentation which includes intellectual disability and progressive neurological involvement. Behavioural phenotypes associated with these disorders include high rates of challenging behaviours and hyperactivity. However, little previous research has attempted to examine relationships between different aspects of the behavioural phenotypes, and the social and environmental contexts in which these behaviours occur. The present study aims to address these issues.

**Methods:** A bottom up informant report semi structured interview was conducted with 4 primary caregivers of males with MPS II and III; questions were sensitive to the progression of the disorders over time. Relationships identified between behavioural features and social/environmental contextual factors were used to provide additional structure to a subsequent informant report interview. This interview was administered via telephone to 26 primary caregivers of children with MPS II and III (ages 6 –12 years) and 8 corresponding secondary caregivers. Behaviours and relationships were operationally defined. Inter-rater and inter-informant reliability indices were calculated and used to generate a reliable coding.

**Results:** Profiles of challenging behaviour showed similarities and differences across participants with MPS II and MPS III but also demonstrated a clear progression over time. Importantly, clear relationships between behaviours and contextual factors were identified. For example, whilst insistence on sameness – which included lining up objects and preference for a particular object – was prevalent, disruption to such repetitive behaviours typically triggered less disruptive behaviour (e.g. temper outbursts, aggression) than changes to routines or expectations. Hyperactivity was highly prevalent across multiple contexts but could be reduced in certain specific situations.

**Conclusion:** The present findings will inform the development of behavioural assessments appropriate for measuring change linked to rapidly advancing enzyme replacement therapies; and behavioural intervention strategies for challenging behaviour in MPS II and MPS III.

**Keywords:** Behavioural phenotypes, MPS II, MPS III.

## POSTER 21: Change Triggered Temper Outbursts across Behavioural Phenotypes of Neurodevelopmental Disorders

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**Background:** Resistance to change comprises part of the behavioural phenotype of several genetic syndromes including Prader-Willi and Fragile X syndromes (PWS; FXS), and is commonly demonstrated by individuals with a behavioural diagnosis of autism. Further, temper outbursts can be triggered by changes in individuals with these disorders. However, the negative impact for families of temper outbursts relative to other phenotypic behaviours may vary across disorders. As part of a broader project designed to develop and evaluate web-based parent resources for decreasing the incidence of change triggered temper outbursts (PREDICTORS), here we aim to profile the nature of change triggered temper outbursts across individuals with different genetic syndromes or autism.

**Methods:** The caregivers of 50 children (7 –15 years) with a diagnosis of autism, FXS, PWS or Down syndrome, and who were reported to show frequent change triggered temper outbursts, took part. A structured interview (via telephone) identified temper outburst component behaviours; frequency, intensity, duration, and associated reinforcement contingencies of change triggered temper outbursts, and of those arising in other contexts. The Vineland Adaptive Behavior Scales Survey indexed developmental delay. Autism characteristics and features of outbursts commonly demonstrated during typical development were measured using the Autism Screening Questionnaire and Temper Loss Scale from the Multidimensional Assessment of Preschool Disruptive Behaviour respectively (web-based administration).

**Results:** Temper outbursts showed similarities in component behaviours across participants, regardless of diagnosis. However, the relative frequency, severity, and role of reinforcement for change triggered versus non change triggered outbursts, varied across individuals and across behavioural phenotype.

**Conclusion:** Findings will inform the development of the PREDICTORS intervention, which will target individuals with change triggered temper outbursts across several disorders. The differences in the profile of change triggered outbursts across behavioural phenotypes are important for informing an efficient approach to identifying individuals likely to benefit from the intervention.

**Keywords:** Temper outbursts, behavioural phenotypes, neurodevelopmental disorders.

## POSTER 22: Neurodevelopmental Outcomes in Individuals with Heavy Prenatal Alcohol Exposure and a FASD Diagnosis, With and Without Exposure to Neglect: A Natural Experiment in Patients from a National FASD Clinic

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**Background:** The clinical overlap between neglect and prenatal alcohol exposure is large. Humans experimental design is complex and potentially unethical. Natural experiments are required to explore outcomes. Such a natural experiment occurred in the Fetal Alcohol Spectrum Disorders (FASD) clinic. Two groups, one with significant comorbid neglect and another with nil to minimal neglect.

**Methods:** The national FASD clinic sees individuals aged 6 plus for confirmation of FASD diagnosis as well as assessing wider neurodevelopmental conditions such as Autistic Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorders (ADHD) and underlying cognitive, communicatory and sensory processes. 44 cases with significant neglect were compared with 35 individuals with minimal to no neglect on the above areas. Categorical data was compared using chi squared analysis. Wider underlying analysis is ongoing at the time of abstract submission.

**Results:** No significant differences were seen on initial analysis between the two groups on age, gender, ability to form attachments, FASD diagnoses, ASD diagnoses or ADHD diagnoses. Wider underlying trends and profiles continue to be analysed.

**Conclusions:** This suggests that Prenatal alcohol exposure and a FASD diagnosis cause effects neurologically and neurodevelopmentally independent of neglect. It should therefore be considered as an important factor when assessing such individuals. The relationship with neglect requires further exploration but would suggest the two may well act in a compound manner on neurological function.

**Keywords:** Fetal Alcohol Syndrome, Fetal Alcohol Spectrum Disorders, Alcohol Related Neurodevelopmental Disorder, Neurodevelopmental Disorder Associated with Prenatal Alcohol Exposure, Neglect Attachment, Natural Experiment.

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## POSTER 23: Incontinence in Persons with Mowat-Wilson Syndrome

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**Background:** Mowat-Wilson Syndrome (MWS) is a congenital syndrome caused by deletion or mutation of the ZEB2 gene on chromosome 2q22. MWS is characterized by a distinctive facial appearance, severe intellectual disability and other anomalies, i.e. seizures or congenital heart defects. Most individuals have a sociable demeanour, but one third show psychological problems. The aim of the study was to investigate incontinence and psychological problems in MWS.

**Methods:** 35 children (mean 10.5 years) and 8 adults (mean 24.8 years) with MWS were recruited through a worldwide MWS support group. The Parental Questionnaire: Enuresis/Urinary Incontinence, as well as the Developmental Behavior Checklist (DBC) were completed by parents or care-givers.

**Results:** 97.5% of persons with MWS were affected by at least one subtype of incontinence. 72.5% had nocturnal enuresis (NE), 74.4% daytime urinary incontinence (DUI) and 82.1% faecal incontinence (FI). Incontinence was still high in adults (100% vs. 97% in children). 38.2% of the children and 37.5% of adults reached a clinically relevant DBC score. The majority was affected by physical disabilities: seizures (86%), congenital heart defects (44.2%), Hirschsprung disease (39.5%) and anomalies of the urogenital tract (39.5%).

**Conclusion:** Incontinence rates in children and adults with MWS are high. All had physical disabilities including anomalies of the urogenital tract, so that both functional and organic incontinence could be present. About 40% of persons with MWS were affected by psychological problems. Due to the high prevalence rates, a screening for organic and functional incontinence and psychological problems in persons with MWS is recommended.

**Keywords:** Mowat-Wilson Syndrome, incontinence, enuresis, encopresis, behavioural problems.

## POSTER 24: Incontinence in Boys with Fragile-X-Syndrome

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**Background:** Fragile-X-Syndrome (FXS) is caused by a mutation on the X-chromosome (Xq27.3). Male persons with a full mutation have typical dysmorphic signs, moderate intellectual disability and psychological problems (ADHD, autism, anxiety). 20 –40% are affected by incontinence. The aim of the study was to clinically assess and diagnose subtypes of incontinence and psychological problems in children with FXS in their home environments.

**Methods:** In 22 boys with FXS (mean age 11.0 years) and 22 healthy controls (mean age 11.1 years), sonography (rectum, bladder), uroflowmetry, 48-h-bladder diary, physical examination, IQ test, parental psychiatric interview and questionnaires regarding incontinence and psychological symptoms (CBCL) were performed in a home setting.

**Results:** Boys with FXS had higher rates of incontinence than controls: nocturnal enuresis (NE) 45.5% vs. 4.5%, daytime urinary incontinence (DUI) 36.4% vs. 0%, faecal incontinence (FI) 31.8% vs. 0%. The most common subtypes in FXS boys were primary non-monosymptomatic NE (n=8), urge incontinence (n=3) and non-retentive FI (n=7). 90.9% boys with FXS had a psychological comorbidity, e.g. ADHD, anxiety, obsessive-compulsive and tic disorders. Incontinence and behavioural symptoms were not associated.

**Conclusion:** Boys with FXS have a higher risk for physical disabilities, psychological disorders and incontinence than healthy boys. Constipation does not seem to be a major problem in FXS. As effective treatment is available for children with intellectual disabilities, we recommend offering assessment and therapy to all children with FXS and incontinence or psychological symptoms.

**Keywords:** Fragile-X-Syndrome, incontinence, enuresis, encopresis, psychological disorders.

## POSTER 25: Occupational Outcomes for Adults with Neurodevelopmental Disorders

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**Background:** A key concern for parents of children with neurodevelopmental disorders is for the quality of their future adult life. An important part of this future is the daily vocational and educational activities of these individuals. We aim to describe and categorise these activities and to explore predictors of these outcomes.

**Methods:** Parents and carers of 60 individuals with the following neurodevelopmental disorders: Angelman syndrome (N = 13), Cri du Chat syndrome (N = 7), Cornelia de Lange syndrome (N = 12), Fragile X syndrome (N = 20) and Prader-Willi syndrome (N = 8) aged 18 –56 (M = 27.60, SD = 9.09) reported the daytime activities of the people they care for. Their responses were coded based on criteria from Taylor and Seltzer's (2012) Vocational Index. Binary logistic regressions were performed to explore predictors of successful outcomes. Data collection is ongoing.

**Results:** Most participants (48%) attended a sheltered vocational setting (e.g. day centre or sheltered workshop; 28% >10 hours per week; 10% < 10 hours per week; 10% hours unspecified,) 32% had no vocational or educational activities, 15% were enrolled in non-degree seeking education or were volunteering in the community for less than 10 hours per week. Two people (3%) were in paid employment in the community with support (1 for >10 hours per week, 1 for <10 hours per week), one person was in paid employment without support. The participants' median score on the Vocational Index was 3 (out of 9). Preliminary results suggest that age and daily living skills may predict scores above the group median on the Vocational Index (p<.05).

**Conclusion:** There are a variety of vocational outcomes for adults with neurodevelopmental disorders which are not always captured in employment statistics. High quality vocational activities should be encouraged particularly for those with strong daily living skills.

**Keywords:** neurodevelopmental disorders; adult outcomes; occupation; education; daytime activities.

## POSTER 26: GABA Abnormalities in Prader Willi Syndrome

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**Background:** Maladaptive behaviours such as temper outbursts, aggression and skin picking (PWS) are a leading cause of morbidity for individuals and their families. People with PWS have a high frequency of these behaviours and the pattern of these is similar across different people with PWS. This suggests that there is a genetic and neurobiological base predisposing people to these behaviours. The aim of this study is to investigate the neurochemistry of the PWS brain with the intent to provide a direction for future research in understanding the link between gene, brain and these maladaptive behaviours.

**Methods:** Magnetic Resonance Spectroscopy was used to examine GABA, glutamate and glutamine concentration levels in the anterior cingulate cortex of 15 individuals with PWS and 15 typically developing age- and gender-matched controls. The Developmental Behaviour Checklist (DBC) was used to measure emotional and behavioural problems in participants with PWS.

**Results & Conclusion:** Preliminary findings will be presented at the conference.

**Keywords:** Prader Willi syndrome, magnetic resonance imaging, GABA, glutamate

## POSTER 27: From Task Switching Deficits Associated with Behavioural Phenotypic Temper Outbursts in People with Prader-Willi Syndrome to a Cognitive Training Video Game to Reduce Such Outbursts

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**Background:** Resistance to change and associated temper outbursts – which comprise part of the behavioural phenotype of Prader-Willi syndrome (PWS) – have been linked to executive functioning deficits in task switching. We are developing a video game to train switching in children with PWS using a human-centred design process. Measuring children's behavioural and physiological states during engagement with games can provide an index of factors – such as high motivation; non-minimal arousal; and complex feedback – that promote optimal learning transfer.

**Methods:** 15 entertainment games were evaluated using online questionnaires by seven children (7 – 15 years) with PWS and their parents, to isolate motivating features. Based on these features, a first-stage prototype game was developed and evaluated by participants, also using online questionnaires. Further evaluation sessions of later-stage prototypes – including face to face visits and recordings of behaviour and physiological arousal – contrasted specific game features (e.g. alternative control systems) for their ability to promote conditions of optimal learning transfer.

