12th SSBP International Research Symposium and the 2009 SSBP Educational Day

Listening to genetic disorders: from molecules to management

14th – 16th October 2009, Cambridge, UK

Table of Contents

Welcome

Dear colleagues,

On behalf of the SSBP, welcome to our 12th International Research Symposium and the 2009 SSBP Educational Day. We are delighted to be joined by so many of you from around the world. One thing is clear: the study of learning and behavioural problems associated with genetic disorders is now firmly embedded into mainstream science and genetic disorders are emerging as exciting research models in translational neuroscience. This conference, generously sponsored by the Tuberous Sclerosis Alliance, is entitled *Listening to genetic disorders: from molecules to management*. We hope that there will be lots of interesting things to listen to during the conference, and that you will hear all sorts of new things in expected and unexpected places.

On behalf of the Tuberous Sclerosis Alliance, we welcome you to the meeting. Individuals with tuberous sclerosis complex (TSC) have so many medical issues to deal with, but it is often the behavioral and neurocognitive issues that are most debilitating and difficult for the person and their families. We are hopeful that this conference will lead to new insights, new collaborations and new research that will improve the lives of individuals with TSC and other genetic disorders.

On behalf of Corpus Christi College, we welcome you to Cambridge – in the year that the University celebrates its 800th anniversary. Corpus is one of the smallest Colleges in Cambridge, and we hope you will enjoy its intimate atmosphere. Enjoy also the sense of history as you walk past St Bene't's church – the oldest building in Cambridge, dating from the early part of the 11th century – and the Eagle pub, where Watson and Crick first announced their discovery of the structure of DNA.

Petrus J de Vries	Vicky H Whittemore	Christopher J Howe
Chair: SSBP	TSAlliance	Corpus Christi College

Scientific Committee

Petrus J de Vries, MBChB, MRCPsych, PhD
Consultant in Developmental Neuropsychiatry & Chairperson: SSBP
Conference Chair

Vicky Whittemore, PhD
Chief Scientific Officer
TSAlliance, USA
Conference Co-chair

Christopher J Howe, MA, PhD, ScD
Professor of Plant and Microbial Biochemistry
University of Cambridge & Fellow of Corpus Christi College
Conference Co-chair

Patricia Howlin, PhD
Professor of Clinical Psychology
Institute of Psychiatry, London

Howard Ring, MBBS, MRCPsych, MD
University Lecturer in Developmental Neuropsychiatry
University of Cambridge, UK

About Corpus

Broadly speaking, Cambridge University comprises the Departments and the Colleges, although the latter are all largely independent in their finance and their governance. Students are admitted to Colleges rather than the University, and each College conducts its own selection for admission. Most of the staff members in the different University departments are also Fellows (i.e. staff members) of one of the Colleges. Students receive their lectures and practical classes in the Departments, but they also have small-group tutorials in their Colleges. So the Colleges are much more than just halls of residence.

Corpus was founded in 1352, when England was beginning its recovery from the devastation of the Black Death, by two religious organizations in Cambridge, the Guild of Corpus Christi and the Guild of the Blessed Virgin Mary. They pooled their resources for the purpose and our full name is therefore "The College of Corpus Christi and the Blessed Virgin Mary in Cambridge", although we are usually known just as "Corpus", and our foundation by townspeople, rather than wealthy aristocrats or royalty, makes us unique among the Colleges. You will see our emblems of the Pelican, a symbol of Christ in the Mass (Corpus Christi), and the Lily, a symbol of the Virgin Mary, throughout the College. The original heart of the College is Old Court, which dates from our foundation and is the oldest enclosed court in any Oxford or Cambridge College. It was here that Marlowe and Fletcher, famous English playwrights, lived as students.

The College holds the finest private collection of early English manuscripts in the world, given to it by Matthew Parker. He was Archbishop of Canterbury under Elizabeth I and Master (i.e. the head) of the College, as well as the object of the phrase "Nosey Parker". He amassed a priceless collection of manuscripts that had been dispersed when the monasteries were closed by Henry VIII, and entrusted it to the College. However, under the terms of his will, if manuscripts are lost, the entire collection is transferred to Gonville and Caius College, and then in turn to Trinity Hall. Each year, the Master of Gonville and Caius carries out an audit of the collection and, assuming the results are satisfactory, the Fellows of Corpus celebrate with a grand dinner. Happily, the collection has not yet left! We also have the finest collection of early silver of any of the Colleges. When most of the Colleges lost theirs in the Civil War of the 17th Century, the Fellows of Corpus were each given an item of silver and told to hide it and return it when the War was over. Remarkably, everything was returned. Before graduating all students (swine flu permitting!) drink from the 14th century horn given us by the founders.

The College is also home to one of the newest pieces of public art in Cambridge, the Corpus Clock. Located at the corner of Bene't Street and King's Parade, it features a mythological beast, the Chronophage, and was unveiled by Steven Hawking in 2008.

About the Sponsors

The Tuberous Sclerosis Alliance (TSAlliance) (www.tsalliance.org)

The TSAlliance is a US-based not-for-profit organization established in 1974 as the National Tuberous Sclerosis Association (NTSA), which remained its title until 2000. Four mothers of children with TSC founded the organization to provide fellowship, generate awareness, pursue more knowledge and provide hope to those who share the common bond of facing the daily challenges of TSC.

Tuberous Sclerosis Alliance

During its 30 years of existence and growth, the TSAlliance has expanded its mission to improve the quality of life for individuals and families affected by tuberous sclerosis complex through the stimulation and sponsorship of research, the development of programs, support services and resource information, and the development and implementation of public and professional education programs designed to heighten awareness of TSC.

Programs and Support Services

The TSAlliance actively advocates in government relations, striving to increase visibility of TSC in Congress and within the National Institutes of Health (NIH). The organization's goal is to engage government institutions in basic scientific and clinical research on causes and remedies for TSC.

The TSAlliance builds networks through online services, conferences and volunteer outreach programs to give the TSC-affected population a sense of community. Members and donors provide the necessary resources to meet the overall goals and objectives of the organization by their volunteer efforts and contributions.

Outreach and Advocacy

The TSAlliance outreach and advocacy program collaborates with individuals and families in their efforts to obtain entitlements (social security and medical benefits), appropriate educational opportunities (placements and vocational services), and transitional issues, which include, but are not limited to, housing and community connections.

This conference was funded by a TSAlliance Conference Grant to Dr Petrus de Vries and the SSBP.

The ERS Charitable Foundation (www.emmory.com)

The Emmory Reagan Shapses (ERS) Charitable Foundation was founded by Marla and Marc Shapses in honor of their daughter, Emmory – an amazing twelve-year-old girl with tuberous sclerosis complex (TSC). Emmory is a bright, eager young girl with an enormous smile and a love for singing. As Emmory has grown, her parents have struggled with the complexities of TSC and the enormous challenge of raising a daughter with special needs. Even with all the medical challenges she faces, educating Emmory is the main focus for the Shapses family. They struggle to find a program that recognizes and builds upon Emmory's many strengths and talents while addressing the unique challenges she faces. The Shapses family has been working full-time for years now to find the program that will unlock Emmory's potential. As they continue their quest to provide the best opportunities for Emmory, they also remain committed to the overall battle, to find a cure for TSC and to improve the lives of all those affected.

Through a Tuberous Sclerosis Alliance Conference Grant, the ERS Charitable Foundation is proud to sponsor the SSBP Educational Day focused on children who have learning and behavioral disorders associated with genetic syndromes, including TSC. Our dream is that one day programs will exist to unlock the potential for all children with genetic syndromes.

About 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

Previous 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, 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, California	10th International
2008	Cologne, Germany	11th International
2009	Cambridge, UK	12th International & 12th Annual

Forthcoming SSBP Meetings

2010	Pavia, Italy
2011	Brisbane, Australia
2012	Europe (City to be confirmed)
2013	South Africa (City to be confirmed)

The SSBP Executive Committee

President Martin Bax, London, UK
Chair Petrus de Vries, Cambridge, UK
Hon. Secretary Leopold Curfs, Maastricht, The Netherlands
Hon. Treasurer Howard Ring, Cambridge, UK
Committee Randi Hagerman, Sacramento, USA (USA West Coast Representative)
James Harris, Baltimore, USA (USA East Coast Representative)
Stewart Einfeld, Randwick, Australia (Australasian Representative)
Roger Freeman, Vancouver, Canada (Canadian Representative)
Honey Heussler, Brisbane, Australia
Jo Moss, London, UK
Kieran O'Malley, Belfast, Northern Ireland
Sarita Soni, Glasgow, UK
Jeremy Turk, London, UK (Educational Activities)
Mark Woodbury-Smith, Hamilton, Canada
Administrative Secretary Robbie Fountain

For any enquiries about SSBP activities or membership, please contact Robbie Fountain (ssbprobbie@aol.com)

About Tom Oppé and the Tom Oppé Distinguished Lecture

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

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

After some years at Great Ormond Street, a research fellowship at Harvard and 2 years in Bristol, he returned to St Mary's Hospital (where he had worked as Lecturer in Child Health), and stayed at St Mary's for the rest of his professional career. He was awarded a CBE in 1984 for services to paediatrics and child health.

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

Previous Tom Oppé Lectures

2008	Hans-Christoph Steinhausen
2007	Petrus J de Vries

A New Prize Lecture for 2010: The Patricia Howlin Prize Lecture

After 9 years as Chair of the SSBP, Pat Howlin stepped down in 2008. At the 2008 Annual General Meeting (AGM) the SSBP membership recommended that a named lecture or prize be instituted in gratitude for Pat's excellent contributions to the society.

Area of Research

Intervention-based research that links directly to the learning or behavioural problems of individuals with genetic syndromes and related neurodevelopmental disorders. Preference will be given to non-pharmacological 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 will be launched at the AGM in 2009. The first award will be made in 2010. 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 of that year. Once approved by the SSBP Executive, the successful candidate will be invited to present the Prize Lecture.

An award certificate will be presented to the winner at the AGM or other appropriate forum.

Keynote Speaker Profiles

David N Franz

David Neal Franz, MD, is Professor of Paediatric Neurology at the University of Cincinnati, USA. He was born and raised in Dayton, Ohio. He received his undergraduate degree in History and Literature from Earlham College in Richmond, Indiana. After completing his training he served as Assistant Professor of Neurology and Pediatrics at Wright State University before returning to Cincinnati Children's Hospital Medical Center.

In 1993 he established the Cincinnati Tuberous Sclerosis Clinic to assist in the medical care of patients who have or are suspected of having tuberous sclerosis. The purpose of the clinic is not to replace care from the child's pediatrician or family physician, but to assist the primary care physician in dealing with those aspects unique to tuberous sclerosis that affect the child's health or development. The basis of the clinic is the realization that people with tuberous sclerosis are different from other individuals who have epilepsy, learning disabilities, behavior problems, etc. The Cincinnati TSC Clinic is now one of the largest in the world.

Dr Franz is very active clinically and in research. He has published widely on TSC and other childhood neurological conditions. He has received numerous honours over the years, including the Manuel Gomez Award from the TSAlliance. Dr Franz is a member of the professional advisory panels for the TSAlliance (USA) and TSDeutschland (Germany).

Rick Guidotti

Rick Guidotti, founder of POSITIVE EXPOSURE, is an award-winning former fashion photographer who has spent the past ten years working internationally with more than sixty advocacy organizations/NGOs and nineteen medical schools, colleges and other educational institutions to effect a sea change in societal attitudes towards individuals living with genetic difference. His work has been featured in newspapers, magazines and journals as diverse as People Magazine, the American Journal of Medical Genetics, The Lancet, Spirituality and Health, the Washington Post, Atlantic Monthly and Life Magazine.

Randi J Hagerman

Randi Hagerman is Professor of Paediatrics and holds an endowed chair in Fragile X research at the University of California, Davis School of Medicine, where she also serves as the Medical Director of the Medical Investigation of Neurodevelopmental Disorders (MIND) Institute. She is internationally recognized as both a clinician and researcher in the Fragile X field and she is the director of the Fragile X Research and Treatment Center at the MIND Institute.

Dr Hagerman received her M.D. from Stanford University where she also carried out her Pediatric residency. She completed a Fellowship in Learning and Disabilities and Ambulatory Pediatrics at UC San Diego and spent the next 20 years from 1980 to 2000 at the University of Colorado where she headed Developmental and Behavioral Pediatrics. She co-founded the National Fragile X Foundation in 1984 in Colorado and developed a world-renowned Fragile X research and treatment center. In 2000, Dr Hagermam moved to UC Davis to be the Medical Director of the M.I.N.D. Institute. With her team, she discovered the Fragile X-associated Tremor/Ataxia Syndrome (FXTAS), a neurological disorder that affects older carriers of Fragile X.

Dr Hagerman's research involves genotype-phenotype relationships, premutation involvement, targeted treatments in Fragile X and the association of Fragile X and autism. She has written over 200 peer-reviewed articles, numerous book chapters on neurodevelopmental disorders and several books on Fragile X including a 3rd Edition of Fragile X Syndrome: Diagnosis, Treatment, and Research which was published in 2002 by Johns Hopkins University Press.

Helen (Honey) Heussler

Honey Heussler is Senior Lecturer at the University of Queensland and Staff Specialist at the Mater Children's Hospital in Brisbane, Australia. She is a developmental & behavioural paediatrician and a qualified sleep physician. Her MD thesis was on the behavioural consequences of Obstructive Sleep Apnoea. Her current areas of research include the role of melatonin in sleep disorders, sleep disorders in genetic syndromes, and the impact of sleep disorders on performance and phenotype.

She has wide clinical interests and is involved in a number of specialised clinics including Prader Willi Syndrome, Smith Magenis syndrome and VCFS. Other research interests include molecular and genetic relationships to Autistic phenotypes and ADHD & specific cognitive phenotypes.

Dr Heussler has been a member of the SSBP since 2006 and was elected to the SSBP executive committee in 2008.

Anthony J Holland

Tony Holland is Professor of Learning Disability Psychiatry and holds the Health Foundation Chair in Learning Disability at the University of Cambridge, UK. He trained in Medicine at University College and University College Hospital, London, qualifying in 1973. After some years in General Medicine he then trained in Psychiatry at the Maudsley Hospital and Institute of Psychiatry in London. After his psychiatric training, he held a MRC Research Fellowship in Psychiatric Genetics, undertaking a study of the relationship between Down Syndrome and Alzheimer's disease. He held a senior academic post at the Institute of Psychiatry and until 1992 was also Consultant Psychiatrist with the Mental Impairment, Evaluation and Treatment Service at the Bethlam Royal and Maudsley Hospitals. From 1992 to 2002 he held a University Lecturer's post in the Section of Developmental Psychiatry in the University of Cambridge, and in 2002 was awarded the Health Foundation Chair in Learning Disability to be held in the Department of Psychiatry in the University of Cambridge.