**Results:** In entertainment games, children enjoyed shape-based puzzles but preferred controlling a character and collecting items. Interestingly, jigsaw engagement and hoarding contribute to the PWS behavioural phenotype. First-stage prototype evaluations indicated that children were motivated to play and understood general gameplay but did not fully comprehend the relevance of specific tasks (indicating some complexity of feedback). The game was thus judged as a sound basis for further development. Contrasts between specific game features later in the development process and how these informed game refinement will be presented.

**Conclusion:** Knowledge of a behavioural phenotype and its associations with other levels of functioning can inform where to target cognitive training and where to expect change. The present prototype game will be evaluated for its capacity to mediate improvements in task switching and reductions in change triggered temper outbursts.

**Keywords:** temper outbursts, task switching, Prader-Willi syndrome, cognitive training, human-centred design, serious games.

## POSTER 28: Developing a New Cognitive Informant Questionnaire for People with Down Syndrome

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**Background:** The London Down Syndrome Consortium (LonDownS) is investigating individual differences, including cognitive abilities, in people with Down syndrome (DS). For this we are using both informant questionnaires and cognitive assessments. Existing informant questionnaires were designed for the typically developing population however, and some of the questions are not suitable for people with intellectual disabilities (ID). To overcome this issue we have developed a new questionnaire with more applicable questions.

**Methods:** We created 66 questions in three domains: memory, executive functioning and language. Half the questions were reverse phrased to reduce response bias. Questions had three options: never/rarely true, sometimes true, and often/always true. Parents or carers of adults with DS completed the questionnaire. Questionnaire validity was assessed firstly by comparing scores for adults with dementia / significant cognitive decline to those aged 41+ without decline, and secondly by correlating questionnaire scores with Kbit-2 scores (a measure of general cognitive abilities) and Short Adaptive Behaviour Scale (ABS) scores.

**Results:** Questionnaires were collected for 128 individuals aged 16 –84 (68 males, 60 females). The three domains showed high internal consistency (Cronbach's alpha memory=0.92, executive function=0.93, language=0.87). The questionnaire showed high test retest reliability (n=33, intraclass correlation=0.95, $p<0.001$) and interrater reliability (n=54, intraclass correlation=0.84, $p<0.001$). Questionnaire results significantly differed between those with dementia / significant cognitive decline and those without decline ($t(49)=0.75$, $p<0.001$). Questionnaire scores significantly correlated with Kbit-2 and Short ABS scores ($r=0.55$ and $r=0.76$ respectively, both $p<0.001$).

**Conclusion:** We have developed a reliable and valid informant scale to assess cognitive abilities in people with DS that can be used with all individuals regardless of their level of ID. In the future this scale could be used as a standardised measure for cognitive abilities in DS and other IDs, and have potential for detecting improvements in clinical trials and measuring cognitive decline.

**Keywords:** Down syndrome, cognitive abilities, memory, executive function, language.

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## POSTER 29: Relationship Between Recurrent Infections and Cognitive Abilities and Decline in Down Syndrome

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**Background:** People with Down syndrome (DS) show large variability in their cognitive profiles. Some people have a mild intellectual disability (ID), while others a more severe ID. Individual differences are also seen for cognitive decline; some people receive a dementia diagnosis in their 40s while others do not show decline in their 60s. The London Down Syndrome Consortium (LonDownS) is investigating factors influencing these differences. Recurrent infections, in particular chest infections, are common in DS, and here we present data for the relationships between recurrent infections and cognitive abilities and decline in DS.

**Methods:** We compared scores from the Kbit-2 (a measure of general cognitive abilities) and the short Adaptive Behaviour Scale (ABS) for adults aged 16 –35 who have (n=34) and do not have (n=39) a history of recurrent infections. We investigated the prevalence of recurrent infections for 'extremes' of the dementia phenotype; those diagnosed with dementia before age 55 (n=23), and those not diagnosed with dementia aged 55+ (n=13). Genetic analysis for variations in genes implicated in immune system function (e.g. the HLA complex) is on-going.

**Results:** Scores on the Kbit-2 and short ABS were poorer for adults who have history of recurrent infections compared to those who do not. History of recurrent infections was more common in adults diagnosed with dementia before age 55 compared to those not diagnosed with dementia aged 55+.

**Conclusion:** History of recurrent infections is associated with poorer abilities in DS, and is linked to an early onset of dementia. The explanation for this may relate to increased microglial activation and cytokine production following infections, resulting in neuronal damage. Alternatively, poorer immune system function and poorer abilities / early dementia onset may represent an overall 'poorer health' phenotype, or there may be a mediating factor influencing both immune function and aspects of neuronal function.

**Keywords:** Down syndrome, cognitive abilities, adaptive abilities, dementia, cognitive decline, recurrent infections.

## POSTER 30: Avoidant/Restrictive Food Intake Disorder (ARFID) in a Girl Affected by Marfan Syndrome (MFS)

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**Background:** MFS is an heritable disorder of connective tissue, transmitted as an autosomal dominant trait, characterized by the mutation in fibrillin 1 gene (FBN1). The diagnosis of MFS is often complex because of the evolution of the phenotype with age and also because of the inter-individual variation in the clinical presentation even among the affected family members. MFS is often associated with a wide range of psychiatric problems like anxiety disorders, depressive disorders, schizophrenia, neurodevelopmental disorders and Eating Disorders (ED). We report a 16 years old girl (BL) who came to observation for a selective feeding successively diagnosed as ARFID.

**Methods:** BL (Kg 43, H 165 cm, BMI 16.9) was evaluated from clinical, instrumental and psychometric point of view.

**Results:** The patient presented ligamentous laxity, long-limbed body habitus suggestive for MFS. The echocardiographic evaluation showed mild dilatation of aortic root, with rectilinear sinotubular junction and enlarged ascending aorta (z score = 2). The eye examination was normal. Sanger sequencing of the FBN1 gene identified the c.7501G>A (p.Val2501Ile) variant/mutation MFS. The eating disorder was consistent with DSM-5 criteria for ARFID. Eating Disorder Inventory-2 showed the presence of dissatisfaction with her own body. A mild intellectual disability (IQ=57;VIQ=61;PIQ=62) and reduced adaptive levels in the socialization and communication domains of the Vineland Adaptive Behavior Scales were also documented.

**Conclusion:** BL is affected by ARFID, (mild) intellectual disability and adaptive disorders associated with MFS. We underline the importance of multidisciplinary assessment in ED associated with marfanoid habitus.

**Keywords:** Marfan syndrome, selective feeding, intellectual disability.

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## POSTER 31: Effect of Specialist ASD Built Environment on Behaviours of Individuals: A Mixed Methodology Evaluation of Service Change

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**Background:** During the relocation of an old continuing care unit for 7 people with Autistic Spectrum Disorders (ASD) and Challenging behaviours, due to closure of the old hospital site. An opportunity arose to develop a purpose built environment with architectural involvement. The evidence base for building design in people with ASD is poor and where it is available is not evaluated. The move here was only in terms of the built environment. All other staff and activities remained unchanged. As part of the move it was decided as far as possible in a clinical setting to evaluate the effectiveness of this move.

**Methods:** A single researcher conducted a series of qualitative and quantitative measures in the 6 months prior to the move and also 2 months after the move in the new unit. These included direct time point observations and qualitative interviews with staff and carers about their experiences before and after the move. Paired quantitative data was analysed and qualitative data was thematically analysed by the core researcher and another member of the team independently.

**Results:** Quantitative analysis showed that when engagement measures were combined into a single group significant differences were seen ($p = <0.05$). In other areas some changes were seen but not to a statistically significant level. Qualitatively negative pre move statements were replaced with positive post move statements about the environment for the people. One individual who had previously remained in self chosen isolation reporting to our researcher he was happy.

**Conclusions:** By designing an environment that encourages engagement and removes transition as far as possible it is possible to deliver improvements in a person's quality of life when all else remains unchanged. This remains one of the very few studies showing the beneficial impact of building design as an intervention for challenging behaviours.

**Keywords:** ASD, Building design, Challenging behaviour.

## POSTER 32: Incontinence in Persons with Angelman Syndrome

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**Background:** Angelman Syndrome (AS) is a congenital syndrome caused by a microdeletion or uniparental disomy on chromosome 15q11-13 with a prevalence of 1:10 –20,000. AS is characterized by impairments in intellectual, neurological and motor functioning, as well as psychological problems. Individuals with AS often have severe intellectual disability, ataxia, seizures, dysmorphic facies, an inability to speak and a happy, sociable disposition with inappropriate laughter. The aim of the study was to investigate the rate of incontinence and associated psychological problems in AS.

**Methods:** 90 children (4 –18 years) and 54 adults (18 –31 years) with AS were recruited through a parent support group (55.6% male, mean age 15.1 years). The Parental Questionnaire: Enuresis/Urinary Incontinence, the Incontinence Questionnaire-Pediatric Lower Urinary Tract Symptoms (ICIQ-CLUTS), as well as the Developmental Behavior Checklist for parents (DBC-P) or for adults (DBC-A) were filled out by parents or care-givers.

**Results:** 85.6% of individuals with AS were affected by at least one subtype of incontinence. 81% had nocturnal enuresis (NE), 61.4% daytime urinary incontinence (DUI) and 53.9% faecal incontinence (FI). The rate of incontinence declined in adults (74.0% vs. 95.3% in children). 50.6% of the children and 34.1% of adults had a clinically relevant DBC score. Incontinence was not associated with psychological symptoms.

**Conclusion:** Children with AS have high rates of incontinence, which decrease with age. Many adults are still affected by NE, DUI or even FI. Screening, assessment and treatment of incontinence in children with AS is recommended.

**Keywords:** Angelman syndrome, incontinence, enuresis, encopresis, behavioural problems.

## POSTER 33: Associations Between Inhibition, Working Memory and Theory of Mind in Rubinstein-Taybi Syndrome

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**Background:** The development of working memory and inhibition may be prerequisite to fully fledged Theory of Mind (ToM), which depends on holding multiple perspectives in mind, while inhibiting previously held perspectives. Exploring these associations in intellectual disability (ID) is important for understanding how individuals navigate the social world. For example, reduced stranger awareness has been noted in Rubinstein-Taybi syndrome (RTS) along with deficits in ToM, inhibition and working memory. To date, associations between these cognitive skills have not been explored in RTS.

**Methods:** 24 individuals with RTS (mean age: 20.89; range = 6.75 – 44.42) participated. Participants completed a measure of general cognitive ability (The Mullens Scales of Early Learning or Wechsler Abbreviated Scale of Intelligence) and scaled batteries of ToM, inhibition and working memory tasks. Parents completed the Behaviour Rating Inventory of Executive Function – Preschooler.

**Results:** Participants were assigned a ToM developmental age based on their performance. A strong positive association was found between ToM age and inhibition on the direct assessments (R =.70; $p <$.001), and with parental ratings of inhibition. Greater working memory capacity was associated with better ToM task performance (R =.81; $p <$.001). The associations with inhibition remained significant when partial correlations were conducted to control for MA (R =.47; $p =$.020 & R = -.40; $p =$.020).

**Conclusion:** This study is the first to explore associations between inhibition, working memory and ToM in RTS. An inhibition deficit could account for poor performance on ToM tasks in RTS. Further research should explore the direction of this association. When working with individuals with RTS around social situations it may be useful to focus on the development of inhibitory control. The importance of understanding the correlates of ToM in the wider ID population will be discussed.

**Keywords:** Rubinstein-Taybi syndrome, Working Memory, Inhibition, Theory of Mind.

# POSTER 34: Stress, Psychological Morbidity and Perceived Social Support Among Parents of Children with Down Syndrome and Co-Morbid Autism Spectrum Disorder

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**Background:** With the widely perceived 'Down syndrome advantage', the pressures of raising a child with Down syndrome (DS) and co-morbid autism spectrum disorder (ASD) may go undetected. In children with both disorders DS is invariably the primary diagnosis, due to the presence of easily recognised physical traits, and obtaining a subsequent clinical diagnosis of ASD can be difficult. The fact the children do not show the characteristic patterns of development associated with DS (i.e. good sociability and relatively low levels of behavioural problems) may increase parental stress. Furthermore, the particular difficulties faced by parents may not be adequately recognised by DS-specific parent support groups, resulting in lower levels of perceived support. However, to date, there has been no research into stress among parents of children with DS and co-morbid ASD.

**Methods:** Fifty parents of children with DS were assessed for levels of stress, psychological morbidity and perceived social support. The children were clinically observed for ASD and parental outcomes were compared between those children who met the threshold for ASD and those who did not. Regression analyses were used to assess potential contributory factors, including child ASD severity, adaptive behaviour and challenging behaviour.

**Results:** Parents of children in the DS+ASD group reported a higher level of stress than parents of children in the DS-only group. However, no group differences were identified in psychological morbidity or perceived social support. Of the predicted factors only child challenging behaviour and perceived social support contributed to stress, with perceived social support also affecting parent psychological morbidity.

**Conclusion:** The challenging behaviour in this group, as well as stress reported by parents, indicates that existing services for families with children with autism might be helpful. Research shows that equipping parents with the skills to manage their children's behaviour can lead to reduced stress and improved relationships.

**Keywords:** Down syndrome, autism spectrum disorder, co-morbid, stress, social support.

## POSTER 35: Prevalence of Autism and ADHD in Down Syndrome: A Population -Based Study

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**Background:** The purpose of this study was to investigate the prevalence of autism spectrum disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) in a population-based group of children and adolescents with Down syndrome (DS) and to relate the findings to level of intellectual disability (ID) and to medical conditions.

**Methods:** In a population-based cohort of 65 children and adolescents with DS (5 –17 years), 41 individuals for whom parents gave consent for participation were clinically assessed with regard to ASD and ADHD. Main instruments used were the Autism Diagnostic Interview-Revised (ADI-R), Autism Diagnostic Observation Schedule (ADOS), SNAP-IV and the Adaptive Behaviour Assessment System-Second Edition (ABAS-II).

**Results:** High rates of ASD and ADHD were found; 17 (42%) and 14 (34%) of the 41 children met DSM criteria for ASD and ADHD respectively.

**Conclusion:** Children with DS and coexisting neurodevelopmental/neuropsychiatric disorders in addition to ID and medical disorders constitute a severely disabled group. Based on the results we suggest screening to be implemented for both ASD and ADHD, at the age of 3 –5 years and early school years, respectively, to make adequate intervention possible.

**Keywords:** Down syndrome, Autism, ADHD, Intellectual disability.

## POSTER 36: A Novel Approach to Validating Autism Spectrum Disorder Candidate Genes Identified in Sequencing Studies

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**Background:** Autism spectrum disorder (ASD) is a highly heritable but genetically heterogeneous disorder. Both single nucleotide variants in specific genes and structural chromosomal copy number variants (CNVs) are implicated in the aetiology of ASD. It is emerging that there is considerable overlap between candidate genes for ASD and intellectual disabilities (ID) and/or schizophrenia. Next generation sequencing has increased the rate of discovery of genes conferring risk to ASD. We present a novel methodological approach combining whole exome sequencing (WES) findings in ASD with CNV data from adults with ID and psychiatric disorders. We aim to consolidate novel ASD risk genes by describing the psychiatric phenotype in overlapping loci.

**Methods:** We identified 107 candidate genes from WES data which are predicted to be enriched in ASD. These were mapped to a dataset of CNVs in 567 patients with ID and co-morbid psychiatric disorders from London, Barcelona and Leuven. CNV loci containing the WES ASD candidate genes were identified and compared against the Simons Foundation Autism Research Initiative (SFARI) autism gene database to ascertain whether they had previously been described in ASD. The phenotype of patients with CNVs in these overlapping regions was examined, including psychiatric diagnosis, ASD symptomatology and family history.

**Results:** We describe several CNV loci present in our cohort of adults with ID and psychiatric disorders which overlap with ASD candidate genes identified in WES data; some of these CNVs have not been associated with ASDs before. The phenotype of individuals with CNVs at these loci is described.

**Conclusion:** We present an approach to validate novel ASD genes identified in sequencing studies using CNV data. Our findings provide further evidence to implicit a subset of novel ASD candidate genes and suggest these genes have pleiotropic effects on neurodevelopment when perturbed.

**Keywords:** Autism spectrum disorder, intellectual disabilities, psychiatric disorders, copy number variants, whole exome sequencing.

# SSBP Syndrome Sheets 2015

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

# Angelman Syndrome

## Alternative names

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

## First description

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

## Genetic aspects

Angelman syndrome is caused by a disruption of the maternally inherited proportion of chromosome 15q11.2-13 (Clayton-Smith & Laan, 2003; Knoll *et al.*, 1989) via four known genetic mechanisms (Jiang *et al.*, 1998). Approximately 70% of cases are caused by a de novo deletion (Knoll *et al.*, 1989). The deletion can be further categorised as a 'Class I' or 'Class II' depending on the amount of information missing (Sahoo *et al.*, 2006), with Class I deletions representing a larger deletion, encompassing Class II. The majority of deletions in Angelman syndrome are Class II, with an estimated prevalence of between 55 and 60% of de novo deletions (Christian *et al.*, 1995). 2-7% of cases are caused by Uniparental Disomy (Engel, 1993; Prasad & Wagstaff, 1997), where two copies of the paternal chromosome are inherited, 2-8% of cases are caused by a mutation in the UBE3A gene (Kishino, Lalande, & Wagstaff, 1997) and 2-5% of cases are caused by an imprinting centre defect (Bürger *et al.*, 1997). Between 5-20% (dependent upon sample and extent of molecular investigations) of individuals with the physical and behavioural features of Angelman syndrome show no identifiable abnormalities in the 15q 11-13 region (Clayton-Smith & Laan, 2003; Williams, Lossie, & Driscoll, 2001). The genetic association between Angelman syndrome and Prader-Willi syndrome has evoked interest in genomic imprinting (see Brown & Consedine, 2004; Haig & Wharton, 2003 for an excellent discussion).

Many of the features of the syndrome are thought to result from impaired expression of UBE3A. This gene is found throughout the brain and has a role in proteic scavenging processes. This expression is normally determined epigenetically by a methylation pattern which is specific to the maternally inherited chromosome. Abnormal imprinting in various regions of the brain and the cerebellum are probably responsible for most of the phenotype. Angelman syndrome phenotype has been associated with mutations in the X-linked methyl-CpG-binding protein 2 (MECP2) which has been implicated in Rett syndrome.

## Incidence/prevalence

Prevalence rates vary between 1 in 10,000 and 1 in 40,000 live births (Buckley, Dinno, & Weber, 1998; Clayton-Smith, 1993; Petersen, Brøndum-Nielsen, Hansen, & Wulff, 1995). Reports on the male to female ratio of Angelman syndrome are inconsistent, with estimates given between 1:1 to 1:2 (Saitoh *et al.*, 1994; Smith *et al.*, 1996).

## Physical phenotype

Craniofacial features include microbrachycephaly, short, hooked nose, prognatism, wide smiling mouth, widely spaced teeth and hypopigmentation (Williams *et al.*, 2006). Facial change with age, with a 'coarsening' of facial characteristics into adulthood (Sandanam *et al.*, 1997).

Children and adults are reported to have difficulties with movement and balance (Williams *et al.*, 2006) and ataxic gait thought to be caused by cerebellar dysfunction (Chéron, Servais, Wagstaff, & Dan, 2005). Scoliosis may develop, especially in less mobile patients. Axial hypotonia is present from birth. Limb hypertonia predominating at the lower extremities appears in infancy. Early onset of seizures in Angelman syndrome (< 3 years) is reported in over 80% of individuals (Williams *et al.*, 2006) and seizures persist into adulthood (Laan, den Boer, Hennekam, Renier, &

Brouwer, 1996). Abnormal EEG is found in most cases of Angelman syndrome (Boyd, Harden, & Patton, 1988) regardless of the presence of seizures (Laan & Vein, 2005).

## Behavioural aspects

The behavioural phenotype of Angelman syndrome is characterised by heightened levels of laughing and smiling, a happy demeanour, excessive sociability, aggression, impulsivity and sleep disorders (Horsler & Oliver, 2006a). Early work suggested that frequent laughing and smiling was neurologically driven, and therefore environmental factors were not influential (Williams, Frias, & Opitz, 1982). However, careful experimental manipulation of the environment identified that both the frequency and duration of these behaviours are related to environmental context, namely adult interaction (Horsler & Oliver, 2006b; Oliver, Demetriades, & Hall, 2002). Increased prevalence of aggression, not self-injury, is reported (Arron, Oliver, Moss, Berg, & Burbidge, 2011), with typical topographies including hair pulling and skin grabbing (Summers, Allison, Lynch, & Sandier, 1995). Although it has been suggested that social motivation underpins the heightened aggression in Angelman syndrome, this is not shown consistently in the literature (Allen *et al.*, 2010; Radstaake *et al.*, 2013; Strachan *et al.*, 2009).

## Cognitive aspects

Angelman syndrome is associated with a severe to profound intellectual disability, with deficits found in all areas of adaptive behaviour and cognition (Gentile *et al.*, 2010; Peters *et al.*, 2004). Comparisons across cognitive skills suggest relative strengths in socialisation (Peters *et al.*, 2004) and deficits in learning and attention (Jiang *et al.*, 2010; Walz & Benson, 2002). Although broad communication difficulties are shown (Clayton-Smith & Laan, 2003), Angelman syndrome is associated with particular deficits in expressive language; the majority of children and adults are non-verbal with limited alternative communication skills (Calculator & Black, 2010; Jolleff & Ryan, 1993; Penner, Johnston, Faircloth, Irish, & Williams, 1993).

Genotype-phenotype correlations have been reported (Gentile *et al.*, 2010), with a de novo deletion associated with a greater deficit across all areas of cognition compared to ICD, UPD and UBE3A mutation. Comparisons across the deletion classes (Class I and Class II) highlight Class I deletions (larger amount of information missing) as being associated with lower levels of adaptive and cognitive functioning, including expressive language (Sahoo *et al.*, 2006; Varela, Kok, Otto, & Koiffmann, 2004).

## Life expectancy

It is estimated that life span may be 10-15 years shorter (Williams, Driscoll, & Dagli, 2010), although this has not been examined directly.

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*Mary Heald and Chris Oliver*
*(updated August 2014)*

# Autism Spectrum Disorder

## Classification

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

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

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

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

## Associated conditions

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

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

## Genetics

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

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

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

## Prevalence

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

## Physical Phenotype

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

## Life expectancy/natural history

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

## Behavioural and cognitive characteristics

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

## Outcome

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

## Websites

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

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*Patricia Howlin, 2013*

# CHARGE Syndrome

**First Description**

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

**Genetics/aetiology**

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

**Incidence/prevalence**

While most sources estimate incidence at 1/10,000 births, a comprehensive study of individuals in the Netherlands found between 1:15,000 and 1:17,000 (Janssen *et al.*, 2012).

**Physical phenotype**

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

been proposed (i.e., Verloes, 2005). Diagnosis is difficult because there is great variability in presence and severity of the features.

CHARGE has become the most common cause of congenital deaf-blindness (after "other" and "unknown"). Vestibular difficulties are present due to missing or malformed semi-circular canals and otoliths. Swallowing difficulties are common due to cranial nerve dysfunction. Other problems include gastroesophageal reflux, airway difficulties, chronic otitis media, sinusitis, detached retina, scoliosis, chronic constipation with megacolon, and sleep disturbances.

Cranial nerve anomalies are common in CHARGE with as many as 92% having symptoms of at least one anomaly. It is speculated that in some cases all 12 cranial nerves might be affected, but the most common are I, V, VII, VIII, and IX/X.

**Behavioural and psychiatric characteristics**

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

**Neuropsychological characteristics**

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

**Useful websites/associations for more information**

- www.chargesyndrome.org
  – US CHARGE foundation
- www.chargesyndrome.org.uk
  – UK support group
- www.chargesyndrome.org.nz
  – Australasian support group
- www.cmich.edu/colleges/chsbs/Psychology/charge
  – CHARGE research lab focused on behaviour

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*Timothy S. Hartshorne, May, 2015*

# Coffin-Lowry Syndrome

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

## Genetics and molecular biology

The *RPS6KA3* gene encodes a growth factor regulated serine-threonine protein kinase, Rsk2 (alternate names: p90$^{RSK2}$, MAPKAPK1B, ISPK-1), which acts at the distal end of the *Ras*-Erk1/2 signalling cascade. Mutations in the *RPS6KA3* gene are extremely heterogeneous and lead to premature termination of translation and/or to loss of phosphotransferase activity of the RSK2 protein. For the vast majority of mutations so far reported, no consistent relationship has been observed between specific mutations and the severity of the disease (Delaunoy *et al.*, 2006). However, expression of some features was found to be associated with particular truncating mutations in a few patients (Nakamura *et al.*, 2005).

## Incidence / Prevalence

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

## Physical features and natural history

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

Female heterozygotes show variable involvement that can range from short stubby digits with normal appearance to quite marked facial dysmorphism. Ventriculomegaly has been observed in several affected males and females.

Although accurate information is not available the paucity of reports of older affected males suggests

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that their life expectancy is reduced in contrast to that of females who can survive well into old age. Reported causes of death in affected males include myocarditis, pneumonia and inhalation during a convulsion. Several males have succumbed to complications following general anaesthesia for correction of orthopaedic problems or dental extraction (Hanauer & Young, 2002, Hunter, 2002).