Prof Holland has been a member of the SSBP for many years.

Patricia Howlin

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

Prof Howlin has been a member of the SSBP for many years, and stepped down as Chairperson of the SSBP in 2008.

Ayla Humphrey

Ayla Humphrey is an Affiliated Lecturer in the Department of Psychiatry, University of Cambridge and is Consultant Clinical Psychologist and Professional Lead for Child Psychology in the Cambridgeshire & Peterborough NHS Foundation Trust. She completed her Ph.D. in Clinical Psychology at Columbia University and a post-doctoral fellowship in Clinical Psychology at Albert Einstein College of Medicine, Schneider Children's Hospital. Her research interests include early development of children with Tuberous Sclerosis, specific learning disorders in children referred to mental health services and remedial and supportive approaches for children with Asperger's and high functioning Autism.

She is the clinical lead for the development of the first holistic neurorehabilitation service in the UK for children with acquired brain injury and the first specialist school in Cambridgeshire for children with high functioning Autism and Asperger's. Professional and research affiliations include: Collaboration for Leadership in Applied Health Research and Care (CLAHRC), named researcher; Cambridge Neurosciences, University of Cambridge, named researcher in Cognitive and Behavioral Neurosciences; Professional Advisory Committee, Tuberous Sclerosis Association.

Annette Karmiloff-Smith

Annette Karmiloff-Smith was until 2003 Head of the Neurocognitive Development Unit at the Institute of Child Health in London where she ran a research team studying infant and child development. She now occupies a Professorial Research Fellowship at the Birkbeck Centre for Brain and Cognitive Development, University of London. She has a "Doctorat en Psychologie Génétique et Expérimentale" from the University of Geneva, where she studied Piaget. She has been elected a Member of the Academia Europaea, a Fellow of the British Academy and a Fellow of the Academy of Medical Sciences. In 1995, she was awarded the British Psychological Society's Book Award for excellence in the literature of psychology for her book *Beyond Modularity (MIT Press, 1992)*. Her co-authored book, *Rethinking Innateness: A Connectionist Perspective on Development*, (MIT Press, 1996) was nominated for the 1997 APA Eleanor Maccoby Prize. In 2002 she won the European Science Foundation Latsis Prize for the Cognitive Sciences and was awarded honorary doctorates from the universities of Louvain and Zhejiang. In 2004, she was awarded a CBE. This year she received the BPS Research Board Lifetime Achievement Award, and an honorary doctorate from the University of Amsterdam. She is the author of 7 books and over 200 chapters and articles in scientific journals, as well as a series of booklets for parents on different aspects of foetal, infant and child development. Professor Karmiloff-Smith has 2 daughters and 7 grandchildren.

Brendan Manning

Brendan Manning is Assistant Professor at the Harvard School of Public Health. He completed his doctoral training at Yale University in 2000 and joined the laboratory of Dr Lewis Cantley at Harvard Medical School as a postdoctoral fellow. During his time in the Cantley laboratory, he identified TSC2 as a novel downstream target of the protein kinase Akt and found that this tumour suppressor lies at the heart of a signalling network critical for cell growth control through the mammalian target of rapamycin (mTOR). In 2004, Dr Manning joined the faculty of the Department of Genetics and Complex Diseases at the Harvard School of Public Health to continue this work. His laboratory uses a combination of biochemistry, genomics, proteomics, cell biology, and mouse genetics to study signal transduction pathways involving the Akt, TSC2, and mTOR proteins. This research is aimed at understanding the pathophysiology of diverse human diseases, including genetic tumour syndromes, cancer, and metabolic diseases, and revealing opportunities for therapeutic intervention.

Chris Oliver

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

Prof Oliver was Honorary Treasurer of the SSBP from 2001–2007.

Pierre Roubertoux

Pierre L. Roubertoux was trained in Statistical Psychology (Thèse d'état, 1979) and in Biology (Thèse d'état 1983). He was elected as Professor of Statistics in 1981 and as Professor of Genetics and Neuroscience (1983) at Paris V University. He created and directed the first laboratory for behavioural genetics (genetics, neuro-genetics and behaviour) in France at the CNRS and University of Paris V. In 1997 he moved to direct a department in Orléans (Institut de transgénose of the CNRS).

Professor Roubertoux investigated the genetic correlates of complex traits and of their neuronal bases (aggression, handedness, cognition, cerebellum patterns of foliation, corpus callosum, development) with wide genome scanning strategies in mice. He made several incursions in the field of human genetics (twins, autistic disorders, Huntington disease, muscular dystrophy). He is now Emeritus and works in Marseille at INSERM (Génétique Médicale, Génomique Fonctionnelle). His scientific activities are focussed on intellectual disability (mitochondrial neuronal defects associated with mitochondrial DNA polymorphisms, mouse models of trisomy 21). He is a past President of the Behavior Genetics Association. He is also a musicology graduate.

Mustafa Sahin

Mustafa Sahin is Assistant Professor of Neurology at Harvard Medical School. He graduated in Biochemistry from Brown University, completed doctoral training in Neurobiology at Yale University, and postdoctoral research training in Developmental Neurobiology at the Children's Hospital, Boston. Following graduation from Yale Medical School, he completed his residency in Child Neurology at Children's Hospital, Boston. In 2000, he joined the faculty at Harvard Medical School.

As a practicing child neurologist and a broadly trained neurobiologist, Dr Sahin has established and directed the Multidisciplinary Tuberous Sclerosis program at Children's Hospital Boston. This Program consists of a team of ten physicians from seven departments dedicated to treating all aspects of Tuberous Sclerosis Complex. Dr Sahin is also a member of the Tuberous Sclerosis Alliance Professional Advisory Board. The research in the Sahin laboratory is directed at understanding the cellular mechanisms of axon guidance and its relationship to neurological dysfunction. Based on his research accomplishments, Dr Sahin was awarded the Young Investigator Award by the Child Neurology Society in 2005 and John Merck Scholar Award in 2009.

Alcino Silva

Alcino Silva is Professor in the Departments of Neurobiology, Psychiatry and Psychology at University of California, Los Angeles. He completed his postdoctoral studies with Susumu Tonegawa at the Massachusetts Institute of Technology. The rigorous high standards of the laboratory, together with its climate of intellectual freedom, allowed Dr Silva to develop and fine-tune an approach that continues to be used to this day. From MIT, Dr Silva went to Cold Spring Harbor Laboratory in 1992 and set up his own laboratory where he had a leading role in the development of the field of Molecular and Cellular Cognition. Fifteen years later the field of Molecular and Cellular Cognition includes more than 100 laboratories in America, Europe and Asia, and a new society (Molecular and Cellular Cognition Society) has more than 2000 members.

In 1998 the Silva lab moved to UCLA. Work in the lab focused on learning and memory and on disorders with

cognitive deficits associated with learning. The goal of studies in this laboratory is to derive explanations of cognitive processes that integrate molecular, cellular, and behavioural mechanisms and to find treatments for cognitive disorders.

Earlier in 2009, Dr Silva was awarded the Roche Senior Prize for Translational Neuroscience. Born in Portugal, Dr Silva was also recently awarded the Order of Prince Henry for contributions to molecular and cellular cognition.

Dr Silva was invited to present the 2009 Tom Oppé Distinguished Lecture at the 12th SSBP International Research Symposium.

The 12th SSBP International Research Symposium

Programme

Day 1 (Wednesday 14th October 2009)

9:00 – 10:00	Registration and Coffee (McCrum Lecture Theatre) Set up of Posters (Parker Room)
10:00 – 10:15	Welcome and Introductions *Petrus de Vries & Vicky Whittemore*

Session 1: Molecular Aspects of Cognition and Behaviour (Chair: Vicky Whittemore)

10:15 – 11:00	Talk 1: **Keynote: How the TSC-mTOR story has led to targeted interventions for genetic disorders** *Brendan Manning, Boston, USA*
11:00 – 11:20	Talk 2: **Dysfunction of protein synthesis mediated by mTOR-dependent signalling in Fragile X syndrome** *C.A. Hoeffer, E. Klann, H. Wong, R.J. Hagerman & F. Tassone*
11:20 – 11:40	Talk 3: **Evolution of the TSC1/TSC2-TOR signalling pathway** *J. Serfontein, R.E.R. Nisbet, C.J. Howe & P.J. de Vries*
11:40 – 12:00	Talk 4: **Deregulation of EIF4E in autism: is translation a therapeutic opportunity?** *Z. Miedzybrodzka, M. Neves-Pereira, B. Mueller, D. Massie, J.H.G. Williams, P.C.M. O'Brien, A. Hughes, S-B. Shen & D. St Clair*

12:00 – 13:00: Lunch

Lunch boxes will be handed out in the McCrum Foyer. Please feel free to enjoy lunch in the McCrum Foyer, the Parker Room or the New Combination Room (NCR).

12:00 – 13:00	Set up of Posters (Parker Room)

Session 2: Translation: From Molecules to Man (Chairs: Christopher Howe & Petrus de Vries)

13:00 – 13:45	Talk 5: **Keynote: Neuronal connectivity in Tuberous Sclerosis Complex: translating from mouse to man** *Mustafa Sahin, Boston, USA*
13:45 – 14:05	Talk 6: **Identification of communal pathways in social memory and fear conditioning using mouse chromosome substitution strains** *H. Bruining, O. Stiedl, F.J. Meye, E. Pjetri, H. Oppelaar, H. Van Engeland, H.S. Swaab & M.J.H. Kas*
14:05 – 14:50	Talk 7: **Keynote: Mouse models for cognitive disorders in Trisomy 21** *Pierre Roubertoux, Aix-Marseille, France*

14:50 – 16:00: Tea & Poster Session 1

Tea is available in the McCrum Foyer and in the Parker Room. Posters are on view in the Parker Room.

16:00 – 16:20	Talk 8: **Deep Brain Stimulation (DBS) for self-injury and aggression in Lesch-Nyhan Disease** *J.C. Harris, Baltimore, USA*
16:20 – 16:40	Talk 9: **Deletions of neurexin-1 predispose to a wide spectrum of developmental disorders** *R. Nasir, M. Ching, Y. Shen, S. Jeste, W-H. Tan & B-L. Wu*
16:40 – 17:30	Talk 10: **The 2009 Tom Oppé Lecture: Reversing neurodevelopmental disorders in adults: from the lab to the clinic** *Alcino Silva, Los Angeles, USA*

17:30 – 18:30: Poster Session 2

Posters are on view in the Parker Room.

18:30 – 20:30: Private Viewing, Positive Exposure (Michaelhouse, Trinity Street)

Drinks and Canapés; Introductory talk at 19:00. All conference participants are invited to attend. Michaelhouse is five minutes' walk from Corpus.

Day 2 (Thursday 15th October 2009)

9:00 – 10:00	Coffee & Registration (McCrum Lecture Theatre)

Session 3: Early Development and Social-Cognition (Chair: Patricia Howlin)

10:00 – 10:45	Talk 11: **Keynote: Cognitive development in infants with TSC: an additive model of genetic, electrophysiological and anatomical abnormality** *Ayla Humphrey, Cambridge, UK*
10:45 – 11:05	Talk 12: **Assessing the motoric phenotype in neurodevelopmental disorders** *J.H.G. Williams, M. Mon-Williams & P. Culmer*
11:05 – 11:25	Talk 13: **Age-related change in social behaviour in children with Angelman syndrome** *D. Adams, H.K. Horsler, R. Mount & C. Oliver*
11:25 – 11:45	Talk 14: **Impaired and preserved sociability, social interaction skills and stranger discrimination in Cornelia de Lange, Angelman and Cri du Chat syndromes** *J. Moss, P. Howlin, P. Tunnicliffe, J. Petty, G. Griffith, R. Hastings, S. Beaumont, R. Yates & C. Oliver*
11:45 – 12:05	Talk 15: **Linking social cognition and executive functioning to phenotypic behaviours in Rubinstein Taybi syndrome** *L.A. Powis, J.E. Waite, I. Apperly, S. Beck & C. Oliver*
12:05 – 12:25	Talk 16: **Familial aggregation of regression among children with Autism Spectrum Disorder** *R.P. Goin-Kochel, S.U. Peters & E. Duku*

12:30 – 13:30: SSBP Annual General Meeting (McCrum Lecture Theatre)

12:30 – 14:30: Lunch and Poster Session 3

Lunchboxes will be available from 12:30 (for those not attending the AGM), and after the AGM for those attending it. Please feel free to enjoy lunch in the McCrum Foyer, the Parker Room or the New Combination Room (NCR). Posters are on view in the Parker Room.

Session 4: Neuropsychological Skills in Genetic Disorders (Chair: Jo Moss)

14:30 – 14:50	Talk 17: **Trajectories of cognitive, linguistic and adaptive functioning in Williams syndrome** *P. Howlin, S. Elison & C. Stinton*
14:50 – 15:10	Talk 18: **Cognitive functioning in Neurofibromatosis Type 1: Influence of maturation and ADHD-symptomatology** *S. Huijbregts, A. Noort, L. de Sonneville & H. Swaab-Barneveld*
15:10 – 15:30	Talk 19: **Executive function profiles of males and females with an additional X chromosome** *N. R. Lee, G.L. Wallace, C.R. Weddle, M. Liverpool, L.S. Clasen, J. Blumenthal, R.K. Lenroot & J.N. Giedd*

15:30 – 16:30: Tea & Poster Session 4

Tea will be available in the McCrum Foyer and in the Parker Room. Posters are on view in the Parker Room.

16:30 – 16:50	Talk 20: **Lateralised spatial attentional bias and white matter tract connectivity in Tuberous Sclerosis Complex (TSC)** *D.L. McCartney, E.T. Bullmore, J. Suckling, G.B. Williams, J. Cross & P.J. de Vries*
16:50 – 17:10	Talk 21: **Unimodal and cross-modal attention deficits in Fragile X syndrome: developmental trajectories and predictors of within-group heterogeneity** *G. Scerif, K. Cornish, V. Cole, E. Longhi & A. Karmiloff-Smith*
17:10 – 17:30	Talk 22: **Executive function deficits and emotion recognition problems in boys with Klinefelter syndrome, relation to autism symptoms?** *H. Swaab, H. Bruining, S. van Rijn, M. Bierman, L. de Sonneville & H. van Engeland*
17:30 – 18:15	Talk 23: **Keynote: The importance of cross-syndrome comparisons: A neuroconstructivist approach** *Annette Karmiloff-Smith, London, UK*

18:15 – 18:30: Closing Remarks & Conference Feedback (Vicky Whittemore & Petrus de Vries)

18:30: Take-down of posters
Please remove posters from the poster boards in the Parker Room.