## Behavioural characteristics

Cognitive deficiencies in CLS male patients are prominent, but markedly variable in severity, including between siblings. However, the vast majority of patients are severely affected, with IQ scores ranging from moderate to profound (between 15 and 60). Very mild cases of the disease have been reported, with in particular in a few families only non-syndromic mental retardation (Field et al., 2006). Delay in speech acquisition is particularly common with most reported males having a very limited vocabulary. Despite the limited verbal abilities, the communication skills are good and affected individuals are usually cheerful, easy going, and friendly.

Cognitive function of female carriers may be variably affected: it can range from normal intelligence to moderate mental retardation. Frequently, they are reported to have learning difficulties at school. Obesity and psychiatric illness (depression, psychotic behavior, and schizophrenia) have been described in few female carriers. Epilepsy may occasionally develop. Stimulus-induced Drop Episodes (SIDE) may occur in response to unexpected auditory of tactile stimulus (Rojnueangnit et al, 2013)

## Available guidelines for behavioural assessment/ treatment/management

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

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*André Hanauer, June 2010*
*Revised Stewart Einfeld, 2015*

# Coffin Siris

### First description and alternative names
The Coffin Siris syndrome was first described by Grange Coffin, MD and Evelyn Siris, MD in 1970. The researchers described three affected girls with intellectual disability, postnatal growth retardation, lax joints, brachydactyly of the fifth digits with absent nails, dislocation of radial heads, and absence of the fifth terminal phalanges (Coffin & Siris 1970). Alternative names include "Dwarfism-Onychodysplasia", "Short Stature-Onchyodysplasia", "Fifth Digit syndrome", and "Mental Retardation and Hypoplastic 5thFingernails".

### Genetics and molecular biology
Coffin-Siris syndrome is a SWI/SNF complex disorder (Tsurusaki et al, 2014). McPherson *et al.* (1997) describes a 1 male to 3 females distribution, but Fleck *et al.* (2001) found the distribution to be 10 males to 8 females. Both autosomal dominant and autosomal recessive inheritance have been suggested by various studies (McPherson *et al.* 1997).

Studies have examined the candidate region for Coffin Siris. An infant with findings consistent with Coffin Siris syndrome was reported to have an apparently balanced translocation with breakpoints at 1q21.3 and 7q34 (Mcpherson *et al.* 1997). Other research suggested a candidate region for Coffin Siris at 7q32->34 (McGhee *et al.* 2000). A partial trisomy 9p gene change has also resulted in a Coffin Siris phenotype (Temtamy *et al.* 2007). Coffin Siris investigations continue.

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

### Physical features and natural history
Minimal clinical criteria for the diagnosis of Coffin Siris syndrome include developmental delay, hirsutism, coarse facies, feeding problems, and hypoplasia or aplasia of the distal fifth digits and nails. Additional characteristics of Coffin Siris syndrome include feeding or sucking difficulties, wide mouth, thick lips, hypotonia, flat nasal bridge with broad nose, sparse scalp hair, thick and laterally placed eyebrows, microcephaly, abnormal ear placement, abnormal or delayed dentition, high arched palate, delayed bone age, coxa valga, frequent otitis media, and respiratory infections (Fleck *et al.* 2001). Head circumference-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.

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

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

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

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

**Useful Websites**

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

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*Judith Hiemenga,  Srinivasan Sathyanarayanan*
*& Joann Bodurtha, 2010*
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# Cornelia de Lange Syndrome

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### First description and alternative names

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

### Incidence/prevalence

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

### Genetics

CdLS is caused by a deletion in the NIP-BL gene on chromosome 5 (locus 5p13) in 20% to 50% of cases (Gillis *et al.*, 2004; Krantz *et al.*, 2004; Miyake *et al.*, 2005; Tonkin *et al.*, 2004). Additional mutations on the SMC3 gene on chromosome 10 (Deardorff *et al.*, 2007), X linked SMC1a and HDAC8 genes (Deardorff *et al.*, 2012a; Musio *et al.*, 2006) and more recently identified RAD21 mutations (Deardorff *et al.*, 2012b) are reported to account for a smaller proportion of cases. All genes are involved in the structure and regulation of the cohesin complex which is crucial for neural maintenance and repair (Deardorff *et al.*, 2012b; Lui & Krantz 2009). It is probable that there are further unidentified mutations relevant to the cause of CdLS.

The NIP-BL gene is expressed in the developing skeleton and soft tissue of the limbs, hands, spinal column, face and head including the ear canal, the atrial and ventricular areas of the heart, oesophagus, trachea and lungs (Tonkin *et al.* 2004). Individuals with NIP-BL mutations show large variability in presentation but a larger proportion of these individuals appear to be more severely affected by the syndrome with more severe intellectual disability and limb abnormalities (Gillis *et al.* 2004; Bhuiyan *et al.* 2006). In contrast, mutations in SMC1A and SMC3 have currently been found to result in a milder presentation of the CdLS phenotype with less severe intellectual disability and fewer physical abnormalities (Deardorff *et al.* 2007).

### Physical features and natural history

Individuals with CdLS typically have a low birth weight, small stature, upper limb abnormalities (25%) and hirsutism, although those with a milder presentation seem less affected by these problems (Deardorff *et al.* 2007; Kline *et al.* 2007). Distinctive facial features, including: synophrys, long, thick eye lashes, a long and prominent philtrum, a thin upper lip; and a downturned mouth appear characteristic of most individuals with the syndrome (Kline *et al.* 2007). CdLS is associated with many health problems. Some of the most commonly occurring problems include: 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 (Cochran *et al.*, 2015; Moss *et al.*, 2009; Nelson *et al.*, 2013; Oliver *et al.*, 2011). Gastro-intestinal disorders associated with CdLS create an increased risk of early mortality due to aspiration, leading to pneumonia in some cases. Early assessment and intervention of gastro- intestinal difficulties is of utmost importance in individuals with CdLS.

### Behavioural characteristics

Self-injurious behaviour is generally thought to be more common in people with CdLS than in the general intellectual disability population (Sloneem *et al.* 2009) and reported to be influenced by social reinforcement for some individuals (Arron *et al.*, 2006). There is a notable association between 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 been consistently reported (Basile *et al.,* 2007; Berney *et al.*, 1999; Bhyuian *et al.*, 2006; Moss *et al.*, 2008; Nakanishi *et al.*, 2012; Oliver *et al.*, 2011; Strivastava *et al.*, 2014). This association with ASD is not solely accounted for by associated intellectual disability (Moss *et al.*, 2008), although the profile of ASD characteristics appears to be different to that of idiopathic ASD (Moss *et al.*, 2012; Moss et al, 2013). Extreme shyness and social anxiety are characteristic of many individuals with CdLS and an unusually high number of individuals with CdLS are reported to show characteristics of selective mutism. These difficulties may become more prominent with age (Goodban, 1993; Nelson *et al.*, 2014; Richards *et al.*, 2009).

There is emerging evidence indicating broad age-related changes in CdLS including increased anxiety, low mood, social withdrawal and challenging behavior (Berney *et al.*, 1999; Cochran *et al.*, 2015; Nelson *et al.*, 2014; Oliver *et al.*, 2011; Sarimski, 1997) alongside the early onset of physical signs of ageing (Kline *et al.*, 2007). Biological processes that occur downstream from the genetic mutations responsible for CdLS have been implicated in these reported changes with age (Gimigliano *et al.*, 2012; Kline *et al.*, 2007).

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

A recent study by Reid (2010) demonstrated impairments in aspects of executive function including impairment on tasks requiring generativity (verbal fluency), flexibility and inhibition (rule switch) but not working memory. Digit span (backwards) and verbal

fluency skills were significantly negatively correlated with chronological age in CdLS but not a contrast group of individuals with DS, indicating increased deficits in these areas with age.

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

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

**Physical features and natural history**

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

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

**Behavioural characteristics**

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

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

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

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

ASD characteristics are not considered to be strongly associated with the CdCS (Moss *et al.*, 2008) and have been reported to be less severe relative to a matched control group (Claro *et al.*, 2011). In fact,

several studies report social interaction skills as being a relative strength of individuals with CdCS (Carlin, 1990; Cornish & Pigram, 1996). Specifically, Moss *et al.*, (2013) report that communication skills used to solicit social interaction (indicative of social motivation) occurred significantly more frequently in individuals with CdCS relative to matched contrast groups of individuals with Cornelia de Lange and Angelman syndromes during structured social observations.

**Neuropsychological characteristics**

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

**Useful websites/associations/resources for more information**

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

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*P Tunnicliffe, J Moss, & C Oliver, July 2015.*

# Down Syndrome

Original description was by J. Langdon Down in 1886. Trisomy 21 was first reported in association with Down syndrome (DS) by Jérôme Lejeune and colleagues in 1959.

## Incidence/prevalence

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

## Genetics

The presence of a complete or partial third copy of human chromosome 21 (Hsa21) is the cause of DS. Partial copy should include all or part of the long arm of Hsa21.This excess of genetic material leads to a dysregulated expression of certain genes. The functional impact of these changes could be a direct result of the action of the proteins expressed in excess by the Hsa21 genes, or indirectly, through the proteins that they regulate. In any case the effect will be different according to the protein involved (Fillat, 2014). The nuclear compartments of trisomic cells undergo modifications of the chromatin environment influencing the overall transcriptome, and gene expression dysregulation domains may therefore contribute to some trisomy 21 phenotypes (Letourneau, 2014).

More than 450 genes have been identified on human chromosome 21. The development of new mouse models, either trisomic for different chromosome segments or for individual genes, has helped narrow the focus to those genes likely to be important contributors to the DS phenotype. Of particular interest are the findings relating to 2 genes located within the putative DS critical region of chromosome 21. These are dual-specificity tyrosine-regulated protein kinase 1 (DYRK1A) and DSCR1.

DYRK1A is particularly expressed in the hippocampus, cortex, cerebellum, and heart—regions affected in DS and overexpressed in fetal DS. Transgenic mice that overexpress DYRK1A show learning and memory deficits. Further, DYRK1A phosphorylates tau protein, and this change is known

to be important in initiating the cascade of processes leading to amyloid formation in Alzheimer dementia.

DSCR1 is overexpressed in Alzheimer patients and causes abnormalities in synapse function in DS individuals. DYRK1A and DSCR1 act synergistically to regulate the transcription factor NFATc, which plays a critical role in the development of the central nervous system (Einfeld, 2010).

The origin of supernumerary Hsa21 in free trisomy is in most cases the maternal meiosis. The risk of recurrence (not allowing for maternal age) is low. About 2% of DS results from an unbalanced translocation (material from one chromosome breaking off and "sticking to" another). This often involves chromosomes 21 and 14, and is usually a "one-off" event. In some cases a parent also has a (balanced) translocation (with no overall disruption of genetic material), and the risk of recurrence is high. 21 to 21 translocations also occur. Mosaicism is a term used to describe the presence of two (or more) cell lines within the body. In DS this means one cell line with trisomy 21 and one unaffected cell line. About 3% of DS probably results from mosaicism (many cases may not be diagnosed). The proportion of affected and unaffected cell lines varies, as does the intellectual impairment. Transient myeloproliferative disorder and megakaryoblastic leukemia of DS are associated with mutations in the GATA1 gene in conjunction with trisomy 21.

## Physical features

Two types of phenotypes are observed in trisomy 21: those seen in every patient and those that occur only in a fraction of affected individuals. For example, cognitive impairment is present in all patients with DS, so as muscle hypotonia and Alzheimer disease neuropathology after 35 years (Antonarakis, 2004). Motor dysfunction is highly prevalent among individuals with DS, who exhibit clumsy sequences of movements, and poor control in programming motor sequences, their timing and force. Motor dysfunction in DS is accompanied by hyporeflexia and reduced muscular strength and tone (Dierrsen 2012) On the contrary, congenital heart defect occurs only in

~40% and atrioventricular canal in ~16% of patients. Duodenal stenosis/atresia, Hirschsprung disease and acute megakaryocytic leukemia occur 250-, 30- and 300-times more frequently, respectively, in patients with DS than in the general population. In addition, for any given phenotype there is considerable variability (severity) in expression. DS is also associated with an increased incidence of autoimmune disorders, such as autoimmune thyroiditis, primary sclerosing cholangitis, insulin dependent diabetes mellitus, celiac disease and alopecia areata. On the other hand, DS seems be protective against other conditions, such as multiple sclerosis, Crohn disease, neuroblastoma and the development of most solid tumors, which are rarely reported in association with DS.

Most adults with DS are of short stature (70%), with a characteristic facial appearance. The eyes seem to slope upwards and outwards as a result of alterations in the structure of the surrounding tissues. The nose has a wide bridge, and the head an unusual shape ("brachycephaly"). Protruding tongue is present in 45%. Limb abnormalities include a single transverse crease on the palm (85%), a large cleft between the first and second toes, and relatively short upper arms. People with DS are prone to disorders of the thyroid gland (15% develop hypothyroidism during childhood or adolescence). Ninety percent of all DS syndrome patients have a significant hearing loss, usually of the conductive type. Sight problems (44-71%) are common in DS of advanced age, and in a large percentage of the general population.