19:30: Pre-dinner drinks (Old Combination Room (OCR))

20:00 – 23:00: Conference dinner (Corpus Hall)
Dress code: jacket and tie.

Abstracts for Oral Presentations

Talk 1: Keynote: How the TSC-mTOR story has led to targeted interventions for genetic disorders

B. D. Manning
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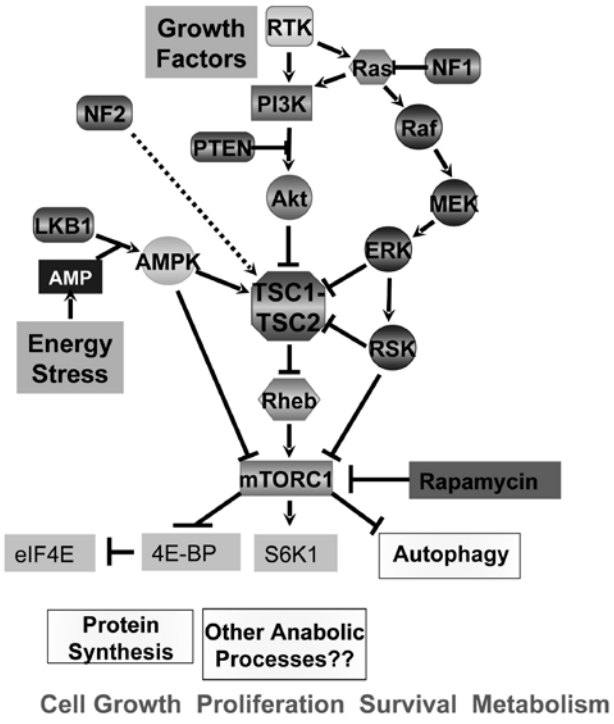

The process of translation of mRNAs into protein is exquisitely regulated in both a temporal and spatial manner. Proper control of protein synthesis is critical to many developmental and physiological processes, including synaptic plasticity and the wiring of neuronal circuits. Signal transduction pathways regulate translation initiation, in large part, through activation or inhibition of the mammalian target of rapamycin (mTOR). Studies over the past 9 years from diverse fields of biology have demonstrated that aberrant activation of mTOR is a shared molecular event in the development and progression of many genetic tumour syndromes. It is now clear that the major pathways regulated by the tumour suppressors mutated in these diseases (e.g., NF1, NF2, PTEN, LKB1, TSC1, TSC2) converge on the control of mTOR and much progress has been made in understanding the molecular details of these pathways. Nowhere is this more evident than in the tuberous sclerosis complex (TSC) disease. TSC is a tumour syndrome that is accompanied by severe neurological manifestations, including a high incidence of epilepsy, autism spectrum disorders, and cognitive deficits. Advances in our biochemical understanding of the normal regulation and functions of the TSC1-TSC2 complex, which is disrupted in TSC, have led directly to the testing of mTOR inhibitors, in both preclinical and clinical studies, for the treatment of the diverse pathological manifestations of this disease. The ongoing research on TSC serves as an important disease model, providing both mechanistic and therapeutic insights into neurodevelopmental disorders.

Keywords: tuberous sclerosis complex, mTOR, neurodevelopment, intracellular signalling

Talk 2: Dysfunction of protein synthesis mediated by mTOR-dependent signalling in Fragile X syndrome

C.A. Hoeffer[1], E. Klann[1], H. Wong, R. J. Hageman[2] & F. Tassone[2]

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Background: Multiple studies have revealed the important role played by the mTOR (mammalian target of rapamycin) signaling pathway in learning and memory. All components of the mTOR pathway, which is involved in protein synthesis-dependent phase of synaptic strengthening, are present in dendrites suggesting a role for mTOR in local translation. mTOR drives local translation through phosphorylation of its downstream targets, including the eukaryotic initiation factor 4E-binding protein (4E-BP), which permits eIF4E to bind to eIF4G and be phosphorylated by Mnk1. The 70kD ribosomal protein S6 kinase (S6K1) and the eukaryotic elongation factor 2 (eEF2) are two additional mTOR substrates involved in translation control. These substrates in turn regulate translational initiation and rates of peptidyl elongation.

Hyposphorylated 4E-BPs inhibit translation of a number of mRNAs, mRNAs by sequestering eIF4E. Loss of eIF4E activity especially impacts mRNAs with high CGG content and complex 5'UTR structure via steric hinderance. The mRNA encoded by the Fragile X gene (FMR1) bears these features. FMR1 contains a CGG repeat element in the 5'UTR. Expansion above 200 CGG repeats leads to Fragile X syndrome (FXS) through hypermethylation of the promoter, silencing and consequent absence of the encoded protein, FMRP.

Method: FMRP is an RNA-binding protein, which plays an important role in translational repression. Thus, we have investigated whether altered mTOR signaling is present in subjects with FXS.

Results: Our preliminary findings indicate that translation control mediated by the mTOR pathway is compromised in FXS. Peripheral blood leukocytes of FXS subjects, who lack of FMRP, displayed phosphorylation of translation factors and kinases involved in translation control. Specifically, a significant increase in the phosphorylation of both S6K1 and eIF4E, which is consistent with elevated basal translation, was detected in FXS subjects.

Conclusion: The observed increases in translational signaling suggest excessive basal translation in FMRP-deficient cells, and this activity may contribute to the cognitive and behavioral deficits observed in subjects with FXS. Thus, altered phosphorylation of mTOR substrates and their effectors could represent putative biological markers of cognitive impairment in FXS and the assessment of their levels in FXS lymphocytes could complement existing molecular testing.

Keywords: mTOR, FraX, 4E-BP, eIF4E

Talk 3: Evolution of the TSC1/TSC2-TOR signalling pathway

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Background: The TSC1/TSC2-TOR signalling pathway regulates important cellular processes including protein synthesis, in response to signals including growth factors and nutrient availability. The disruption of this pathway is involved in a number of genetic disorders with associated behavioural phenotypes. Homologues of pathway components have been reported in animals, fungi, plants and protozoa, leading to the perception that the whole pathway is evolutionarily conserved throughout eukaryotes. Models based on fungi and animals have been widely used in molecular studies of the pathway.

Method: To test the distribution of key components of the TSC1/TSC2-TOR signalling pathway we searched genomic and EST databases for homologues of AMPK, PTEN, PI3K, Akt, TSC1, TSC2, TOR, Rictor, Raptor, 4EBP and S6 kinase. The genomic databases included representatives of the Opisthokonta (which include fungi and animals), and other major eukaryotic groups. Putative homologues were compared to mammalian sequences to test for conservation of domain content and order, as well as important amino acid residues.

Results: Some components of the pathway were present in all groups searched while others were present only in particular eukaryotic lineages. Results show that the pathway was built up from a simpler one, present in the ancestral eukaryote, coupling cell growth to energy levels. Additional elements, such as TSC1 and TSC2, were 'bolted on' in particular eukaryotic lineages. Sequence comparisons indicate that a number of important residues in proteins such as human TSC1 and TSC2 are not conserved in homologues from other organisms.

Conclusion: The TSC1/TSC2-TOR pathway is not universal throughout eukaryotes, but the distribution of its components allows us to make new proposals about early eukaryotic evolution. The sequence comparisons call into question how well the signalling pathway in humans can be modelled using proteins from other organisms.

Keywords: eukaryote evolution, Tuberous Sclerosis Complex, signalling pathway evolution, mammalian target of rapamycin, mTOR

Talk 4: Deregulation of EIF4E in autism: is translation a therapeutic opportunity?

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Background: In this paper we discuss the role of genetic predisposition to abnormal translation as a cause of autistic features.

Method: Mapping of a translocation in a child with severe autism demonstrated disruption of the eukaryotic transcription initiation factor 4E gene, EIF4E. We went on to identify a single base insertion within an hnRNPK binding site within the EIF4E promoter in four affected siblings from two of 120 unrelated families from the AGRE cohort. Luciferase and EMSA assays showed that this promoter mutation upregulates expression of EIF4E.

Results: EIF4E is a rate limiting step in cap dependant translation, and has already been shown to be key in learning and memory through its effects on synaptic plasticity. EIF4E is a downstream target of pathways already implicated in autism including PTEN/TSC/mTOR and Fragile X.

Conclusion: Our work provides an intriguing insight into the mechanism of autistic features in these disorders. Although EIF4E mutation is itself an uncommon cause of autism, we propose that correction of aberrant translation through pharmacological manipulation of EIF4E could give therapeutic benefit in those whose autism is caused abnormalities in the genetic pathways that are mediated through EIF4E.

Keywords: eIf4E, TSC, mTOR, autism spectrum disorder

Talk 5: Keynote: Neuronal connectivity in Tuberous Sclerosis Complex: translating from mouse to man

M. Sahin
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An over-riding unresolved question in tuberous sclerosis complex (TSC) is what causes the neurological problems in this group of patients. It has been hypothesized that the physical presence of cortical hamartomas (also known as tubers) causes seizures. However, it is clear that a patient with TSC can have epilepsy without any cortical tubers on neuroimaging. Furthermore, several studies have failed to show a consistent correlation between the tubers and the presence of autistic features. Observations from mouse models of TSC lend support to these observations. For example, Tsc1 or Tsc2 heterozygous mice show impaired learning in hippocampal-dependent learning tasks and/or impaired social behaviour, but they do not demonstrate any cortical tuber or other structural abnormalities with their brains. Taken together, these observations suggest that neurological dysfunction may arise independent of cortical tubers in the TSC brain. We hypothesized that the TSC1/TSC2 protein complex is crucial not only for determining cell size, but also for determining neuronal connectivity in the central nervous system (CNS). We have generated three lines of evidence that support this hypothesis:

1. Axon specification: In the CNS, most neurons have a single axon and multiple dendrites. Establishing this unique polarized structure is critical for proper function of the CNS. We have shown that TSC/mTOR pathway components are expressed in neurons in a polarized manner. We found that overexpression of TSC proteins suppresses axon formation while loss of Tsc1 or Tsc2 function in cultured neurons leads to increased axon number. We further linked this critical function of TSC1/2 to the control of the protein level of the SAD-A kinase, which is required for axon formation in the mouse brain. When TSC is non-functional, SAD-A proteins levels are increased via the activation of the mTOR pathway in neurons.
2. Axon Guidance: The aberrant neuronal polarity phenotype seen in TSC mutants requires loss of both normal alleles of *Tsc1* or *Tsc2*. However, most neurons in a TSC patient's brain are thought to be heterozygous for the mutation. Thus, we investigated a role for TSC proteins that would be affected in the haploinsufficient state. We found that retinal neurons from *Tsc2* heterozygous mice project aberrantly to their CNS targets *in vivo* and display abnormal growth cone collapse in response to axon guidance cues.
3. Myelination: Finally, using a neuron-specific knockout of *Tsc1* gene in mice generated by the Kwiatkowski laboratory, we started to investigate the role of TSC1/2 protein complex in post-natal brain development. We found that one of the most striking abnormalities in the neuron-specific knockout of *Tsc1* was a marked reduction in CNS myelination. Treating these mice with an mTOR inhibitor starting in the first week of life rescued the myelination phenotype and improved the survival and neurological prognosis of the mice. These observations suggest that in the TSC brain there may be miswiring of neuronal connections that are independent of the benign tumours and that these wiring disruptions may contribute to the development of neurological symptoms (epilepsy, autism and intellectual disability) in TSC patients. We are now investigating in detail how the TSC1/2 genes contribute to the wiring of the neural circuitry. To address this question, we are taking a multi-pronged approach studying the structure and the function of the neuronal circuits in mouse models and the patients with TSC.

Keywords: TSC, neuronal connectivity, axon specification, axonal guidance, myelination

Talk 6: Identification of communal pathways in social memory and fear conditioning using mouse chromosome substitution strains

H. Bruining[1], O. Stiedl[2], F. J. Meye[1], E. Pjetri[1], H. Oppelaar[1], H. van Engeland[1], H. S. Swaab[1,2,3] & M. J. H. Kas[1]

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[3] *Department of Child and Adolescent Studies, Leiden University, The Netherlands*

Introduction: The contribution of genetic loci in complex behavioural traits is highly aided with novel powerful mouse genetic mapping populations such as chromosome substitution strains (CSS). In CSS strains, one chromosome of the background strain C57BL/6J is substituted by the corresponding chromosome of donor strain A/J (e.g., CSS1 has chromosome 1 of the A/J strain in a C57BL/6J genetic background). Phenotypical differences in one of these strains indicate involvement of the particular replaced chromosome in the behaviour observed. This method allows rapid identification of QTLs for complex traits. The current study aims to find genetic components of the communal regulation of social memory and fear conditioning (FC) by assessing temporal aspects of memory formation in CSS strains.

Method: The 21 strains of the CSS panel (C57BL/6J-Chr#A/NaJ) were screened to identify QTLs that regulate social discrimination (SD) in a time dependent manner. The selected strains with short term or long term SD were tested in a battery of other memory paradigms and in well characterized paradigms of FC. In addition, long term potentiation (LTP) as a measure for hippocampal involvement was assessed in the selected strains.

Results: Consequent temporal impairment of social and non-social memory functions was found within the same CS-strain. This may reveal shared or different genetic pathways on the substituted chromosome. The current phenotypic refinement of specific temporal SD deficits suggests a communal genetic contribution of temporal development and extinction of the expression of discrimination capacities and fear responses.

Conclusion: The identified QTLs can be further mapped to find novel genetic variations for components of proper memory functioning and to compare these with synthenic regions in the human genome. This may elucidate candidate genes involved in common social memory pathways that may be relevant for neuropsychiatric syndromes with impaired social cognitive and memory performance.

Keywords: mouse genetic mapping, chromosome substitution strains, CSS, long term potentiation, LTP

Talk 7: Keynote: Mouse models for cognitive disorders in Trisomy 21

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Background: Trisomy 21 (TRS21) also called Down syndrome is the most frequent genetic cause of mental retardation. Although the presence of an extra copy of *Homo sapiens* chromosome 21 (HSA21) is known to be at the origin of the syndrome, we do not know which 225 HSA21 genes have an effect on cognitive processes.

Method: Mouse models of TRS21 have been developed using syntenies between HSA21 and *Mus Musculus* chromosome 16, 10 and 17 (MMU16, MMU10 and MMU17). Available mouse models carry extra fragments of MMU16 or of HSA21 that cover all of HSA21 (chimeric HSA21) or MMU16 (Ts16); some carry large parts of MMU16 (Ts65Dn, Ts1Cje, Ms1Cje), while others have reduced contiguous fragments covering the D21S17-ETS2 region or single transfected genes. This offers a nest design strategy for deciphering cognitive (learning, memory and exploration) and associated brain abnormalities involving each of these chromosomal regions.

Results: Studies with mouse models confirm the crucial but not exclusive contribution of the D21S17-ETS2 region encompassing 16 genes to cognitive disorders. A region encompassing two genes including Dirk1A prevails in cognitive disorders. The putative genes associated to brain and cognitive disorders in TRS21 act via a cascade process. This was demonstrated by a systematic study of the transcripts of the non-HSA21 nuclear genes in the mice carrying segmental trisomies covering the D21S17-ETS2 region.

Conclusion: The complexity of the genetic and transcriptional processes in TRS21 should be considered as offering a wide diversity for therapeutic targets.

Keywords: trisomy 21, cognitive disability, transcription, mouse models

Talk 8: Deep Brain Stimulation (DBS) for self-injury and aggression in Lesch-Nyhan Disease

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Developmental Neuropsychiatry Clinic, Johns Hopkins Hospital, Baltimore, MD, USA

Background: LND is an X-Linked neurodevelopmental disorder that results from a genetic mutation involving the gene encoding for the purine salvage enzyme HPRT. The clinical features include hyperuricemia, generalized dystonia, compulsive self-injurious behaviour (SIB) with tissue damage, aggression towards others and cognitive impairment. The cognitive and behavioural features are an epigenetic consequence of the enzyme deficit on emerging brain systems. In studies in lizards and in squirrel monkeys lesions to the Globus Pallidus internus (GPi) result in the elimination of a stereotypical aggressive display without effects other species typical behaviours.

Method: Literature review and discussion of DBS surgery in Lesch Nyhan Syndrome. DBS surgery is conducted in the consciously sedated or fully anesthetized state with MRI guidance, with either 2 or 4 electrode placement. Four electrode placement targets stimulating electrodes to both the motor (posterior) and limbic circuits (anterior) in the GPi bilaterally. Baseline dystonia, SIB, aggression, cognitive measures, psychiatric status, and quality of life require assessment.

Results: In case reports from 3 countries DBS is shown to result in reductions in dystonia and complete elimination of SIB in 4 reported cases. The first of these is free of SIB seven years following surgery. In one case, using 4 electrode placement documented by video recording before and after surgery, resulted in both self-injury and aggressive behaviour showing significant changes following DBS.

Conclusion: The success of DBS in individual cases for self-injury and aggression in LND has elicited considerable interest. A proposed model will be presented that reviews issues in the safety and efficacy of DBS that must be considered before DBS is recommended.

Keywords: Lesch Nyhan Disease, self-injurious behaviour, aggressive behaviour

Talk 9: Deletions of neurexin-1 predispose to a wide spectrum of developmental disorders

R. Nasir[1,2], M. Ching[1,2], Y. Shen[2,3,4], S. Jeste[2,5], W.-H. Tan[2,6] & B.-L. Wu[2,3]

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Background: Neurexin-1 (NRXN1), an evolutionarily conserved structural component of the synaptic complex, is essential for proper synaptic function. Research has implicated mutations in neurexin-1 (NRXN1) in a variety of conditions including autism, schizophrenia, and nicotine dependence. To our knowledge, there have been no published reports describing the breadth of the phenotype associated with mutations in NRXN1.

Method: We present a medical record review of patients with deletions involving exonic sequences of NRXN1. We ascertained cases from 3450 patients referred clinically for comparative genomic hybridization (CGH) testing from March 2007 to January 2009. Results: Twelve patients were identified with exonic deletions of variable size and location along the NRXN1 gene. Four cases were confirmed *de novo* deletions and 5 were parentally inherited from a mildly affected or unaffected parent. The phenotype of individuals with NRXN1 deletion is variable and includes autism spectrum disorders, mental retardation, language delays, and hypotonia. There was a statistically significant increase in NRXN1 deletions in our clinical sample compared to control populations described in the literature ($p<0.0001$).

Conclusion: Our study suggests that deletions of NRXN1 predispose to a wide spectrum of developmental disorders. As more patients are identified through CGH strategies, long term follow up and detailed phenotyping will be essential for a clearer understanding of the NRXN1 deletion phenotype.

Keywords: Comparative genomic hybridization, Neurexin-1

Talk 10: The 2009 Tom Oppé Lecture: Reversing neurodevelopmental disorders in adults: from the lab to the clinic

A. J. Silva

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Recent findings in mice suggest that it is possible to reverse certain neurodevelopmental disorders in adults. Changes in development, previously thought to be irreparable in adults, were believed to underlie the neurological and psychiatric phenotypes of a range of common mental health problems with a clear developmental component. As a consequence, most researchers have focused their efforts on understanding the molecular and cellular processes that alter development with the hope that early intervention could prevent the emergent pathology. Unexpectedly, several different animal model studies published recently, including animal models of autism, suggest that it may be possible to reverse some neurodevelopmental disorders in adults: addressing the underlying molecular and cellular deficits in adults could in several cases dramatically improve the neurocognitive phenotypes in these animal models. For example, mutations in the Neurofibromatosis Type 1 (NF1) gene, encoding Neurofibromin, a p21Ras GTPase Activating Protein (GAP), cause learning disabilities and attention deficits. Our studies have shown that the learning and memory deficits of a mouse model of NF1 (*nf1*$^{+/-}$) are caused by excessive Ras/MAPK signaling leading to hyperphosphorylation of synapsin I, and subsequent enhanced GABA release, which in turn result in impairments in the induction of long-term potentiation (LTP), a cellular mechanism of learning and memory. Consistent with increased GABA-mediated inhibition, we found evidence for hypoactivation of key brain regions in fMRI studies of NF1 patients. Recently, we discovered that statins, at concentrations ineffective in controls, can reverse the enhanced p21Ras activity in the brain of adult *nf1*$^{+/-}$ mice, rescue their LTP deficits, and reverse their spatial learning and attention impairments. Strikingly, recently completed pilot clinical trials (collaboration with the Elgersma laboratory in Rotterdam) uncovered suggestive evidence that statins may also be able to reverse cognitive deficits in children with NF1. Similarly, our laboratory has also studied the molecular and cellular mechanisms underlying cognitive deficits associated with Tuberous Sclerosis (TSC). We found that hyperactive hippocampal mTOR signaling leads to abnormal hippocampal CA1 LTP and consequently to deficits in hippocampal-dependent learning. Remarkably, our results showed that a brief treatment with the mTOR inhibitor rapamycin in adult mice can rescue not only the synaptic plasticity, but also the behavioural deficits in this animal model of TSC. These and other recent related findings from other laboratories studying Down Syndrome, Rett Syndrome, and Fragile X provide hope to millions of individuals afflicted with a wide range of neurodevelopemntal disorders, including autism, since they suggest that it may be possible to treat or even cure them in adults.

Keywords: Neurofibromatosis Type 1, Tuberous Sclerosis Complex, translational medicine, neurocognition, mouse models

Talk 11: Keynote: Cognitive development in infants with TSC: an additive model of genetic, electrophysiological and anatomical abnormality

A. Humphrey

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Although an association between seizures and cognitive impairment in the context of Tuberous Sclerosis Complex (TSC) has been established, there is no evidence to support or to dispute the hypothesis that the onset of seizures itself causes impairment of cognitive function. Neuroanatomical, neurophysiologic, and, or genetic factors may all be associated with impaired cognitive function in the absence of seizures as has been recently shown in mouse models of TSC. This presentation will address the following questions: 1) Is there a causative relationship between onset of diagnosed seizures and cognitive impairment in young children with TSC? 2) If so, are there specific epilepsy factors that are associated with cognitive function in young children with epilepsy and TSC?

Two studies will be presented. The first study comprised a sample of 11 infants with a diagnosis of TSC, under the age of three years, no confirmed seizures or seizures which had lasted for less than two weeks. The second is a study of 20 infants under the age of 3. Infant development was assessed every three months prior to onset of seizures and a maximum of three assessments following the onset of seizures. Profiles varied considerably with some children showing cognitive regression before the onset of identified seizures, some children showing regression after several months of seizures and some children making cognitive gains after sustained control of seizures. The second study of 20 infants under the age of three years found moderate correlations between epilepsy severity and cognitive function.

Our findings suggest that cognitive impairment seen in children with TSC and seizures may occur before clinical seizures are identified. Mechanisms to explain this may include undiagnosed electrophysiological abnormalities raising the question of anti-epilepsy medications before the onset of clinical seizures. Disruption to neurological development as a primary consequence of the TSC mutation may also be a factor contributing to cognitive impairment in TSC before seizure onset. Consideration will be given to an additive model of cognitive impairment in TSC with primary genetic effects and secondary epilepsy and tuber effects.

Keywords: tuberous sclerosis complex, infants, neurocognition

Talk 12: Assessing the motoric phenotype in neurodevelopmental disorders

J. H. G. Williams[1], M. Mon-Williams[2] & P. Culmer[3]

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Background: Impaired motor control is characteristic of many genetically determined neurodevelopmental disorders though this aspect has been relatively unexplored as current methods of assessing motor skills in clinical settings are limited in objectivity and accuracy. We have developed the Clinical Kinematic Assessment Tool (CKAT) for recording the end-point of human movement on a portable computer with a touch-sensitive screen that research nurses and students can easily use in educational and clinical settings.

Study 1

Method: We predicted that performance on CKAT tasks would correlate with performance on a motor skills questionnaire. Primary school children performed tasks that included copying, tracing, dynamic-tracking and goal-directed action to a 'jumping' target. Measurements included path length, movement time, path accuracy and normalised jerk. In addition, parents completed a questionnaire which rated children's coordination problems.

Results: Tracking error and the extra time taken to hit a jumping 'dot' were the only two predictors of coordination problems. Furthermore, tracking error showed a step-wise increase with a coordination problem score above 4 points. This correlation was independent of IQ and age.

Discussion: The measures which specifically predicted day-to-day coordination problems were obtained from time-constrained tasks, suggesting that low visuo-motor processing speed might be a specific factor in determining coordination problems in primary school children.

Study 2

Method: We measured imitation skills by comparing kinematics of actions performed by a model and an imitator. As the model performed actions on CKAT they were video-taped. Kinematics of actions performed by imitators as they attempted to copy them as accurately as possible were then also collected.

Results: Correlations between model and imitator provided measures of imitation skill.

Conclusions: Overall, our method shows the potential for easy and reliable acquisition of data in clinical or school settings for objective assessment of the motoric phenotype.

Keywords: motor development, Clinical Kinematic Assessment Tool, CKAT, kinematics

Talk 13: Age-related change in social behaviour in children with Angelman syndrome

D. Adams, K. Horsler, R. Mount & C. Oliver

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

Background: Angelman syndrome is characterised by elevated levels of laughing and smiling behaviours. Recent research has hypothesised that such behaviours may be driven by genomic imprinting. Kinship theory of genomic imprinting suggests that individuals with Angelman syndrome are genetically predisposed to show behaviours such as laughing and smiling in order to increase access to social resources in a competitive setting. If this is the case, it could be hypothesised that laughing and smiling will decrease as the child grows older and, normally, is less reliant on maternal resources. However, there has been limited research into the relationship between age and behaviour in Angelman syndrome. In this study we aimed to investigate the relationship between age and laughing and smiling behaviours in children with Angelman syndrome.

Method: Children with Angelman syndrome were exposed to three experimentally manipulated conditions; proximity only, restricted social interaction and social interaction. The frequency of child and adult behaviours were compared using cross-sectional (n=24) and longitudinal (n=12) comparisons.

Results: Overall, children smiled the most in the social interaction condition and the least in the proximity only condition confirming the effect of social interaction on these behaviours. In both the cross-sectional and longitudinal studies smiling and laughing behaviours decrease with age, but only within the social interaction condition.

Conclusions: The results of this study provide further evidence that laughing and smiling in Angelman syndrome is not simply sporadic, but can be evoked by specific components of social interaction. It has also provided evidence for a decrease in the duration of laughing and smiling with age but only when eye contact is present. This trajectory of a decline in resource soliciting behaviours with age is consistent with predictions based on kinship theory.

Keywords: Angelman syndrome, social behaviour, smiling, behavioural phenotype, genomic imprinting

Talk 14: Impaired and preserved sociability, social interaction skills and stranger discrimination in Cornelia de Lange, Angelman and Cri du Chat syndromes

J. Moss[1], P. Howlin[1], P. Tunnicliffe[2], J. Petty[2], G. Griffith, R. Hastings, S. Beaumont, R. Yates & C. Oliver[2]

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[2] *Cerebra Centre for Neurodevelopmental Disorders, School of Psychology, University of Birmingham, Birmingham, UK*

Background: Differences in social behaviour in Cornelia de Lange (CdLS), Angelman (AS) and Cri du Chat (CdCS) syndromes are frequently reported in the behavioural phenotype literature. In this study we adopt a comparative approach to investigating social interaction skills, sociability and stranger discrimination in these syndromes.

Method: Participants were 60 individuals aged 2 to 19 years with CdCS (N=20; mean CA =9.0; SD=4.8), CdLS (N=20; mean CA=12.1; SD=3.4) and AS (N=20 mean CA =10.4; SD=4.7). The CdCS group scored significantly higher on the Adaptive Behavior Composite score of the VABS-II compared to the AS and CdLS groups (p<001). The Social Communication Questionnaire (SCQ) and the Sociability Questionnaire for people with Intellectual Disability (SQID) were employed in order to assess the presence of autistic characteristics and levels of sociability. An observational assessment of sociability, social interaction skills and stranger discrimination was also conducted.

Results: The CdLS group scored significantly higher than the CdCS group on the social interaction subscale and total score of the SCQ (p,≤.01). Significantly more individuals with AS (93.8%) and CdLS (100%) scored above the cut off for autism spectrum disorder compared to individuals with CdCS (p.001). The difference between the proportion of individuals scoring above the cut off for autism approached significance (p=.058). The AS group scored significantly higher than the CdLS and CdCS groups on the total score of the SQID with both familiar and unfamiliar adults (p<.02). The CdCS group scored significantly higher on total score of the SQID with familiar adults only (p<.02). Analysis of the observational assessments is ongoing but preliminary analyses suggest that our observations are consistent with the profile of scores on the SCQ and SQID.

Conclusions: The findings confirm previous reports of lower levels of sociability and heightened levels of autistic like characteristics in CdLS. These impairments do not appear to be accounted for by degree of intellectual disability. While individuals with AS score highly on measures of autism spectrum disorder, and at a similar level to those with CdLS, they also show a heightened level of and indiscriminate sociability with both familiar and unfamiliar adults. This profile is unlikely to be accounted for by degree of intellectual disability. Finally, individuals with CdCS demonstrate good social interaction skills, few autistic like impairments and heightened levels of sociability with familiar adults only.