Obstructive sleep apnea occurs in over half of children with DS aged 2–4years and is related to otolaryngological problems associated with the disorder and to the atlantoccipital instability.

## Life expectancy

Life expectancy has improved markedly over the past 50 years, largely as a result of antibiotic treatment of respiratory tract infections. Survival into the 8th decade is unusual but not extraordinary. The presence of an AVSD often leads to heart and lung failure in early adult life. Although changes in blood cells are relatively common, leukaemia is not particularly common (affecting about 1%).

## Behavioural characteristics

Fewer behaviour problems compared to controls with cognitive disability have been described in DS but more frequent than in sibling or in controls with normal IQ. Children with DS may be at a lower risk for significant behavioural comorbidities in that they show a lower profile of maladaptive behaviours compared to children with other intellectual disabilities. However, in comparison to typically developing age-matched peers, children with DS show higher rates of inattention, oppositional behaviours, and impulsivity-(Dykens, 2007)

17.6 % of individuals with DS aged less than 20 years have a psychiatric disorder, most frequently a disruptive behaviour disorder such as attention deficit hyperactivity disorder (6·1%), conduct/oppositional disorder (5·4%), or aggressive behaviour (6·5%). Twenty five % of adults with DS present a psychiatric disorder, most frequently a major depressive disorder (6·1%) or aggressive behaviour (6·1%).The dual diagnoses of DS and autism has gained much attention; although the association has always been appreciated, recent reports suggest a frequency as high as 7% and great delays in diagnosis. The stereotype of people with DS as happy, placid individuals with a gift for mimicry is not borne out by recent behavioural research. "Stubbornness" and obsessional features seem to be over-represented, and many people with DS react adversely in situations involving conflict.

No significant associations between age and the range or severity of any behavioural and emotional items were found in adult DS subjects without dementia. This suggested a more positive pattern for ageing adults with DS than has been previously described (Makary 2014).

## Cognitive characteristics

Cognitive disability is present in all patients with DS. Most children and adults with DS function in the mild or moderate range of intellectual disability. About 10% have a low average-borderline degree of intellectual disability. A minority have a severe or profound cognitive impairment. In DS patients, the average IQ score is around 50, with individual values ranging from 30 to 70 (Rachidi, 2007).

Almost all children with DS have a relatively specific expressive language impairment. Expressive language deficit in syntax is greater than expressive language deficit in the lexicon. Comprehension of words is typically more advanced than nonverbal cognition. Cognition deficits in verbal working-memory and delayed recall has been described.

Cognitive abilities tend to be greater among people whose DS is caused by mosaicism for trisomy 21.

In adults with DS, neuropathological changes typical of Alzheimer's disease usually develop by the fifth decade of life. Adults with DS are much more likely to develop dementia of Alzheimer type than the general population. On post-mortem examination, almost all adults with DS over the age of 35 have the brain changes characteristic of Alzheimer's disease but only about 45% of those over 45 years of age have clinically apparent dementia. The triplication of the amyloid precursor protein gene (APP) is a candidate for causing dementia in DS. However, additional Hsa21 genes may modulate the effects of APP triplication (Dierssen 2012).

Clinical signs and symptoms of Alzheimer's disease are noted in 75% of DS individuals over 60 years of age, and are most frequently seizures (58%), change in personality (46%), focal neurological signs (46%), apathy (36%), and loss of conversational skills (36%). Seizures appear to be associated with rapid cognitive decline in demented individuals with DS. In any adult for whom the diagnosis of Alzheimer's disease is being considered, a complete medical assessment should be done to detect any treatable disorders such as thyroid disease or depression.

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# Foetal Alcohol Syndrome/ Alcohol Related Neurodevelopmental Disorder

**First description and alternative names**

FAS was first observed in Nantes by paediatrician Paul Lemoine in 1968 who described similar dysmorphic facial features and growth delays in 127 infants of pregnant alcohol-drinking mothers. Fetal Alcohol Syndrome (FAS) was coined in Seattle by David Smith and Ken Jones in 1973(1,2).The Institute of Medicine in 1996 delineated Full FAS, Partial FAS, and Alcohol Related Neurodevelopmental Disorder (ARND) based on the presence or absence of facial dysmorphology and /or growth retardation (3). ARND replaced the old term Fetal Alcohol Effect (FAE). FAS Spectrum Disorders, an umbrella term, was introduced by O'Malley & Hagerman in 1998, refined to Fetal Alcohol Spectrum Disorders (FASDs) by Streissguth & o'Malley in 2000 (4,5). In 2013 DSMV proposed a new diagnostic guidelines for those with neurodevelopmental disorders associated with prenatal alcohol exposure (NDDPAE 315.8) but without facial features. It requires features to be ruled into a diagnosis with other factors ruled out. This was the first time this was included in an international diagnostic manual.

**Genetics and molecular biology**

Both FAS and ARND are teratogenic conditions, but recent research is beginning to study the epigenetic effects of prenatal alcohol exposure. For example, the major liver pathway of oxidative metabolism which produces acetaldehyde by cytotoxic alcohol dehydrogenase is also accompanied by a reduction in NAD to NADH. There is a subsequent alteration in the cellular redox triggered by a change in the NAD/NADH ratio which may result in gene activation resulting in a change in gene expression. Increasingly the impact of prenatal alcohol on epigenetic mechanisms has also been investigated. For example studies have demonstrated that prenatal alcohol exposure has the ability to modify methylation of the retrotransposon prior to the AVY gene in genetically inbred mice, leading to differences in coat colors (17). A wide range of mechanisms beyond this have been identified, from direct apoptotic damage, interneuronal signaling

deficits and damage to scaffolding proteins interfering with neural migration (18).

**Incidence/ prevalence**

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

**Physical features and psychiatric characteristics**

Characteristic facial features include short palpebral fissures, thin (flat) upper lip, flattened philtrum, flat midface. Growth retardation less than the 10th percentile for height and weight. Low birth weight for gestational age, decelerating weight over time not due to nutrition, disproportional low weight-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, Autism and Schizoaffective Disorder. Personality Disorders seen are, Avoidant, Dependent, Schizoid, Passive/Aggressive and Borderline. Presence or absence of facial dysmorphology or growth features do not clinically correlate with the psychiatric presentation or structural brain damage in FASD (5,8, 11, and 12).

## Neuropsychological Deficits

70-75% of patients with FASD do not have intellectual disability. The neuropsychological profile consistently shows a Complex Verbal and Non-Verbal Learning Disorder affecting multiple domains of functioning including attention, impulsivity, working memory, executive function, processing speed, social skills, interpersonal relatedness and language development. It includes a Mathematics Disorder and/ or Disorder of Written Expression and/or Reading Disorder, and evidence of a Mixed Receptive/ Expressive Language Disorder with specific deficits in social cognition and social communication. Vineland Adaptive Behavioral Scale (VABS) shows Functional Deficits in daily living skills, socialization and communication. Those with higher functioning in some areas can often mask their difficulties until external pressures lead to higher level abilities such as executive functioning being less effective. Simple functions are often intact. For example an individual can sequence and switch separately but not when these two tasks are combined. Working memory deficits tend to be verbal working memory deficits rather than numerical having implication as to how these skills are tested. (3, 5, 8,9,10, 13).

## Brain structural abnormalities

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

## Brain neurotransmitter and neurophysiological abnormalities

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

## Available guidelines for behavioral assessment/ treatment/management strategies

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

## Useful websites /associations for more information

- www.fasdaware.co.uk
- www.fasdtrust.co.uk
- www.nofas.co.uk
- www.fasd.ie
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*Raja Mukherjee, Kieran D O'Malley, May 2015*

# Fragile X Syndrome

## First described

Martin & Bell (1943): families with sex-linked inheritance for learning difficulties & characteristic physical features. Lubs (1969) identified the chromosome fragile site just above the tip of the X chromosome's long arm. Sutherland (1977) confirmed the importance of a folate-deficient culture in revealing the site. Verkerk *et al.* (1991) described the multiple CGG repeat sequence at Xq27.3 producing local hyper-methylation and impaired protein synthesis of FMRP. This protein is an RNA binding protein that transports mRNAs to the synapse and typically inhibits translation. The lack or deficiency of FMRP in fragile X syndrome causes enhanced transcription of many proteins important for synaptic plasticity. There is enhanced metabotropic glutamate receptor 5 (mGluR5) activity leading to enhanced long term depression (LTD). Treatment with an mGluR5 antagonist is a form of targeted treatment to reverse this neurobiological abnormality and studies are underway to assess treatment efficacy in behaviour and cognition.

## Genetic aspects

Sex-linked transmission, 80% of males with a full mutation (>200 CGG repeats) have intellectual disability and the rest having learning and or emotional problems. In full mutation females, approximately 25% have intellectual disability and an additional 60% have learning difficulties particularly in math, attention and impulsivity in addition to emotional problems. The diagnosis of fragile X syndrome is made by *FMR1* DNA testing. Cytogenetic studies may also show the fragile site but DNA studies are essential to identify the CGG repeat expansion. Carriers have a small CGG expansion of 55 to 200 CGG repeats. They are typically unaffected cognitively although in approximately 10 to 20% intellectual disability or autism can occur in carriers. Carriers have an elevation of their *FMR1-* mRNA level of 2 to 8 times the normal range. This elevation of mRNA leads to a gain-of-function toxicity that can be associated with developmental delay at times but more commonly causes emotional difficulties such as anxiety or depression in about 30%, primary ovarian insufficiency in 20% of female carriers and neurological problems in a subgroup of aging male and female carriers. These neurological problems include neuropathy, autonomic dysfunction, intention tremor and ataxia, and the combination of these problems is called the fragile X-associated tremor ataxia syndrome (FXTAS). FXTAS occurs in approximately 40% of older male carriers and 8% to 16% of older female carriers. Brain atrophy and white matter disease are seen on MRI in those with FXTAS. The premutation disorders including FXTAS and the fragile X-associated primary ovarian insufficiency (FXPOI) do not occur in those with a full mutation because they usually do not have elevated *FMR1*-mRNA levels.

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

## Incidence/Prevalence

The allele frequency of the full mutation is 1 in 2500 of the general population, however many individuals with the full mutation especially females do not have intellectual disability, although their learning difficulties and emotional problems still constitute fragile X syndrome. The premutation is more common and 1 in 130-250 females and 1 in 250-800 males in the general population have the premutation.

Institutionalised individuals with intellectual impairment of unknown origin have rates of fragile X syndrome ranging from 2.5% to 5.9%. The syndrome is the most common inherited cause of learning disability. Approximately 2 to 6% of those with autism have fragile X syndrome and it is the most common single gene associated with autism.

### Physical

Prominent ears are seen in 60% of children and adults usually have a long face and sometimes a prominent jaw. A high arched palate is seen in the majority and strabismus is present in up to 30%. Macroorchidism or large testicles are a feature in adolescence in over 90% of males. A connective tissue dysplasia produces joint laxity, soft velvety skin and flat feet with pronation. This connective tissue problem can also cause aortic dilatation and/ or mitral valve prolapse, typically in adults. Seizures occur in approximately 30% and recurrent otitis media occurs in the majority in early childhood.

### Life expectancy/Natural history

Probably normal except for those who have seizures. Rare cases of sudden death have been reported. Aging studies in individuals with fragile X syndrome have documented a high rate of Parkinsonian symptoms in the 50s and beyond.

### Behavioural characteristics

Intellectual impairment is very variable and may relate to the molecular findings. Those with higher levels of FMRP, such as females and those with an unnmethylared full mutation or mosaic status (some cells with the premutation and some with the full mutation), will have a higher IQ. Verbal intelligence exceeds performance abilities in both affected males and non-learning disabled female carriers, although about 10% of patients will be non-verbal or will have very low verbal abilities. Particular difficulties with numeracy and visuospatial skills are common. The rate of intellectual development diminishes with age, particularly after puberty.

Speech & language development is almost always delayed with dysfluent conversation, incomplete sentences, echolalia, palilalia and verbal perseverations. There is often a jocular quality to speech with narrative, compulsive utterances and swings of pitch ("litany-like"). "Cluttering" refers to the fast and fluctuating rate of talking with marked and frequent repetitions, garbled and disorganised speech, poor topic maintenance, and tangential comments.

Social impairments, autism and ADHD. Social anxiety with aversion to eye contact is present in the majority of children and adults. Approximately 30% will have autism and an additional 30% will have an autism spectrum disorder (including PDDNOS or Asperger's syndrome). The rest are socially responsive and affectionate individuals with good understanding of emotions although autistic like features such as perseverations, hand mannerisms and poor eye contact with shyness are seen in the majority. Self-injury, notably hand biting and scratching provoked by frustration, anxiety and excitement is common. Hand flapping is seen in the majority both with and without autism. Obsessive and compulsive features are common and often lead to rituals and picky eating habits. Mouth stuffing, tactile defensiveness and overreaction to sensory stimuli leading to hyperarousal and tantrum behaviour is seen in the majority. Approximately 30% have aggression, and anxiety associated with hyperarousal is a component of this aggression. Hyperactivity is seen in about 80% although attention problems and impulsivity without hyperactivity can be seen especially in girls with the full mutation.

Individuals with fragile X syndrome typically respond well to a stimulant medication after 5 years of age. Selective serotonin reuptake inhibitors (SSRIs) help anxiety and can be used even in those under 5 y, although activation can be seen in about 20%, requiring a lowering of the dose or discontinuation. Atypical antipsychotics, most notably aripiprazole, when used in low dose helps to stabilize mood, decrease aggression, improve attention, and decrease anxiety. Minocycline is a targeted treatment for fragile X because it lowers matrix metalloproteinase 9 (MMP9) levels and preliminary data suggests improvement in the majority of patients. Arbaclofen, a GABAB agonist has also been shown to benefit patients with fragile X syndrome particularly those with autism or high levels of irritability. Preliminary data from mGluR5 antagonist treatment of adult with fragile X syndrome suggests benefits also.

## Resources

- **The Fragile X Society**, 53 Winchelsea Lane, Hastings, East Sussex, TN35 4LG. 01424 813 147

- **The National Fragile X Foundation**, P.O. Box 37, Walnut Creek, California, 94597, USA. 800-688-8765

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

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*Randi Hagerman, September 2010*

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# Klinefelter Syndrome (47,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 47,XXY genotype.

**Genetics and molecular biology**

The vast majority of KS is due to the numerical chromosome aberration 47,XXY; some cases may have 46,XY/47,XXY mosaicism, or structurally abnormal X chromosomes. The additional X chromosome arises from non-disjunction either during germ-cell development or in early embryonic cell divisions. Approximately 50% of non-disjunctions appear to be of paternal origin. The cause of the non-disjunction in not known.

**Incidence/prevalence**

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

**Physical features and natural history**

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

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

**Behavioural and psychiatric characteristics**

Individuals with 47,XXY are at increased risk for behavioural problems and psychiatric disorders. School aged children frequently show problems with anxiety and mood disorders, self-esteem, and socialization. Socialization problems frequently relate to inhibition and anxiety, and may become more pronounced during adolescence. Adults are at greater risk of depression related to low testosterone. 47,XXY individuals are considered to be at greater risk for psychosis. Brain imaging data has shown abnormal brain activation patterns and decreased brain volumes, particularly in frontal and temporal regions.

**Neuropsychological characteristics**

The effects on neurocognitive function widely, with many 47,XXY individuals having normal or above average cognitive capacity. On a group level mean IQ values fall within the normal to low normal range, and are depressed approximately 10 points below what would be expected based on siblings. Verbal ability may be more severely affected than nonverbal. 70-80% of 47,XXY individuals across several studies have had identified language problems. There may be difficulties with articulation, phonemic processing and word retrieval, in addition to more generally delayed expressive language and verbal fluency skills

Some studies have reported relatively more pronounced deficits in verbal IQ than performance

IQ, although this is not universal. Executive function capacities such as attention and impulse control may be impaired, although available studies are sparse. Several studies have reported impairments in both fine and gross motor skills. Cognitive features are thought to be a consequence of lack of fetal androgen.

Brain imaging may demonstrate significant changes in brain volumes but this does not clearly correlate with cognitive features. Underactivity of brain centres serving social cognition is evident.

## Available guidelines for behavioural assessment/treatment/management

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

## Useful websites/associations for more information

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

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*Rhoshel K Lenroot, 2010*
*Revised: Stewart Einfeld, 2015*

# Lesch-Nyhan Disease (LND)

### Alternative names

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

### First description

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

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

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

### Incidence

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

### Genetic aspects

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

There are probably a few thousand individuals with this disease in the world. The mutations are in the HPRT1 gene located on the long arm of the X chromosome. Remarkably, over 600 different mutations have been identified in different families (O'Neill and others). The product of the normal gene is the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) which recycles purines from DNA and RNA. Because it is an X-linked recessive mutation, it ought to occur only in males, but there have been several documented cases in females – thought to be a consequence of events explained by the Lyon Hypothesis. Since the 1960's we have known that because of the lack of HPRT, there is an over-production of uric acid and subsequent uric acid stone formation. (Xanthine stone formation is due to dose specific issues of allopurinol.) Unfortunately, treatment of the elevated serum uric acid with allopurinol does not have an impact on the neurobehavioral manifestations of the disease.

**Physical phenotype and the basal ganglia**

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

**Cognitive aspects:**

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

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

**Behavioural aspects:**

The behavioural phenotype of Lesch-Nyhan Disease, physical and emotional self-injury, including severe self-mutilation and aggressive behaviour, are generally involuntary in nature. The self-injurious behaviour is not under the patient's control nor does the patient desire it. These self-destructive behaviours usually begin between ages three and six and often escalate as the patient ages and the patient is more physically able to cause self-injury. The first manifestations of physical self-injury are lip biting, finger biting, and biting of the oral cavity. Modes and patterns of 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 behaviours, include hitting, kicking, head-butting, biting others, spitting, swearing, ethnic slurs, inappropriate remarks to the opposite sex, frequently changing opinions, and/or lying.

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

**Treatment:**

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

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

The use of medications for treating the behavioural component of this disorder is controversial yet most children and adults with LND are treated with different medications. No medication has been found to reverse the so-called 'Lesch-Nyhan behaviours', either motor or behavioural. Selective ignoring is a methodology that is designed to extinguish self-destructive emotional or physical behaviour in the LND patient. It requires the caretaker to ignore such behaviour by the LND patient towards said caretaker so that the behaviour

decreases or ceases. Along with selective ignoring, the use of redirection is also found to be helpful. At times controversial, the use of protective devices is essential, yet often problematic for patients and institutions not familiar with the care of LND patients. Professionals unfamiliar with LND may perceive the use of these protective devices from a traditional paradigm of restraints – which is to say, the use of these devices against a patient's will. When protective devices are requested by the patient -- and used to safeguard the patient from him or herself -- the outcome is an extraordinary feeling of comfort and safety. Not allowing the use of protective devices when requested violates the autonomous rights of the patient. In Lesch-Nyhan Disease self-injury far exceeds that associated with other developmental disabilities, and, of course, is a consequence of the neurotransmitter and cell function abnormalities characterizing the disorder. Although not all individuals with this condition demonstrate severe behavioural manifestations, it is reasonable to say that all benefit from the use of protective devices at some point during their lifetime. It is extremely important to note that the Joint Commission and the US government's CMS requirements both include exceptions to the restraint standards for patients with LND. Issues regarding removal of teeth is addressed above (See exceptions to the CMS standard: 482.13 (e) (6).)

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

**Life expectancy**

Life expectancy is a difficult issue to address as the extent of the associated clinical conditions of Lesch-Nyhan Disease has not yet been fully characterized. Fortunately, due to the use of allopurinol, which acts as a substrate for xanthine oxidase, patients with this

disorder should no longer die of renal complications. There is a suggestion that some patients may die suddenly in their twenties and thirties possibly as a consequence of an unexplained neurological event. Certainly, as the accompanying clinical conditions are managed a longer life expectancy can be anticipated.

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*Gary E. Eddey, 2014*

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# Mowat-Wilson Syndrome

### First description and alternative names

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

### Incidence/prevalence

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

### Genetics

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

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

### Physical features and natural history

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

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

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

### Behavioural characteristics

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

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

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

## Neuropsychological characteristics

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

## Useful websites/
## associations for more information

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

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

# Neurofibromatosis Type 1 (NF1)

### Genetics

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

### Incidence/prevalence

About 1 in 2,500 births.

### Physical features

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

### Life expectancy

Depends on nature and severity of clinical features.

### Brain abnormalities

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

### Behavioural characteristics

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

### Cognitive characteristics

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

### Treatment

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

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*Stephan Huijbregts 2015*

# Noonan Syndrome

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

### Associated conditions
NS is a genetically heterogeneous disorder, with different causative mutations in the RAS-MAPK pathway. Syndromes with shared pathogenetic mechanisms and clinical overlap with NS include Cardio-Facio-Cutaneous (CFC) syndrome, Costello syndrome, Neurofibromatosis type 1 (NF1), Noonan syndrome with multiple lentigines (formerly called LEOPARD syndrome), Noonan syndrome-like disorder with loose anagen hair (NSLH), and CBL-associated syndrome. They are grouped into the neurocardiofacialcutaneous syndrome family, or the Ras-opathies (Tartaglia *et al.*, 2011).

In the past, Noonan syndrome has -incorrectly- been referred to as 'Male Turner syndrome', 'Female pseudo-Turner syndrome', 'Turner phenotype with normal karyotype', 'Ullrich-Noonan syndrome' and 'Pterygium Colli Syndrome, included'. Although the NS phenotype has resemblance to the phenotype of (Ullrich-)Turner syndrome, the genotypes differ. Other syndromes with different genotypes but some phenotypical similarities to NS are William's syndrome and Aarskog syndrome (Van der Burgt, 2007).

### Genetics and molecular biology
NS may occur on a sporadic basis or in a pattern consistent with autosomal dominant inheritance, with a predominance of maternal transmission. In approximately 50% of the patients a missense mutation is found in the *PTPN11* gene on chromosome 12 (12q24.1). Germline mutations in twelve other genes of the Ras-MAPK pathway have been identified as causative in NS and closely related disorders: *SOS1* (about 10% of the cases), *RAF1* (5-15%), *KRAS* (<2-5%), *NRAS* (<2-5%), *BRAF* (<2%), *SHOC2* (<2%), *MAP2K1 (MEK1)* (<2%), *MAP2K2, CBL* (<1%), *RIT1* (<1%), *A2ML1* (<1%), *SPRED1,* and *HRAS*. In about 25% of the patients with a clinical diagnosis of NS, no mutation can be found yet (Pasmant *et al.*, 2009; Tartaglia *et al.*, 2011; Aoki *et al.*, 2013; Vissers *et al.*, 2015).

### Incidence/prevalence
The incidence of NS is estimated between 1 in 1000 to 1 in 2500 live births (Allanson, 2010).

### Physical features and natural history
Key characteristics are 1) short stature, 2) typical facial dysmorphology (wide-spread eyes, drooping eyelids, and low-set, posteriorly rotated ears with a thickened helix) and 3) congenital heart defects (pulmonary valve stenosis, hypertrophic cardiomyopathy, atrial septal defect). Some additional features are hematologic and ectodermal anomalies, skeletal anomalies, lymphatic dysplasia, cryptorchidism, and a webbed neck. Neonatal feeding difficulties and failure to thrive are present in the majority of infants with NS. Phenotypical expression is highly variable and often milder in adulthood than in youth. The diagnosis is primarily made on clinical grounds, by observation of cardinal features. The most widely used scoring system was developed in 1994 and updated and validated in 2010 (Van der Burgt *et al.*,1994; The Noonan Syndrome Guideline Development Group, 2010). Life expectancy for patients with NS is fairly normal, unless there are major complications of heart disease. Premature delivery is the main source of morbidity.

### Behavioural characteristics and psychopathology
A distinctive pattern of behavioural characteristics can not be recognised, although there are some indications for an increased risk for behavioural problems in children, characterised by social problems,

stubbornness, restlessness, and impulsivity. Traits from the autism spectrum and ADHD symptoms have been reported in children with NS in comparison with their nonaffected siblings (Adviento *et al.*, 2013; Pierpont *et al.*, 2015). Classical psychiatric syndromes have only incidentally been described for NS and mainly concern cases of anxiety disorders, obsessive-compulsive disorders, and mood disorders. In adults, alexithymic traits seem to be present more often, as well as elevated levels of psychological and social distress (Verhoeven *et al.*, 2008; Wingbermühle *et al.*, 2009; 2012a). In comparison with women with Turner syndrome alexithymia and impairments in emotion recognition seem to be less pronounced (Roelofs *et al.*, 2015).

### Neuropsychological characteristics

Neuropsychological findings show intelligence scores in a wide range, with a mildly lowered average intelligence. Language and motor development are often delayed. In children, a highly variable cognitive profile has been found, with indications for impairments in visual processing and language development, weaknesses in memory function (inconclusive results mention problems in working memory, long-term verbal memory and immediate visual memory), mild deficits in selective and sustained attention, and suboptimal planning and organisational skills (Wingbermühle *et al.*, 2009; Alfieri *et al.*, 2011a,b; Pierpont *et al.*, 2010; 2013; 2015). These cognitive impairments may explain learning problems and an increased need for special education.