Keywords: Social communication questionnaire, sociability questionnaire, autistic like behaviour, autism spectrum disorder

Talk 15: Linking social cognition and executive functioning to phenotypic behaviours in Rubinstein Taybi syndrome

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Background: Rubinstein Taybi syndrome (RTS) affects approximately 1 in 125,000 live births and results from micro-deletions within chromosome 16 (16p.13.3). Individuals with RTS present with a social phenotype characterised by high levels of sociability and over-familiarity with strangers. High levels of repetitive behaviours are also evident. In this study we aimed to identify the causal cognitive mechanisms underlying these behaviours by building upon previous work linking Theory of Mind (ToM) and social behaviour, and executive dysfunction and repetitive behaviours.

Method: We used a developmental trajectory approach to assess 30 individuals with RTS. Social cognitive ability was assessed using a scaled battery of tasks assessing both ToM and early skills that develop prior to ToM acquisition. An executive functioning battery assessed inhibition, working memory and cognitive flexibility. All participants received an IQ assessment. Parental report questionnaire measures were used to assess levels of social and repetitive behaviour.

Results: Our data indicate a potentially unique profile of social cognitive strengths and weaknesses. Early developing social cognitive skills dependent upon motivation for social contact are spared relative to mental age. Later developing ToM skills are delayed relative to mental age. In addition, a strong negative correlation (Spearman's rho = 0.85; P = <0.01) is found between verbal working memory span and repetitive speech.

Conclusion: We propose an impaired ToM ability in individuals with RTS underpinned by executive dysfunction. We highlight that impaired social cognition taken together with strong motivation for social contact may leave individuals particularly vulnerable to social exploitation. Furthermore, we propose that that repetitive questioning in individuals with RTS may be a coping mechanism to compensate for an inability to hold and manipulate verbal information in working memory.

Keywords: executive functioning, repetitive behaviours, Rubinstein Taybi syndrome, sociability, social cognition, behavioural phenotype

Talk 16: Familial aggregation of regression among children with Autism Spectrum Disorder

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Background: The development of autism is not uniform across affected children. Some show developmental delays from birth or shortly thereafter, whereas others may experience seemingly typical development for several months--in some cases, up to two-and-a-half years--followed by a loss of previously acquired skills. One study noted that parents witnessing this latter presentation, referred to as regressive autism, more often believe in environmental as opposed to genetic causes of the disorder. However, it is unclear whether regression in autism is better explained by environmental factors or whether there could be genetic liability.

Method: Data from the Autism Genetic Resource Exchange (AGRE) were analyzed for siblings who met criteria for an autism spectrum disorder (ASD) per the Autism Diagnostic Observation Schedule (ADOS) and for whom regression data were available on the Autism Diagnostic Interview-Revised (ADI-R; N = 1527, 78.7% male; M age = 8.1 years, SD = 4.5). Frequencies of skill loss (regression) were calculated by type of loss. Twin correlations were computed for all monozygotic (MZ; n = 38) and dizygotic (DZ; n = 37) twin pairs to assess the potential for heritability of language and/or social-skill loss in ASD.

Results: Among this sample, 529 (34.6%) had experienced some form of skill regression, with 358 (23.4%) experiencing a language loss and 355 (23.3%), a social-skill loss. Tetrachoric twin correlations for language loss were .85 (MZ) and .17 (DZ) and for social-skill loss, .80 (MZ) and .67 (DZ).

Conclusion: Preliminary twin analyses demonstrated (a) greater concordance for language regression among MZ than DZ twins, suggesting strong genetic effects and (b) the influence of both genetic and shared environmental effects for social-skill regression. To make full use of this large sibling sample, continued analyses employ Intraclass Correlation Coefficients (ICC's) for categorical variables to measure the extent to which regression varies within versus between sibships.

Keywords: autism spectrum disorder, twins

Talk 17: Trajectories of cognitive, linguistic and adaptive functioning in Williams syndrome

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Background: Little is known about trajectories of cognitive functioning in adults with Williams syndrome and there are conflicting findings concerning patterns of change over time.

Method: We investigated cognitive, linguistic and adaptive functioning in adults with Williams syndrome (WS) aged 19 to 55 years, using both cross sectional (n=92, mean age 32 yrs) and longitudinal (n=47, mean age 37 yrs) cohorts. Individuals in the longitudinal study had initially been assessed 12 years previously.

Results: Data from both the cross sectional and follow-up studies indicated that IQ was generally in the mild LD range (55–65) and there was no indication of any significant change in IQ over time. Verbal IQ was consistently slightly higher than Performance IQ. There were no improvements in language over time, and on formal tests of language, comprehension scores were generally higher than expressive language scores. In contrast, adaptive behavior scores had increased significantly in the longitudinal sample, and were significantly higher in older individuals in the cross-sectional sample.

Conclusion: The findings of the present study, based on a total of 121 individuals with Williams syndrome and using both longitudinal and cross-sectional research designs, indicate that, unlike certain other syndromes, there is no evidence of a decline in cognitive ability from the early adult years through to the mid-fifties. Although language skills showed little improvement over the years, IQ scores remained very stable and adaptive behaviours improved steadily with age. The findings indicate the importance of continuing education and training for individuals with Williams syndrome throughout adult life.

Keywords: Williams syndrome, cogntive and language development, outcome in adulthood

Talk 18: Cognitive functioning in Neurofibromatosis Type 1: Influence of maturation and ADHD-symptomatology

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Background: Neurofibromatosis Type 1 (NF1) is a genetic disorder (incidence 1:3000) leading to low neurofibromin levels, which are associated with tumor growth and loss of neuronal growth control. Cognitive impairment is present in approximately 50% of NF1 patients. In this study, we investigated the exact nature of the cognitive problems, the influence of maturation (do NF1-patients "catch up" as they get older?), and the role of co-occurring ADHD (estimated incidence in NF1: 25–50%) in explaining cognitive problems.

Method: Thirty-two NF1 – patients (mean age 12.3 years, SD 4.0) and 32 unaffected NF1-siblings (mean age 13.1 years, SD 3.9) were compared on a selection of cognitive tasks, measuring (verbal and spatial-temporal) working memory, inhibitory control, task switching, and motor function. All tasks are characterized by different levels of complexity in different task conditions, requiring different levels of cognitive control. Data were analysed using repeated measures analyses of variance, with level of required cognitive control as within-subjects factor. Age and ADHD-status were introduced to the analyses as additional between-subjects factors or as covariates.

Results: Group by condition interactions were observed for tasks measuring working memory [verbal: $F(1,62) = 14.8$, $p < .001$; spatial-temporal: $F(1.62) = 5.6$, $p = .021$], inhibitory control [$F(1,62) = 6.5$, $p = .013$], and motor function [$F(1,59) = 4.2$, $p = .045$], indicating larger group differences with higher cognitive control demands. Group by age interactions for inhibitory control, task switching and motor function indicated greater differences among younger participants (age < 12). Group by condition interactions, however, remained significant, indicating the persistence of a cognitive control deficit into adolescence. ADHD-symptomatology was more prevalent among NF1-patients compared to controls and was related to outcome variables, but could not explain group differences or group by condition interactions.

Conclusion: NF1-patients are characterized by a cognitive control deficit that is not explained by ADHD-symptomatology or maturation.

Keywords: Neurofibromatosis Type I, cognitive control, ADHD, maturation

Talk 19: Executive function profiles of males and females with an additional X chromosome

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Background: Research has suggested that the neuropsychological phenotypes of Klinefelter's (XXY) and Trisomy X (XXX) syndromes are characterized by executive function (EF) weaknesses. However, EF has not been examined extensively in a large sample of young people with XXY and XXX utilizing both laboratory and parent-report measures. Here we aimed to describe the EF skills of a large sample of children and young adults with XXY (n=59; mean age: 14±5 years; mean IQ: 98.65±15.63) and XXX (n=37; mean age: 10±5 years; mean IQ: 94.78±15.04) relative to two groups of gender – and age-matched typically developing control participants – one matched on socioeconomic status (SES) and one matched on IQ. Both groups were anticipated to present with EF weaknesses, particularly relative to SES-matched controls. Based on prior research, it was expected that males with XXY would have more pronounced deficits on EF tasks with greater verbal demands, while females with XXX would have impaired performance across verbal and nonverbal domains.

Method: Participants completed EF tasks (Verbal Fluency, Trailmaking, Stockings of Cambridge [SOC], Spatial Working Memory [SWM]) as part of a neuroimaging and neuropsychological study of sex chromosome variation. Parents completed the Behavior Rating Inventory of Executive Function (BRIEF).

Results: SES-matched controls outperformed both the XXY and XXX groups on all EF laboratory tests. When compared to IQ-matched controls, the XXY group demonstrated significant weaknesses on Verbal Fluency and Trailmaking, while the XXX group demonstrated significant weakness on SOC and SWM. Both groups showed EF deficits relative to published norms on the BRIEF.

Conclusion: These results indicate that both groups present with EF weaknesses; however, the pattern of these weaknesses differs. According to parent report, both groups also present with EF difficulties in everyday life. These findings will be discussed in relation to extant neuropsychological and neuroimaging studies of these groups.

Keywords: sex chromosome variation, executive function, CANTAB, BRIEF

Talk 20: Lateralised spatial attentional bias and white matter tract connectivity in Tuberous Sclerosis Complex (TSC)

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Background: Many of the neuropsychological deficits reported in TSC have a spatial attentional component. A visual search eye-tracking task showed that children with TSC paid more attention to stimuli on the right of the display, neglecting stimuli on the left as the task became more difficult. This observation suggested that individuals with TSC may have a lateralised spatial attentional bias during cognitive task performance. This study was designed to look for lateralised spatial bias in adults with TSC using the Line Bisection Task, a clinically widely-used measure of spatial attention or 'unilateral neglect'. Recent brain injury research suggested that white matter tract abnormalities may be sufficient to lead to unilateral neglect in the absence of cortical pathology. Given that white matter aberrations are widespread in TSC we predicted a possible relationship between white matter tract connectivity and lateralised spatial attention.

Method: Eighteen high-functioning right-handed adults with TSC and 14 matched controls underwent cognitive testing and structural MRI including diffusion tensor imaging (DTI). MRI data were analysed using whole brain, rather than region-of-interest, analysis to investigate structure-function correlations.

Results: On the Line Bisection task, the TSC group showed a significant rightward attentional bias ($p = 0.009$; Mann-Whitney U test). This correlated with significantly lower fractional anisotropy (FA), in the right-sided major intrahemispheric white matter tracts and splenium of the corpus callosum. Cognitive task performance did not correlate with a history of epilepsy, or the number, or localisation of cortical tubers.

Conclusion: Our findings confirm the presence of a lateralised spatial attentional bias in adults with TSC that may be subserved by white matter disconnectivity in the right hemisphere. Both the functional and structural deficits may contribute to neuropsychological dysfunction in TSC.

Keywords: unilateral neglect, white matter tracts, DTI, FA, spatial attention

Talk 21: Unimodal and cross-modal attention deficits in Fragile X syndrome: developmental trajectories and predictors of within-group heterogeneity

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Background: Fragile X syndrome (FXS) is associated with striking inattention and hyperactivity. Hitherto, deficits have been investigated using visual stimuli, but clinical evidence points to difficulties in other modalities, such as audition. Critically, attentional deficits in FXS may be exacerbated by the requirement of selecting multimodal stimuli in the real world. We aimed to investigate the impact of FXS on early developmental trajectories of visual, auditory and crossmodal attention. A longitudinal design also aimed to pinpoint the factors predicting individual differences in improvement or stability of these attentional difficulties.

Method: 59 boys with FXS (mean age: 7y 6m, range 3–10) and 129 typically developing children (TD, mean age: 6y 6m, range 3–10) contributed to multiple standardized and experimental measures of general cognitive functioning and attention to visual, auditory and multimodal stimuli, as well as baseline measures of visual and auditory perception over two testing sessions, a year apart.

Results: Younger TD children were less able to attend to stimuli in single modalities than older children, but they benefited from multimodal information. Children with FXS were less accurate in general, and experienced differentially greater difficulties with auditory stimuli compared to visual stimuli. These differences emerged in complex environments, rather than with stimuli in presented in isolation. In addition, children with FXS did not benefit from multimodal information as TD children did. General cognitive functioning, communicative abilities and autistic symptomatology represented complex predictors of concurrent and longitudinal attention in FXS.

Conclusion: An uneven pattern of relative strengths and weaknesses in attentional control by children with FXS underscores the need to investigate difficulties in more than one modality, and certainly with multimodal stimuli. Factors predicting the striking within-group differences also need to be understood more clearly.

Keywords: attention, Fragile X syndrome, developmental trajectories

Talk 22: Executive function deficits and emotion recognition problems in boys with Klinefelter syndrome, relation to autism symptoms?

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Background: Klinefelter syndrome (47, XXY) affects approximately 1 in 700 male individuals. Apart from a variety of phenotypes, cognitive and behavioral dysfunctions are recognized to be associated with this chromosomal pattern. High levels of autism traits in men and boys with Klinefelter syndrome were reported by our group. In the present study the question was addressed whether children with Klinefelter syndrome have EF problems and problems in social cognition that are associated with social problems and autism symptoms.

Method: 56 boys with Klinefelter syndrome (mean age 10.7) were compared to a group of 112 normal control boys, matched on age. Social dysfunction and autism symptoms were measured by the Child Behavior Checklist (CBCL) and the Autism Diagnostic Interview (ADI). Attention regulation was measured by a classic Continuous Performance Task (CPT), inhibition of processing of irrelevant information was indicated by the proportion of impulsive responses (misses) on the CPT. Mental (in)flexibility was indicated by the score on the incompatible response on a set shifting task (SS-VIS) task. In addition, tasks of face recognition and facial emotion recognition were used as measures for social cognition.

Results: 35% of the Klinefelter population had scores above the clinical cut-off point on the social problem scale of the CBCL. 25% of the children did meet the criteria for autism on the ADI. Attention regulation was inadequate in Klinefelter boys (p=.000). They showed much difficulty in inhibition of responses (p=.000) and their mental flexibility was weak (p=0.000). With respect to face recognition the Klinefelter boys were less accurate than controls (p=.001). They also had much more difficulty in fast and accurate recognition of emotional facial expression (p=0.000).

Conclusion: These specific EF functions that are known to be essential in regulation of thought and behavior and the social cognition problems may explain social adaptive problems and autism symptoms.

Keywords: Klinefelter Syndrome, EF, social cognition, Autism traits

Talk 23: Keynote: The importance of cross-syndrome comparisons: A neuroconstructivist approach

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Despite the fact that in this talk I will mainly focus on Williams syndrome (WS), I will argue that to understand fully the subtleties of any developmental disorder, it is crucial to make cross-syndrome comparisons. For example, although at first blush WS and Autism Spectrum Disorder seem very different in their profiles, in fact there are many similarities across these syndromes at the behavioural and cognitive levels, and often it is only by comparing syndromes at the brain level that differences emerge. Cross-syndrome studies help distinguish between what is syndrome-specific or syndrome-general. Cross-domain studies (e.g., of language, number, face processing etc. in the same individuals) reveal what is domain-specific or domain-general, and cross-modality studies (e.g., auditory, visual, tactile in the same individuals) help in distinguishing whether a syndrome shows general deficits across modalities or whether they are modality-specific. A longitudinal combination of these approaches would yield a much clearer profile of each developmental disorder.

Keywords: Williams syndrome, longitudinal studies, neuropsychology, neuroconstructivism, autism spectrum disorder

Abstracts for Poster Presentations

Poster 1: Resolving Misunderstandings: A Longitudinal Investigation of Social Language Skills in Males with Fragile X Syndrome

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Background: This study addressed the ability of individuals with Fragile X syndrome (FXS) to perform a critical sociolinguistic task: signaling noncomprehension of problematic messages when in the role of listener. Abbeduto et al. (2008, AJIDD) recently found that male adolescents and young adults with FXS are less likely to signal noncomprehension than expected for their levels of cognitive development. The present longitudinal study focused on the ability to signal noncomprehension in a younger cohort of males with FXS and examined the factors that contribute to within-syndrome differences in this ability.

Method: Thirty 10 – to 15-year-old boys with FXS were enrolled. They were then assessed up to four times annually. Noncomprehension signaling was assessed using the Abbeduto et al. task. The examiner told the participant which of several pictures to move into various scenes in a book (e.g., Put the red book on the shelf). The examiner's intended referent could oft en be unambiguously identified; however, some messages were problematic and referred to an absent picture, failed to distinguish among pictures, or contained an unknown word. The dependent variable was the number of problematic messages on which the participant signaled noncomprehension (e.g., Which book?). The predictors of noncomprehension signaling examined were age, nonverbal IQ, syntax comprehension, theory of mind, autism diagnostic status, and FMRP level.

Results: Hierarchical linear modeling was used. Although there was considerable variability in the age-related trajectory of noncomprehension signaling, change was negligible for many participants. Nonverbal IQ and FMRP each made independent contributions to the prediction of between-participant (i.e., intercept) differences. Additional analyses will explore the trajectories of noncomprehension signaling for the different types of problematic messages.

Conclusion: Noncomprehension signaling is especially impaired in males with FXS. It appears to be a marker of affectedness (complementing IQ) and thus, a potentially useful outcome measure for treatment studies.

Keywords: Fragile X syndrome, language

Poster 2: Neurodevelopmental and Cognitive Profile of Disorders Associated with Dysregulation of the RAS/MAPK Signaling Cascade

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Background: The crucial role of the RAS-MAPK cascade in cognition had been demonstrated in animal models, particularly in processes controlling neuronal plasticity, memory and learning and in triggering long term synaptic changes. Mutations in genes coding for transducers participating in the RAS-MAPK signaling pathway have recently been identified as the molecular cause underlying Noonan syndrome (NS) and a group of disorders, including LEOPARD (LS), Cardiofaciocutaneous (CFCS) and Costello syndromes (CS).

Method: The profile of cognitive abilities in 49 patients with dysregulation of RAS-MAPK signaling pathway were investigated. In our cohort, 18 with NS/LS were even assessed on Form and motion coherence thresholds to assess their global spatial and motion processing abilities and on the Movement Assessment Battery for Children (M-ABC), a battery of tests used to diagnose dyspraxia.

Results: While mutations affecting transducers upstream of RAS were less frequently associated with mental retardation, mutations in downstream components were generally associated with a more severe cognitive impairment. In patient with PTPN11 mutation, the T468M substitution was associated with a mean IQ significantly higher compared to that of individuals carrying the N308D change. Form coherence patterns were significantly higher in the study group than in the control group while no difference was found on the motion coherence task. Fifteen of the 18 had poor performances on the M-ABC.

Conclusion: Our data support the view that the severity of cognitive involvement in patients with dysregulation of the RAS/MAPK cascade, can be ascribed, in part, to the gene mutated and even the specific molecular lesion.

The discrepancy between form and motion performance in NS/LS indicates that they are more prone to develop a deficit in ventral pathway. Approximately 80% of 18 patients with NS/LS investigated on the M-ABC, a battery of tests used to diagnose dyspraxia, had poor scores.

Keywords: Cardiofaciocutaneous syndrome, Cognitive, Costello syndrome, LEOPARD syndrome, Noonan syndrome, RAS signalling

Poster 3: Atypical Lateralities in Persons with Genetic Disorders and Intellectual Disability

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Background: Previously, it has been shown that intellectual disability is linked to atypical laterality (with more non-right handedness or more mixed-handedness in populations with intellectual disability) but it is not clear if this atypical laterality is the consequence of intellectual disability or a specific feature of the syndrome itself.

Method: To address with question, we assessed hand, foot, and eye laterality in persons with three different genetic disorders and intellectual disability. The sample included 65 participants with Trisomy 21 (T21), 50 participants with Williams Beuren syndrome (WBS), and 22 participants with DiGeorge or 22q11 syndrome. A preference inventory was done twice. All participants performed 15 actions using their hands. Foot preference was assessed with 3 items and eye preference with 2 items. Bishop's card-reaching task once.

Results: As described in the literature, the mean IQ differed between the 3 groups of participants (T21 < WBS < 22q11). Overall laterality profiles were not the same in the three groups. Mixed handedness was more frequent in the group with T21 than in the two other groups, i.e. in the group with the lower cognitive level. When within group analyses were performed, we could not detected significant association between atypical laterality and cognitive level.

Conclusion: Our data suggest that atypical laterality could be due to gene dosage effect, and to developmental disability.

Keywords: handedness, laterality, trisomy 21, Williams Beuren, 22q11

Poster 4: The Aetiological Benefit of Array Comparative Genomic Hybridization (CGH) in Individuals with Neurodevelopmental Disorders

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Background: Array comparative genomic hybridization is replacing conventional karyotyping in the aetiological investigation of individuals with intellectual disabilities and neurodevelopmental disorders.

Method: A prospective, systematic aetiological evaluation of 417 individuals with varying degrees of intellectual disability and/ or neurodevelopmental disorders living in institutions or attending Activity Day Centres was undertaken.

Results: Of these, 112 individuals had either a monogenic or chromosome disorder whilst 102 had an acquired condition. From the remaining 203 individuals, those fulfilling the selection criteria of intellectual disability associated with 2 major dysmorphic features or one major and 2 minor dysmorphic features were analysed using array comparative genomic hybridization (array CGH) at a 1 Mb resolution. Thirty two of the 99 investigated had a copy number variant/CNV/ genomic imbalance, and of these 19 (19%) were considered to be related to the clinical phenotype. This resulted in an added 4.6% increase in the diagnostic rate.

Conclusion: Of these, 112 individuals had either a monogenic or chromosome disorder whilst 102 had an acquired condition. From the remaining 203 individuals, those fulfilling the selection criteria of intellectual disability associated with 2 major dysmorphic features or one major and 2 minor dysmorphic features were analysed using array comparative genomic hybridization (array CGH) at a 1 Mb resolution. Thirty two of the 99 investigated had a copy number variant/CNV/ genomic imbalance, and of these 19 (19%) were considered to be related to the clinical phenotype. This resulted in an added 4.6% increase in the diagnostic rate.

Keywords: Intellectual disabilities, neurodevelopmental disorders, array CGH

Poster 5: The Williams Syndrome Behavioural Phenotype: Associations with Chronological Age and Intellectual Functioning

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Background: Although some research has investigated how cognitive, language and adaptive functioning develop in Williams syndrome, little is known about how the more specific aspects of the Williams syndrome behavioural phenotype change across the life-span, or how behavioural functioning is associated with intellectual functioning. The aim of the study was to examine age associated changes in the Williams syndrome behavioural phenotype and associations between the behavioural phenotype and intellectual functioning.

Method: Semi-structured interviews were conducted with carers of adults with Williams syndrome. Then, based on scores for interview items, composite scores for social and behavioural impairment, self-care and occupational functioning were calculated. Then, cross-sectional analyses were conducted by splitting participants into 3 age groups and comparing these age groups in terms of their composite scores (N=92). For a sub-sample of participants who had been assessed using this same interview in a previous study conducted a decade ago, longitudinal analyses were conducted by analysing any changes in their composite scores over time (N=47). Associations between behavioural composite scores and intellectual functioning were also explored by comparing participant's composite scores with their IQ scores as measured by the WAIS-III.

Results: Cross-sectional analyses revealed that age was not associated with social or behavioural impairment, self-care skills or occupational functioning. However, longitudinal analyses revealed that self-care and occupational skills significantly improved over time and social and behavioural impairment significantly decreased. Some associations were found between composite scores and intellectual functioning. Self-care skills, social impairment and occupational functioning were found to be significantly related to IQ, with better self-care skills and occupational skills and less social impairment being associated with higher IQ. However, severity of behavioural problems did not appear to be associated with intellectual functioning.

Conclusion: Some aspects of the Williams syndrome behavioural phenotype may change significantly over time and may be significantly associated with intellectual functioning.

Keywords: Williams, IQ, WISC, cross-sectional analysis

Poster 6: Genotype-Phenotype Association Studies of Chromosome 8p Inverted Duplication Deletion Syndrome

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Background: Individuals with 8p inverted duplication deletion show a range of clinical features. However, to date, no systematic genotypic –phenotypic association study has been conducted.

Method: We examined 3 patients with inverted duplication deletion 8p using microarray CGH and a comprehensive psychological battery to investigate their genotype-phenotype relationship.

Results: IG was slightly macrocephalic and otherwise big for his age. He was lethargic, did not point or gesture, and made no eye contact. His speech/ language was extremely limited; therefore no IQ test administered. The VABS, which is strongly correlated with IQ, was DQ=51. The Child Behavior Checklist [CBCL] noted both thought problems and withdrawn. The Conners Rating Scale found lack of fearfulness a problem. He also did not want his face to be touched; emotionally labile [cries too easily]. These relate to his score of 32 on the CARS [mildly autistic]. RH was severely impacted. Her IQ = 36 with VABS DQ=20. Her CARS =45.5, indicating severe autism. T-scores on the CBCL noted severe Thought problems, Withdrawn, and Social problems. CPRS note cognitive problems, hyperactive; anxious/shy; perfectionistic; somatic problems, ADHD symptoms, restless/ impulsive; emotionally labile in the top 5%. Her speech/ language was also severely impaired. NM was the least impaired: IQ =56 and VABS DQ=59 His CARS = 21, i.e., not autistic. The Conners found him hyperactive, and the CBCL shows some Thought and Social problems, but not top 5%. Recently, he began to stutter.

Conclusion: Microarray results showed regions of consistency where chromosomal deletions and duplications occurred. NM and GI have terminal deletions with breakpoints between the 8p22 / 8p23.1 boundary. RH and NM have a small deletion near the 8p11.22 / 8p11.23 boundary. Duplicated segments show greater variability among individuals. A common core duplicated region includes all of 8p22, extending midway into 8p21.3, was found in all individuals.

Keywords: 8p, VABS, CBCL, CARS

Poster 7: WAGR Syndrome and Autism Spectrum Disorder?

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Background: WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies, mental retardation), a rare genetic disorder due to heterozygous chromosome 11p13 deletion, has been associated with behavioral and psychiatric problems, including autism spectrum (AS) disorders, with a reported prevalence of 20%. The current study uses "gold standard" research tools for diagnostic assessment of AS symptoms. We hypothesized that behaviors associated with cognitive and visual impairments may mask as AS symptoms in WAGR syndrome.

Method: Patients with WAGR syndrome were recruited to the NIH as partipants of a larger phenotype-genotype correlation study of individuals with 11p deletions. Assessment of AS symptoms was conducted using the Autism Diagnostic Interview-Revised (ADI-R, parent interview), the Autism Diagnostic Observation Schedule (ADOS, direct behavioral observation) and the clinical judgment of doctoral level psychologists. Adaptive behavior and cognitive level were also assessed.

Results: Participants: age 6–25y, 3 males, 5 females with WAGR syndrome. All participants were categorized with mental retardation ranging from mild to profound. Visual impairment ranged from legal blindness to complete lack of vision. Four participants had Wilms tumor during early childhood. Three participants met the "ever" autism cut-off on all domains of ADI-R, while 7 had repetitive behavior above the cut-off for this ADI-R domain. Only one participant continued to meet autism cut-off criteria based on current symptoms. ADOS was completed in 7 participants. None met AS cut-off on the ADOS, and in the clinical judgment of the psychologists, none of the participants met criteria for an AS diagnosis.

Conclusion: Our findings support the need for continued phenotyping of WAGR syndrome patients to ascertain how cognitive, visual, and other phenotypic traits associated with this disorder relate to AS. Previous studies have shown that variables, including diagnoses made <3y and significant cognitive impairment, impact the reliability of an AS diagnosis. As this study continues, these variables will be further investigated.

Keywords: WAGR, ADI-R, ADOS

Poster 8: EEG and Cognitive Performance in Children with Very Early Onset Schizophrenia

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Background: Very early onset schizophrenia (VEOS) or prepubertal schizophrenia is a severe mental disorder with an onset before 12 years of age characterized by language, motor and social deficits. Little is known about the EEG changes in children with VEOS yet. We investigated quantitative EEG (QEEG) data in children with VEOS and the relationship of their changes to cognitive function before and after pharmacological treatment.

Method: QEEG investigation and attention tests (Bourdon-Vos test, Stroop test, Shultz tables) were performed in 26 children (8–14 years of age, mean 11,9±2,7) before and after treatment with typical antipsychotics. All patients were evaluated with the Psychoeducational Profile test (PEP). EEG data before and after the treatment were compared with the EEG of age-matched healthy children from the normative database. Correlation coefficients between EEG spectral power and scores in psychological tests were calculated.

Results: Increased EEG spectral power of the beta-1 and beta-2 activity and decrease of the alpha activity level were found in children with VEOS before treatment in comparison with the EEG of healthy children. There was significant negative correlation of beta-1 and beta-2 activity level with the composite PEP test score in VEOS children. Strong positive correlation between the EEG delta level and the number of mistakes in the Bourdon-Vos test and the beta level (17–22 Hz) in the Stroop test were found as well as significant positive correlation between the response time in the Stroop test and the beta-2 activity level before treatment, but not after it. Antipsychotic treatment notably improved positive symptoms, whereas negative symptoms became more excessive. All tests showed decrease of the attention level after the medication course. The EEG data demonstrated two main changes: increase of the slow activity (delta and theta) and decrease of the beta-activity level.