While extensive cognitive problems seem to be present in childhood, cognition in adults with NS is mainly characterised by a lowered speed of information processing. As described above, social cognitive functions (recognising and expressing emotions) may be impaired as well (Wingbermühle *et al.*, 2012b).

### Available management guidelines

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

### More information

For information on NS in OMIM, online database of human genes and genetic disorders, see: http://www.ncbi.nlm.nih.gov/omim/163950. For details on the Noonan syndrome support group, see: www.noonansyndrome.org.

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*Renée Roelofs, Ellen Wingbermühle, Willem Verhoeven, Ineke van der Burgt, Jos Egger. June 2015*

# 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 althoug there are rare reports of children being born to females with PWS.

## Behavioural and psychiatric characteristics
The main behavioural techniques used to address hyperphagia include preventing access to food e.g. by locking cupboards, low calorie diets, all members of the household having the same diet and ongoing education about the risks of overeating. Appetite suppressants and gastric banding have not been shown to be useful. Octreotide has been shown to decrease concentrations of ghrelin in adolescents with PWS, but does not reduce appetite or BMI (De Waele *et al.* 2008).

Aside from the over-eating, the most common problem behaviours are temper tantrums, usually arising out of frustration or change to a familiar routine, and which can result in extreme aggression; mood swings which do not fulfil criteria for a defined psychiatric disorder; and self-mutilation in the form of skin-picking. Recent evidence suggests that modulation of the glutaminergic pathway may reduce the compulsive behaviours; oral N-acetylcysteine was found to reduce skin picking, although participants with PWS were not compared with a control group (Miller & Angulo 2013).

Relative to others with intellectual disability, people with PWS are more likely to exhibit severe problem

behaviours (Dykens *et al.* 1997). Obsessional traits occur commonly, in particular needing to ask or tell, requiring routines, hoarding and repetitive questioning (Clarke *et al.* 2002). It has been found that people with PWS who are exposed to routines for longer before a change are more likely to engage in temper outburst behaviours (Bull *et al.* 2014).

The mUPD genetic subtype of PWS is strongly associated with the development of affective psychosis (Boer et al 2002). In a UK-wide sample of 119 adults with PWS, 62% of those with mUPD had a diagnosis of psychotic illness compared with 17% of those with a deletion (Soni *et al.* 2008). Atypical symptoms such as hypersomnia and confusion were seen, and those with mUPD had a more severe, difficult-to-treat illness with a poorer outcome compared to those with a deletion (Soni *et al.* 2007). However, once stability has been achieved in psychotic illness, recurrence rates are low (Larson *et al.* 2013). Dementias are now being documented as individuals survive into old age (Sinnema *et al.* 2010). Autism has been reported (Veltman *et al.* 2004); candidate genes for autism have been located within the 15q11-q13 region and there is evidence that those with mUPD may be more severely affected than those with a deletion (Ogata *et al.* 2014)

### Neuropsychological characteristics

The full scale IQ is usually in the mild intellectual disability range, and a mean downward shift of approximately 40 points compared to the general population is seen (Whittington *et al.* 2004). Those with mUPD tend to have better verbal skills and those with a deletion have better visuo-spatial skills. Also seen are poor short-term memory, deficits in sequential processing, poor socialisation skills, deficits in comprehension, abstract reasoning, recognising emotions and appreciating the concept of time.

### Neuroimaging findings

A study by Lukoshe *et al.* (2013) looked at high resolution structural magnetic resonance imaging in children with confirmed PWS. All children with PWS showed signs of impaired brain growth. Those with mUPD showed signs of early brain atrophy. In contrast, children with a deletion showed signs of

fundamentally arrested, although not deviant, brain development and presented few signs of cortical atrophy. The authors suggest that there are divergent neurodevelopmental patterns in children with a deletion versus those with mUPD.

### Physical health and endocrine

The most prevalent physical health problems in people with PWS are scoliosis, respiratory problems, dermatological lesions, hyperlipidaemia, hypothyroidism, Type 2 diabetes mellitus and lymphoedema (Laurier *et al.* 2014).

Growth hormone supplementation can increase height and the rate of growth, decrease mean body fat, improve respiratory muscle function and physical strength and improve facial dysmorphism. However, after cessation of growth hormone therapy, BMI can increase again, and long term therapy may be indicated (Oto *et al.* 2014). Furthermore, cessation of growth hormone therapy may lead to successive deterioration in behaviours in children with PWS (Bohm *et al.* 2014).

A study by Cohen *et al.* (2014) showed that central sleep apnea with associated oxygen desaturations is more prevalent in infants compared with older children with PWS. The authors found that supplemental oxygen was efficacious in treating central sleep apnea in infants and advised routine sleep surveillance for all children with PWS with consideration given to oxygen therapy.

Osteoporosis, osteopenia and fractures are relatively common in people with PWS. Growth hormone treatment can improve bone size and strength but not bone mineral density in people with PWS (Longhi *et al.* 2015).

### Useful websites/associations for more information

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

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*Updated by Sarita Soni, May 2015*

# Rubinstein-Taybi Syndrome (RTS)

## Prevalence

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

## Genetics

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

## Physical features

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

## Behavioural characteristics

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

## Cognitive characteristics

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

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

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*(updated August, 2014)*

# 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.

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## Cognitive and Behavioural characteristics

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

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

## Differential Diagnosis

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

In the very early stages there may be confusion with the degenerative disorders of infancy.
The repetitive movements of the hands has sometimes led to confusion of Rett disorder with Autism and some have recommended classification within the 'autistic spectrum'. However the sociability of people with Rett disorder and their highly characteristic genetic and physical features should make the distinction.
Mutations in the genes CDKL or FOXG1 have been separately reported as leading to very severe developmental disorders, still to be fully characterised but with similarities to Rett disorder.

## Management

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

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*Alison M Kerr, 2010*

# Triple-X Syndrome (47,XXX)

## First description and alternative names

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

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

## Genetics and molecular biology

In triple-X syndrome there is an extra X chromosome in all cells or, in mosaic cases, in almost all cells. Most of the cases are diagnosed through prenatal diagnostic examinations.

In 46,XX females the extra X chromosome is silenced through lionization. The extra X chromosome in triple-X women is also silenced. In 46,XX females one-third of the genes on the X chromosome escape silencing (Migeon 2007). The so-called 'late-replicating' X chromosome is the second X chromosome. In cases of an extra X chromosome there is another 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).

Whether incomplete silencing of the extra X chromosome, the prolonged cell cycle during division or epigenetic phenomena are relevant during development in 47,XXX requires further research.

## Incidence/prevalence

1/1000 females have an extra X chromosome (Otter et al. 2010)

## Physical features and natural history

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

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

## Behavioural and psychiatric characteristics

Low self-esteem seems to be the most common feature (Otter et al. 2010). Social anxiety/shyness and executive dysfunction are common in triple-X girls (van Rijn et al. 2013, van Rijn and Swaab 2015, Lenroot et al. 2014). Social cognitive problems are common in triple X girls, probably due to language disorders (Bishop et al. 2011). Another study in triple X girls showed a developmental pattern that resembled the development of girls with autism with mild or late presenting autism symptoms (van Rijn et al. 2014). Challenging behaviour may be the result of any of these developmental difficulties. Triple X girls living in a stable family function better than triple-X girls in an unstable family (Netley 1986). The triple-X girls seem to be less able to cope in a stressful environment. After

leaving school, most of the girls will find a job that reflects their non-verbal abilities (Robinson *et al.* 1990).

There seems to be a higher prevalence of psychiatric illness in general, especially in (mildly) mentally retarded cases, although we should be careful for there is a paucity of data on development in adults. More specifically, it concerns a higher prevalence of psychotic disorders and adjustment disorders (Olanders 1975).The newborn-screening studies were stopped before the age that psychotic disorders could have become noticeable. Further psychiatric research with standardised psychiatric diagnostic tools is warranted in these females. Adults seem to face physical, social and occupational problems (Otter *et al.* 2012, Stochholm *et al.* 2010, Stochholm *et al.* 2013).

### Scientific progress through neuroimaging findings

Recent neuroimaging findings in girls with an extra X chromosome demonstrated affected brain regions and related phenotypic characteristics such as language delay (thinner cortex was found in the lateral temporal lobes related to language functions), poor executive function and heightened anxiety (increased thickness in the medial temporal lobe in the vicinity of the amygdala, a region important for social cognition and linked to anxiety) through differences in cortical thickness (Lenroot *et al.* 2014). Poor executive function and frontal lobe abnormalities have been suggested to be related (van Rijn and Swaab 2015).

### Neuropsychological characteristics

Data on intelligence are consistent, indicating that the full scale IQ's are almost 20 points lower than what would be expected in the family (Robinson *et al.* 1990). Whether the girls show problems in reading or arithmetic is not uniformly reported in the case reports. Clinical experience suggests that some difficulties during arithmetic lessons result from language disorders. Mild or serious academic problems/special educational needs are quite common (Robinson *et al.* 1990, Bishop *et al.* 2011). Further research is needed to confirm the findings on increased prevalence of attention problems and to explain these attention problems: are they due to receptive language disorder, auditory processing disorders or attention deficit disorder (ADD)(Lenroot

*et al.* 2014)? Clinical experience in treating ADD with medication suggests that the treatment is less effective than in 46,XX cases; however, controlled treatment studies are lacking (Leggett *et al.* 2010).

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

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

### Useful websites/associations for more information

- The Dutch parents' support website: http://triple-x-syndroom.nl/. This website shows many links to scientific papers and useful links, e.g. links to international chat pages for parents and triple-X girls/women. Scientific papers and syndrome sheets are available in several languages: English, French, Spanish, German and Dutch.
- Unique, a parents' support group from the United Kingdom provides a syndrome sheet with information on physical and behavioural developmental issues: http://www.rarechromo.org/information/Chromosome_X/Triple_X_syndrome%20 Trisomy_X%20FTNW.pdf.
- The KS&A (Klinefelter Syndrome and Associates) website provides a brochure and more: http://www.genetic.org/Knowledge/Brochures. aspx_ Especially parents and triple-X girls/women in the United States will find opportunities to meet experts, other parents and triple-X girls/women. KS&A is active in fundraising for the support of scientific research.

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*Maarten Otter, 2015*

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# Tuberous Sclerosis Complex (TSC)

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## 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 an intracellular complex that links a number of intracellular signalling pathways including the AMPK pathway, the MAPK pathway and the PI3K pathway. The TSC1-2 complex functions upstream of mTOR (mammalian Target Of Rapamycin). TSC mutations causes mTOR overactivation, leading to dysregulation of cell growth, proliferation and various other fundamental neurobiological processes (de Vries, 2010, Kwiatkowski *et al.*, 2010). mTOR inhibitors have been approved by the FDA and EMA for the treatment of SEGA and angiomyolipoma associated with TSC. Clinical trials are underway of neurological and neuropsychiatric features of TSC (Curatolo, Moavero & de Vries, 2015)

## Incidence/prevalence

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

## Physical features and natural history

Wide variability of expression. The previously used "diagnostic triad" (of epilepsy, intellectual disability and characteristic facial skin lesions) is seen in only about 30% of people with the disorder. TSC is multi-system and can include hamartomatous growths affecting the brain, skin, kidneys, heart, eyes, teeth, lungs and other organs. About 80% of affected people have a lifetime history of epilepsy. Diagnosis is based on meeting clinical criteria for the disorder (Northrup, Krueger *et al.*, 2013). Mutations are identified in 80-90% of individuals with clinically confirmed TSC.

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

## Behavioural and psychiatric characteristics

Tuberous Sclerosis is associated with a wide range of behavioural, psychiatric, intellectual, academic, neuropsychological and psychosocial difficulties. The term TAND (TSC-Associated Neuropsychiatric Disorders) has been introduced as a summary term for all the bio-psycho-social aspects of the disorder (de Vries *et al.*, 2015) and a TAND Checklist has been developed to aid clinical teams to screen for TAND (de Vries *et al.*, 2015; Leclezio *et al.*, 2015) TSC is associated with high rates of various disruptive behaviours, sleep problems and self-injurious behaviours. Developmental disorders including autism and autism spectrum disorders (ASD) in 40-50%, ADHD and attention-related disorders in 30-50% and intellectual disability in ~50% of individuals. TSC is one of the medical conditions most commonly associated with ASD. In adolescents and adults, very high rates of anxiety and mood-related disorders are reported. Psychotic disorders should raise the possibility of seizure-related psychopathology (de Vries *et al.*, 2015; Kwiatkowski *et al.*, 2010).