Conclusion: Beta-activity level correlates with the severity of disease and the impairment of the executive control functions and possibly reflects hyperexcitability of cortical networks in VEOS children, which somewhat improves after antipsychotic treatment.

Keywords: VEOS, QEEG, cognitive performance

Poster 9: Comparison of ADOS Diagnostic Classifications for Individuals with Fragile X Syndrome Utilizing the Original and Revised Scoring Algorithms

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Background: The Autism Diagnostic Observation Schedule (ADOS) is a widely-used, gold standard tool for the diagnosis of autism and autism spectrum disorder. Gotham et al. (2007) reported on a revised version of the ADOS scoring algorithm which was developed for modules 1 through 3, and incorporates items from the Stereotyped Behaviors and Restricted Interests domain. We were interested in seeing whether the ADOS classifications of individuals with Fragile X syndrome would change when using the new algorithm, what types of changes would be seen, and with what frequency.

Method: We used an existing sample of 304 individuals (246 males, 58 females) with Fragile X syndrome who had been seen previously for research studies utilizing ADOS modules 1, 2 or 3, and re-scored them using the revised version of the algorithm.

Results: Overall, 93 of 304 cases (31%) showed some type of change in their overall ADOS diagnostic classification. 81 of 93 cases (87%) that changed went from less severe to more severe: non-ASD to autism spectrum (n=14), non-ASD to autism (n=9), and autism spectrum to autism (n=58). 12 of 93 (13%) cases that changed went from more severe to less severe: autism spectrum to non-ASD (n=7), and autism to autism spectrum (n=5).

Conclusion: A significant number of the 304 cases analyzed showed some type of change in their ADOS classification, and although changes were seen in both 'directions', a majority (87%) of the cases that changed classification were from less severe to more severe. This suggests that the addition of the repetitive behavior items to the revised algorithm has a significant influence for the classification of autism in the Fragile X population. These findings further support the need for using multiple tools for the diagnosis of autism (see Risi et al. 2006 and Harris et al. 2008).

Keywords: Fragile X syndrome, autism, diagnosis, ADOS

Poster 10: Prevalence of Genetic Testing in CHARGE Syndrome

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Background: Although a gene for CHARGE syndrome (CHD7) was found in 2004, it is not known whether individuals who have a clinical diagnosis of CHARGE are being tested for this gene. We surveyed all participants in our research database. Because genetic testing is expensive, and these individuals have had the diagnosis for a number of years, our hypothesis was that they were generally unlikely to have been tested. We also hypothesized that those who have been tested were more likely to be younger.

Method: Questionnaires were mailed regarding 195 individuals with CHARGE, which yielded a final total of 145. Males constituted 79 or 54.5% of the sample. Ages ranged from two to 39, with a mean of 16.67 (sd=6.03).

Results: More than two thirds (68.3%) had never been tested. Of the 46 who had been tested, 73.9% tested positive for the mutation. More than half (52.2%) of those tested were tested by Baylor College of Medicine in a blood draw that was conducted at a conference on CHARGE in Houston, Texas, in 1999. Of the 24 who were tested at the Houston Conference in 1999, 18 tested positive for the mutation, and 6 did not, for 75% positive. We conducted a t-test between those tested and those not, on age. The results were significant (t=-2.44, p=0.016) with those tested being younger.

Conclusion: There do not seem to be many incentives for testing individuals with CHARGE who have had a clinical diagnosis for many years. A research blood draw was the main source for genetic testing in this group of participants. It is likely that genetic testing for CHARGE will become more routine for infants and young children, but in the meantime, researchers who restrict themselves to those with a genetic diagnosis may not access the broad spectrum of CHARGE that is identified today.

Keywords: CHARGE syndrome, genetic testing

Poster 11: PRODH in Mental Health Disorders and 22 Q11.2 Deletion Syndrome

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Background: A review of hyperprolinemia in our institution identified a number of individuals with 22q11.2 deletion which carries a 30% risk of developing psychosis in adolescence. The gene in the region responsible is controversial. Various mutations in the PRODH gene that lead to variable impairment of enzyme activity have been reported and proline toxicity implicated. Individuals with homozygous PRODH mutations and hyperprolinemia, but without 22q11.1 deletion have also been identified with early mental retardation, autistic features, epilepsy, and psychosis. However, other conditions with elevated proline do not present with psychosis. Mouse studies have demonstrated deficits in sensorimotor gating accompanied by neuro-chemical changes. Many of these are similar to those changes seen in individuals with neuropsychiatric disorders.

We hypothesised that it is another function of PRODH protein or gene that is important, rather than the toxicity of proline. The PRODH protein is also involved in gene regulation and also potentially in glutamate excitotoxicity.

Method: A clinical cohort of children with 22q11 deletion syndrome were investigated for hyperpolinaemia and abnormalities in the PRODH gene. They were then randomised in a cross over design to receive riboflavin or placebo.

Results: We report the results of a small trial of Riboflavin therapy monitored by reduction of proline levels and improvement in neuropsychiatric function. Several genetic mechanisms to explain the apparent haplo-insufficiency in individuals with only a 22q11.2 deletion (and normal other allele) are under investigation.

Keywords: 22q11, PRODH, riboflavin, clinical trial

Poster 12: Analysis of Prader Willi Serum Proteins by Mass Spectrometry

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Background: While significant advances have been made in the classification of the diverse range of clinical presentations of Prader Willi Syndrome (PWS), the underlying molecular and cellular mechanisms responsible for this disorder remain unclear.

Method: To investigate, mass spectrometric analysis has been performed on a cohort of 27 PWS and 50 control blood serum samples.

Results: Analysis of apolipoprotein C-III (apoC-III) glycoforms by linear MALDI-TOF mass spectrometry revealed hyposialation of the glycans in approximately 40% of PWS sera, implying an underlying process modulating apoC-III and potentially other protein O-glycosylation and sialylation. Further to this, quantitative LC-MALDI based proteomic analysis of immunodepleted PWS serum suggested that PWS resulted in more systemic alterations to serum protein expression and/or modification. Since the PWS region of chromosome 15q11–13 encompasses several genes encoding ubiquitination proteins, including UBE3A ligase E6-AP, a more targeted approach utilising proteomic analysis of affinity purified polyubiquitinated leukocyte proteins was employed to further characterise the differences in the "ubiquitome" of PWS patients.

Conclusion: With further refinement these techniques may allow correlation between PWS phenotype and protein expression and modification, and the molecular understanding of this disorder.

Keywords: PWS, mass spectroscopy, apoC-III

Poster 13: 22 Q 11.2 Deletion in a Child Previously Identified with a Mitochondrial Disorder

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Background: In this case reporte we present a 6yo female. Her mother has epilepsy and was treated with sodium valproate and folate during the pregnancy. The girl presented with microcephaly, severe feeding difficulty, developmental delay and hypotonia. She had ongoing significant language delays and was developing a number of behavioural features resulting in poor sleep as well as seizure-like episodes and was reviewed. Her dysmorphic features and low tone were more pronounced and FISH testing revealed 22q11.2 deletion at the age of 5 years.

Method: The girl was investigated for aetiology of her presenting problems.

Results: EEG and MRI of the brain were normal. A muscle and liver biopsy were performed as repeated lactates had been high (7–9mmol/L) with the following results:

Complex I	417	(270–570) (nmol/min/mg)
Complex II	2722	(1400–3200) (nmol/min/mg)
Complex III	375	(260–430) (nmol/min/mg)
Complex IV	4	(27–48) (nmol/min/mg)

Respiratory chain enzymes in liver homogenate were low for Complex IV relative to protein, citrate synthase and Complex II (11%, 8% and 9% respectively). Other enzymes were normal (70% to 176% of control means relative to protein). A diagnosis of respiratory chain complex IV deficiency was made.

Conclusions: There are several genes in the 22q11.2 deletion region but in particular the glutamate transporter (SLC25A18) may affect mitochondrial function. We have since also recognised 2 other children with elevated lactate in the 8–11mmol/L range.

We hypothesise that in some children with 22q11.2 deletion, deficiencies in mitochondrial function may impact on presentation and natural history.

Keywords: 22q11.2, mitochondrial disorders, respiratory chain complex IV deficiency

Poster 14: The Experience of Parents of Children with Sanfilippo Syndrome

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Background: Research about parental experience of rare disorders is limited.

Method: Interpretative Phenomenological Analysis (IPA) was used to explore the experiences and understanding of two parents of children with Sanfilippo Syndrome

Results: Four themes of difference, relationship to help, emotional response and adaptation were revealed in the analysis and are discussed.

Conclusion: IPA can assist understanding of parental experience, a little explored area of research.

Keywords: Sanfilippo Syndrome, Mucopolysaccharide disorders, Parents, Interpretative Phenomenological Analysis

Poster 15: Utility of Child Eating Behaviour Questionnaire in Assessment of Feeding Aversion in Children with Neurodisability

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Background: Feeding aversion can occur in normal development, but can be severe in various neurodevelopmental syndromes. There is controversy over how to manage these children, due to the lack of a validated tool to classify and measure the severity of the problem. We identified the Child Eating Behaviour Questionnaire (CEBQ), developed to measure eating behaviours related to obesity, as a potential tool for assessing children with feeding aversion in clinical practice. We describe our early experience with the CEBQ for assessing feeding aversion and similar problems in neurodisability feeding clinic.

Method: We analyzed the CEBQ collected during routine assessment of sixteen children with neurodevelopmental disorder and feeding aversion referred to tertiary multidisciplinary feeding clinic. The ease of completion by parents of individual items of the questionnaire was assessed. Mean sub-domain scores of CEBQ were compared to population norms. Patterns of CEBQ sub-domain scores were related to other clinical variables.

Results: Significant group differences in mean CEBQ subdomain scores compared to population norms were noted for food responsiveness (mean CEBQ score 1.75 vs population mean 2.20), desire to drink (1.92 vs 2.60), emotional overeating (0.78 vs 1.90), satiety response (2.5 vs 3) and enjoyment of food (2.8 vs 3.5). Non-significant difference in mean scores was noted for fussiness and slowness in eating. A mean of 6 items per child were not answered particularly in emotional overeating, emotional undereating and slow eating subdomains. It was not possible in this small sample to separate underlying eating behaviour phenotypes based on theoretical constructs such as food neophobia, conditioned food aversion and sensory aversion.

Conclusion: The CEBQ has a limited role in classifying and measuring feeding aversion and similar problems in children with neurodisability. We are planning a study to develop such an assessment tool based on the CEBQ.

Keywords: Feeding aversion, CEBQ, neurodisability

Poster 16: Newborn Screening on Fragile X Syndrome: A Pilot Study

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Background: Technological development, new treatments and advocacy efforts are contributing to a push for rapid expansion of newborn screening. However, expanded screening raises a number of concerns and in the case of the FMR1 mutations has been a topic of considerable discussion since the gene was identified. Because phenotypic features are not evident at birth, Fragile X (FXS) must be discerned through abnormalities in development or behavior. The average age of diagnosis is 30–36 months for full mutation males; consequently, children miss the opportunity to participate in early intervention and parents often have additional children with FXS without knowing reproductive risks. Thus, screening for FXS will allow the identification of a greater number of individuals at risk for the disorder or transmitting the disorder.

Method: We have recently begun a pilot study of Newborn Screening in FXS aimed to the determination of allele frequencies in the general population and to the assessment of clinical involvement in the wide variety of Fragile X-related phenotypes in the primary and extended families of the newborn probands identified by newborn screening.

Results: Using our recently developed PCR method for the identification of premutation and full mutation alleles in the FMR1 gene, our preliminary data, based on over 2500 newborn blood spots, indicates that the frequency of occurrence of premutation alleles is greater than that previously reported. We have also started to document the degree of clinical involvement in the newborn proband and the extended family members and our experience will be discussed.

Keywords: FraX, screening, FMR1

Poster 17: Relationship Between Brain Abnormalities and Cognitive Profile in Down Syndrome

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Background: Only few neuroimaging studies have investigated the neuroanatomical correlates for the cognitive profile of individuals with Down Syndrome (DS). In adult with DS significant decreases in the cerebellum, cingulate gyrus, left medial frontal lobe, right middle/superior temporal gyrus and left hippocampus were found. Conversely, significant increases in grey matter (GM) in a superior/caudal portion of the brainstem and left parahippocampal gyrus were found. Also the hippocampus was critically found abnormal. Results, emerging from studies in which operator-dependent volumetric MRI techniques were applied, were not always confirmed by recent automated Voxel based Morphometry (VBM) studies. The goal of this study was to better understand the neuroanatomical substrate for the cognitive profile adolescent with DS. At this aim we applied VBM method, to study the regional distribution of GM density in DS as a function of individual neuropsychological profiles.

Method: Twelve adolescent with genetically confirmed diagnosis of DS (mean [SD] age 15.5 [2.3] years) and 12 typically developing controls (mean [SD] age 15.5 [2.2] years) were recruited for this study. All subjects underwent a neuropsychological assessment and MRI scans (performed at 1.5T).

Results: As expected, the scores of DS group were lower than controls matched for mental age on tests assessing language and short term memory abilities. Unlike controls, DS children showed significant local reduction of GM density in the left cerebellum, medial temporal lobules, bilaterally, and inferior temporal gyrus, bilaterally. Conversely, they showed a significant increase of GM density in the superior and middle right temporal gyrus, superior and inferior frontal gyrus, bilaterally, left putamen and left cerebellar vermian area. In the DS group, associations were found between the GM density and neuropsychological abilities.

Conclusion: The present study shows the ability of VBM to identify patterns of brain abnormalities in pathological children and controls and to associate regional GM changes directly with neuropsychological tests.

Keywords: Voxel based morphometry, children

Poster 18: Communicative Abilities and Behavioural and Emotional Problems in Persons with Comorbid Diagnoses of Down Syndrome and Autism

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Background: Early studies suggested that the combination of autism and Down syndrome (DS) was extremely rare. However, more recent estimates of the co occurrence of DS and Autism vary between 7 and 10 % of the DS population.

The present study was conducted by the National Autism Unit Norway together with Oslo University and Buskerud Hospital.

Method: 13 individuals diagnosed with DS and autism (age 4 to 20 years) were followed over 4 years. The focus of the study was on formal and pragmatic language competence and behavioural and emotional problems. The control sample comprised 47 individuals with DS without autism (age 2–29 years).

Results: In the DS/autism group 4/5 individuals, who had reached adolescence, showed a profound deterioration in their communicative abilities in early adolescence. This decline was not explained by severity of autistic traits (obsessive, compulsive, stereotyped, behaviours or resistance to change) or anxiety related conditions. The only behavioural characteristic that was correlated with the pragmatic decline was a form of apathy (profound lack of interest in both people and activities). In the control group 2/19 adolescents showed this loss of communicative abilities. These individuals showed similar loss of interest as in the DS/autism group, but severity was less marked.