## Neuropsychological characteristics

Global intellectual abilities show a bimodal distribution in TSC. 30% of individuals with TSC have profound global intellectual disability (IQ equivalent <20) and do not show significant developmental gains over time. The remaining 70% fall on a normal distribution curve, shifted to the left. In clinical practice, more than 50% of individuals with TSC will have global intellectual abilities in the normal range. There are, however, high rates of specific neuropsychological deficits in those with normal global intellectual abilities. Specific deficits are most prominent in attentional, executive and visuo-spatial skills. These specific cognitive deficits may be associated with significant scholastic difficulties and impair functional abilities in daily life (de Vries *et al.*, 2015; Kwiatkowski *et al.*, 2010; Tierney *et al.*, 2011).

## Available guidelines for behavioural assessment/treatment/management

International consensus guidelines were drawn up for the assessment of cognitive and behavioural problems in TSC (de Vries *et al.*, 2005). These were revised and are augmented by the new guidelines on screening and assessment (Krueger, Northrup *et al.*, 2013) and by the TAND Checklist (de Vries *et al.*, 2015; Leclezio *et al.*, 2015)

There are currently no TSC-specific treatments available for the neuropsychiatric manifestations of TSC. Clinicians should therefore use evidence-based interventions as for the general population.

Targeted treatments using mTOR inhibitors are currently in clinical trials for the neurocognitive and neurodevelopmental features of TSC (Curatolo, Moavero & de Vries, 2015), but these are not at present recommended outside clinical trials.

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

## Useful websites/associations for more information

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

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*Petrus J de Vries, (updated 2015)*

# Turner Syndrome

### First description

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

### Genetics and molecular biology

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

### Incidence and prevalence

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

### Physical features and natural history

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

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

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

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

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Because of the small stature, which is almost invariable relative to the height of the parents, it has become usual to treat with human growth hormone. The average stature after treatment is increased by a few centimeters, although the condition is not associated with growth hormone insufficiency and high doses are needed to achieve any significant benefit. There is no evidence that treatment with growth hormone benefits psychosocial adjustment, although it may improve self-esteem.

**Behavioural and psychiatric characteristics**

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

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

**Neuropsychological characteristics**

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

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

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

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

**Useful websites/Associations for more information**

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

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*David H Skuse, 2014*

# Velo-Cardio-Facial Syndrome

## Alternative names

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

## Genetics / aetiology

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

## Incidence / prevalence

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

## Physical phenotype

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

## Psychiatric/behavioural disorder

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

## Neuropsychological deficits

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

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

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

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

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

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

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

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*Kieran C Murphy & Frederick Sundram, 2008*

# Williams Syndrome (also known as Williams-Beuren Syndrome)

## First descriptions

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

## Genetic aspects

Williams syndrome is a genetically determined neurodevelopmental disorder caused by a heterozygous deletion of about 1.6 Mb (approx. 25-28 genes) on chromosome 7 (7q11.23). A deletion of the elastin gene (ELN) which occurs in >99% of individuals with WS) is associated with congenital heart disease and connective tissue abnormalities e.g. hernias and premature ageing of the skin. Several genes are also associated with the intellectual disabilities and cognitive deficits observed in WS, including GTF2l, LIMK1 and CYLN2 (see Skwerer & Tager-Flusberg, 2011, for review) Transmission is autosomal dominant and although most cases are de novo occurrences, some instances of parent to child transmission have been reported (Donnai & Karmiloff-Smith, 2000).

## Incidence

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

## Physical phenotype and natural history

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

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

## Behavioural and psychological characteristics

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

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

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

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## Further Information

- www.williams-syndrome.org.uk

*Patricia Howlin, 2014*

# Wolf-Hirschhorn Syndrome

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

## Genetics and Molecular Biology

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

## Prevalence and Mortality

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

## Physical Features

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

## Behavioural and Neuropsychological characteristics

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

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*Gene Fisch 2014*

# XYY Syndrome

### First description and alternative names

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

### Genetics and molecular biology

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

### Incidence/prevalence

The prevalence of 47,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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*Rhoshel K Lenroot, 2010*

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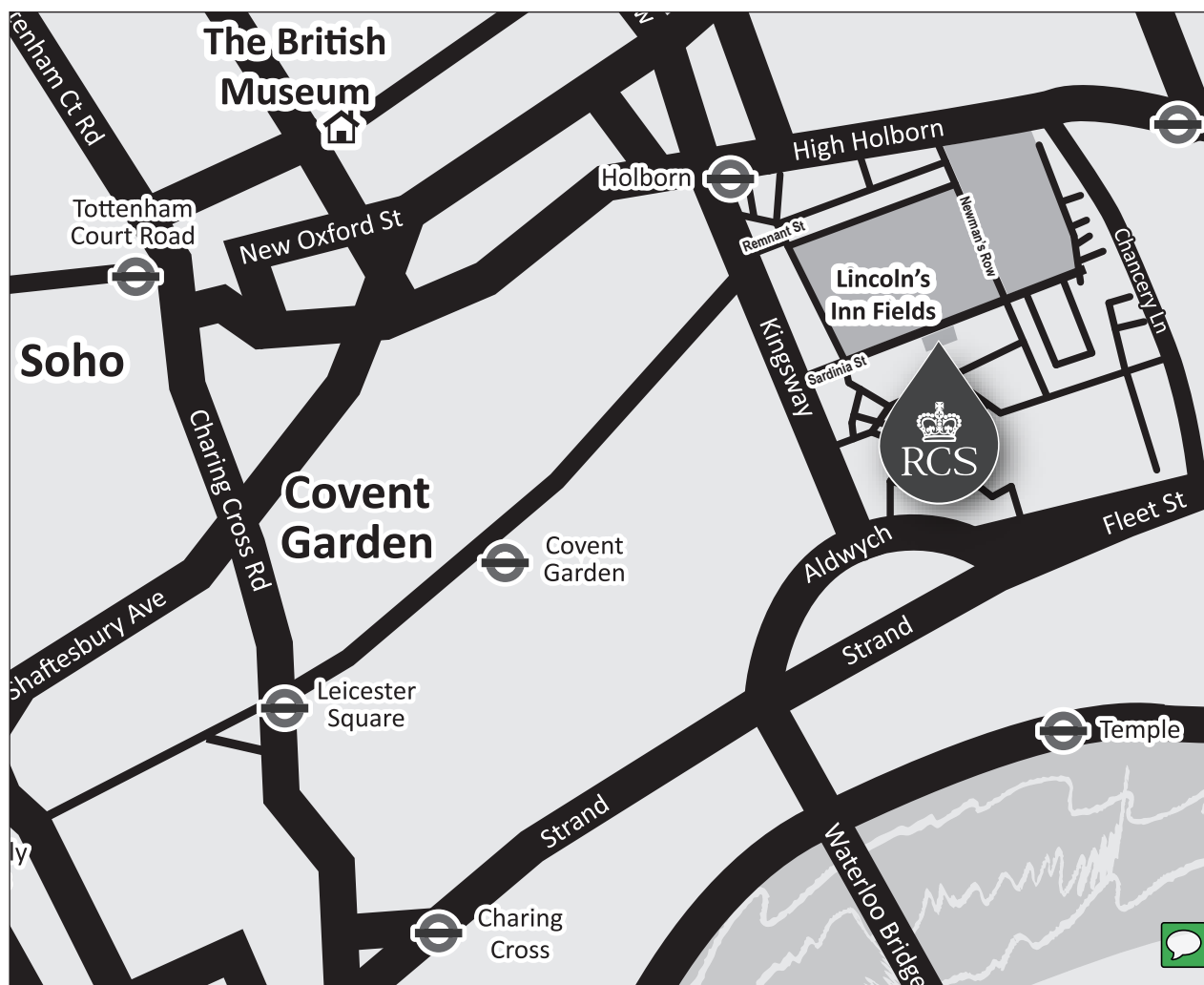
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**On the train:** Euston Station is a 1 minute walk. Kings Cross St Pancras is a 5-10 minute walk
**In the car:** We have no specific parking at the venue, however the nearest parking area would be Euston Station with 230 spaces.
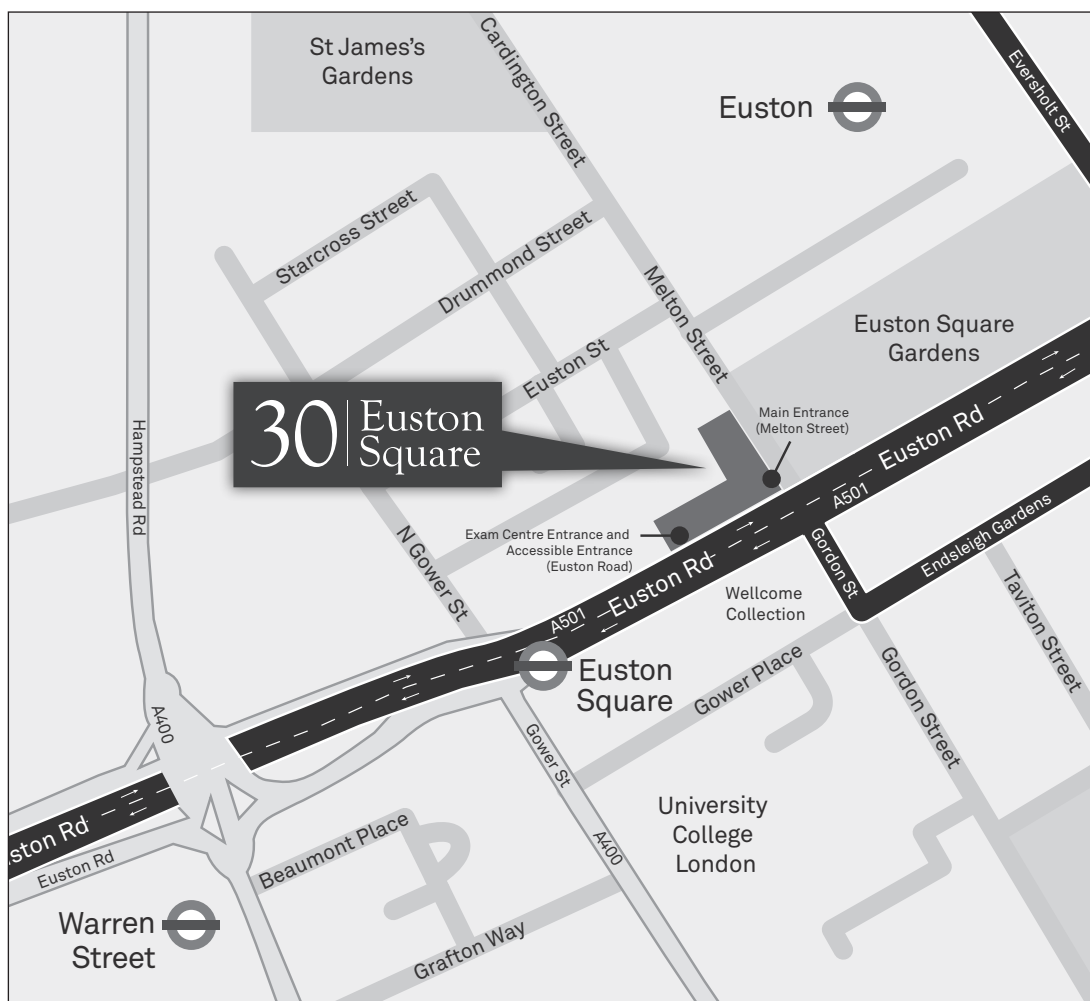
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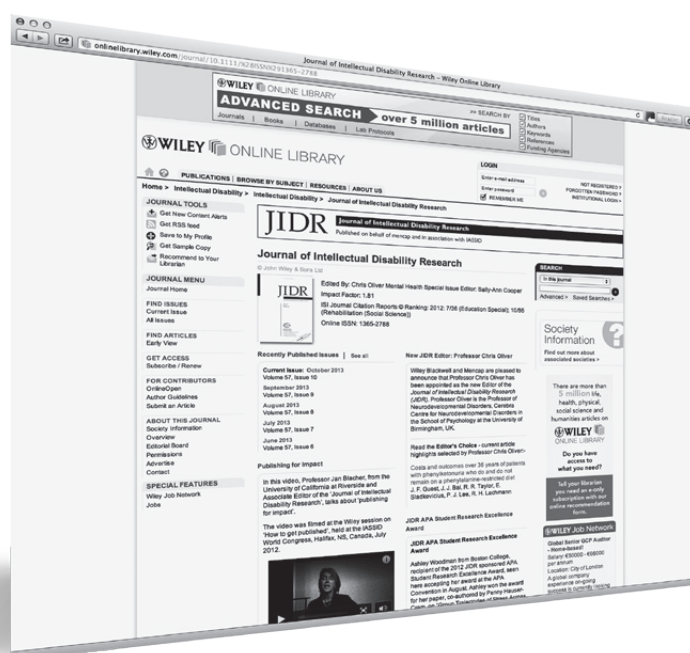
# Acknowledgements

We are extremely grateful to the wide range of people who contributed to this conference. A few specific acknowledgements are warranted:

# Notes

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# Save the date!

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