Conclusion: Individuals with the comorbid condition of Down syndrome and autism are a highly vulnerable subgroup of both the autism and the Down syndrome populations. Clinicians need to be aware of a high risk of deterioration in this group and in particular a profound loss of interest in people and activities. It seems likely that this combination of disorders increases the risk of specific and deteriorating developmental pathways that are not associated with DS or autism alone.

Keywords: Down Syndrome, autism, communication, behavioural problems, emotional problems

Poster 19: Cerebral Serotonergic Function in People With Prader-Willi Syndrome

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Background: Prader-Willi syndrome (PWS) is associated with a significantly increased risk of affective disorder. This pilot neuroimaging study is being undertaken to inform a power calculation, and determine the number of participants who would agree to participate. The aim of the full-scale study would be to establish the extent to which cerebral serotonergic dysfunction is the mediating mechanism between the abnormal expression of imprinted genes in PWS and the observed high risk for affective psychopathology.

Method: Sixteen adults with PWS will be scanned (8 deletion genetic subtype, 8 maternal disomy (mUPD)) through the PWS Association (UK) and medical contacts. Participants must have been free from antidepressant and other relevant drugs within the last six months. Information on participants' psychiatric history will be collected using a modified version of the Schedules for Clinical Assessments in Neuropsychiatry (SCAN). Single Photon Emission Computerised Tomography (SPECT) will be employed to measure the serotonin transporter (SERT) and dopamine transporter (DAT) availability. Co-registration of the SPECT scan with Magnetic Resonance Imaging (MRI) to delineate the volumes of SERT-rich brain areas will increase the rigour of the method. SERT availability will be compared between the two main genetic subtypes and correlated with scores on the affective and psychotic rating scales. Participants' views on their experiences of having brain scans will be gathered using qualitative techniques, to inform how the experience could be positively enhanced for participants of a future study. Key themes will be identified.

Results: To date, 25 individuals who meet criteria and agree to participate have been identified (12 deletion, 5 mUPD, 8 genetic status currently unknown). One participant has undergone the full scanning procedure. Complete results will be presented here.

Conclusion: This study will allow us to ascertain the feasibility of recruiting this population for a larger study. The full study will increase our understanding of genetic influences on psychopathology in PWS and corresponding neurobiological mechanisms.

Keywords: Prader-Willi syndrome, behavioural phenotype, affective disorder, affective psychosis, neuroimaging

Poster 20: Exploring the Development of Numeracy, Literacy, and Attention in Down Syndrome and Williams Syndrome

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Background: Much research has explored the developmental precursors of numeracy and literacy attainment, and has successfully established early cognitive predictors of skills in each area within the typically developing (TD) population. However, less is known about the development of numeracy and literacy skills in children with developmental disorders including Williams syndrome (WS) and Down syndrome (DS). In addition, attention problems in WS and DS are commonly reported; so a closer look at the relationships between different components of attention and numeracy and literacy development within these groups may reveal their potential interactions.

Method: 103 TD children (age 3 – 7 years); 27 WS children (age 5 – 8 years); and 27 DS children (age 5 – 8 years) were tested individually on a range of literacy measures (letter knowledge, phonological awareness, and word reading); numeracy measures (cardinality, and early number skills); cognitive visual attention measures (selective, sustained, and executive attention); and behavioural attention measures (Conner's Attention Scale, Strengths and Difficulties Questionnaire). General functioning was assessed using the British Picture Vocabulary Scale (BPVS-II), and the Pattern Construction Subtest of the British Abilities Scale (BAS-II).

Results: In the TD group, as expected, numeracy and literacy outcome measures were predicted by performance on the precursor measures. Both behavioural attention and cognitive visual attention measures correlated with literacy and numeracy outcomes. However, relationships within the WS and DS groups were less straight forward, with differential impacts of the precursor measures on literacy and numeracy outcomes within each group. In addition, despite both receiving high ratings of behavioural inattention, the atypical groups displayed differing patterns of impairment across subtests of the visual attention measures, suggesting interesting differences in the components of attention impaired within each disorder, as oppose to a shared global deficit.

Conclusion: The importance of exploring the development of multiple aspects of both domain specific and domain general cognitive skills in atypical groups is highlighted. As seen in the present study, the cognitive skills underlying such outcomes may be different from those seen in the typical population, as is the interplay amongst such skills.

Keywords: Down, Williams, scholastic skills, attention

Poster 21: SCN1A Gene Mutations and Severe Myoclonic Epilepsy in Infancy: Is there a Genotype-Phenotype Correlation?

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Background: Severe Myoclonic Epilepsy (SME) is an intractable form of epilepsy of early childhood, nosologically well-defined and of unknown etiology (ILAE 1989). It is an epileptic disorder characterized by seizures, often triggered by fever, a diaper change, or warm baths. Psychomotor delay and mental retardation are observed especially during the second year of life. Mutations in the α-subunit of the first neuronal sodium channel gene SCN1A have been described in patients with SME and in families with generalized epilepsy with febrile seizures plus. In order to establish a clear definition of this type of epilepsy, we studied the EEGs of 60 young patients and the probable effects on the electroclinical picture of SCN1A gene mutation found in 25 infants.

Method: Our cohort included sixty infants, 32 females and 28 males, diagnosed with Severe Myoclonic Epilepsy (SME). The average age of our patients at onset of epilepsy was 5 months average age at last observation was 11years, 8months. We assessed the serial video EEG polygraphs and investigated the mutation of the SCN1A gene in 46 patients. Using the same electroclinical parametres, we compared the two sub-groups (SCN1A – negative/positive) to verify clinical differences.

Results: We found that 33.3% of the infants had a family history of epilepsy and that 30% of them had an onset due to febrile convulsions. Electro-clinical semeiology of the seizures within the 3rd year of life was variegate. Of 46 patients studied for a gene mutation, 25 (54.3%) tested positive. Missense in 13 patients and truncating in 12.

Conclusions: Analyses of the data reported confirms SME is characterized by a high polymorphism of the seizures. The presence of an SCN1A mutation seems to have a correlation with a precocious onset of seizures and an electroclinical sensitivity to light.

Keywords: SCN1A, Severe Myoclonic Epilepsy, SME

Poster 22: 47, XYY Karyotype: Seizures and EEG Characteristics

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Background: 47, XYY is one of the most common chromosomal aneuploidies. The clinical characteristics are an acceleration of stature growth in mid – childhood, mild intellectual disability , intentional tremors. Reports on seizures and EEG results concerning 47, XYY have been sporadic and poorly detailed. The aim of study was to describe the peculiar clinical and EEG patterns in a group of 5 subjects with 47, XYY.

Method: We performed a neurological examination, psychometric tests, EEGs and brain MRIs in five XYY males.

Results: The mean age at onset of epilepsy in four patients was 3 years, 5 months. Three subjects, all with epilepsy, presented intellectual disability; two patients had normal cognitive development. Neurological examination disclosed hyperexcitable deep tendon reflexes in one patient, brachicephaly and muscle hypotrophy in another, whereas hypotonia and motor impairment were present in the other 3 patients. Were evident obesity in one patient and toe syndactyly in two children.

Seizures were of the focal type. EEG showed a pattern characterized by focal spikes and sharp waves over the central-temporal regions of both hemispheres. Brain MRI was normal in three patients; one patient showed a mild asymmetric enlargement of the right lateral ventricle; another patient had gliosis presumably due to anoxia in the perinatal period.

Conclusion: Epilepsy or EEG paroxysmal abnormalities with a peculiar benign pattern very similar to the Rolandic epilepsy pattern seem to be characteristic of 47, XYY aneuploidy.

Keywords: rolandic epilepsy, EEG, 47XYY

Poster 23: Syntactic Competence in Klinefelter Syndrome

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Background: Klinefelter sindrome (KS) is often associated to a wide range of neurological, cognitive and psychological disorders. Neural brain anomalies of these patients correlate with cognitive deficits and crucially with language-based learning disabilities. In the present study we used a version of the syntactic priming paradigm to assess experimentally the syntactic processing abilities of KS patients.

Method: Participants were 8 KS mean age 18;2 (years; months) (IQtot=90, IQv=92; IQp=88) and 8 controls matched for gender and age (±3 months). All controls had typical speech, language, and hearing development, whereas 6 (75%) of the KS males in our sample had been diagnosed with speech and language delays. All participants took part in a syntactic priming task. They were first shown an (active or passive) prime sentence. Then they were asked to describe an unrelated drawing of animate and inanimate entities performing a transitive action, that could be described either with an active or a passive sentence (e.g., "The rock is hitting the man" or "The man is being hit by the rock"). We computed the proportions of active responses out of actives and passives.

Results: Main findings indicated that KS exhibited syntactic priming effects. After a passive prime, KS produced 4% more passives in comparison with the active condition, whereas controls 30% more passives. Interestingly, the exposure to a passive prime hardly significantly affected the production of a canonical passive. A passive prime increased the production of intransitive structures with the patient in the role of subject.

Conclusion: These findings suggest that KS may have difficulty in planning more complex sentence structures (e.g., passives), in favour of simpler options (e.g., intransitive impersonal or truncated passives).

Keywords: klinefelter, syntactic processing

Poster 24: Nance-Horan Syndrome (NHS): Case Report

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Background: Nance-Horan syndrome (NHS; OMIM 302350) is a rare X-linked condition often associated with mental retardation and autistic traits (Toutain, 1997); it is also known as: Brachymetarcarpia-cataract-mesiodens syndrome, cataract-dental syndrome, mesiodens-cataract syndrome, X-linked cataract-dental syndrome, X-linked cataract with hutchinsonian teeth, X-linked congenital cataracts-microcornea syndrome. It was first described by Horan and Nance (1974) as a congenital syndrome affecting both sexes characterized by cataract, impaired vision, supernumerary central incisor diastemas, narrowed incisal edges, anteverted pinnae and short fourth metacarpals . In some patients developmental delay and intellectual disability (ID) are present, in most cases, ID is mild or moderate (80%) and not associated with motor delay. Conversely, a severe mental handicap associated with autistic traits may be observed.

Method: We present the clinical case of D. A. a 27 years old male evaluated through clinical and psychological perspective.

Results: Neurological evaluation shows a global clumsiness. Cerebral MRI documented a mild cerebellar atrophy. Genetic counseling for NHS gene identification in D.A. identified a nonsense mutation in exon 6.This mutation was also found in his mother and in his sister but not in his maternal uncle, confirming the clinical data and the results of haplotype analysis. A mild mental disability is present (global IQ = 62 verbal IQ = 74, performance IQ = 52), characterized by a marked discrepancy among the verbal and performance subtests. At the Colored Progressive Matrices D.A. performed 23/36 (reasoning skills). At the Token Test, D.A. shows a good level of comprehension (31/36). At the Autism Behavior Checklist (Krug, 1980) D.A. showed isolation features, with impaired relationships and limited autonomy skills. At the Adaptive Behavior Inventory D.A. shows difficulties in communication and social areas. D.A. received a late diagnosis of NHS in adulthood.

Conclusion: Mild mental disability, behavioral and social impairments were the first signs that suggested us to investigate his clinical condition.

Keywords: nance-horan syndrome, intellectual disability

Poster 25: Facial Emotion Recognition and Social Behavior Among Males with XXY, Autism Spectrum Disorders, and Typical Development

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Background: Recent research has suggested that males with Klinefelter's (XXY) exhibit difficulties in emotion perception/labeling and social cognition. Nevertheless, no existing study has compared facial emotion recognition (FER) and autistic trait ratings between individuals with XXY and males with autism spectrum disorders (ASD). The aim was to assess FER among males with XXY (n=17; mean age: 18.52±4.11 years; range: 11–25) relative to two groups: typically developing (TD) males (n=34; mean age: 17.70±3.28 years; range: 11–25) and ASD males (n=20; mean age: 17.44±2.99 years; range: 12–24); all matched on age and IQ (>80). The hypothesis was that XXY and ASD males relative to TD males will present with FER weaknesses, particularly for negative emotions (e.g., sadness and fear).

Method: Participants completed the Emotional Multimorph task assessing intensity of emotional expression (in 5% increments) needed for accurate recognition of the six basic emotions. Parents/Caregivers completed the Social Responsiveness Scale (SRS), a measure of autistic traits.

Results: TD males outperformed ASD males in sensitivity to facial expressions of sadness and disgust, and there was a trend for XXY males to outperform ASD males in sensitivity to sad facial expressions. There were no significant FER differences between the XXY and TD groups. Autistic trait ratings were significantly lower for TD males than for both ASD and XXY males (SRS ratings did not differ between the two clinical groups).

Conclusion: Surprisingly, even though males with XXY presented with highly elevated autistic trait ratings (comparable to the ASD group) indicative of everyday social-communication difficulties, they did not exhibit difficulties in FER compared to TD males. In contrast, males with ASD required greater intensity of facial expressions depicting sadness and disgust for accurate recognition than did TD males. These findings will be discussed in relation to the possible ontogeny of social-emotional difficulties present in XXY and ASD groups.

Keywords: XXY, autism, emotion recognition, social behavior

The 2009 SSBP Educational Day

Programme (Friday 16th October 2009)

9:00 – 10:00	Coffee and Registration (McCrum Lecture Theatre)

Morning session (Chair: Petrus de Vries)

10:00 – 10:45	**Educational Day Talk 1: Tuberous Sclerosis Complex** *David Franz, Cincinnati, USA*
10:45 – 11:30	**Educational Day Talk 2: Advances in the assessment and treatment of individuals with Fragile X syndrome** *Randi Hagerman, Sacramento, USA*

11:30 – 12:15: Coffee
Served in the McCrum Foyer and in the New Combination Room (NCR).

12:15 – 13:00	**Educational Day Talk 3: Ageing and Alzheimer's disease in people with Down Syndrome** *Tony Holland, Cambridge, UK*
13:00 – 13:45	**Educational Day Talk 4: Sleep in developmental disorders: effects on development and behaviour** *Honey Heussler, Brisbane, Australia*

13:45 – 15:00: Lunch
Served in Hall.

Afternoon session (Chair: Vicky Whittemore)

15:00 – 15:45	**Educational Day Talk 5: Improving interventions and intervention research for young children with autism spectrum disorders** *Patricia Howlin, London, UK*
15:45 – 16:30	**Educational Day Talk 6: Assessment and management of self-injury and aggression in genetic disorders associated with severe intellectual disability** *Chris Oliver, Birmingham, UK*

16:30 – 16:50: Juice break
Juice and water will be available in the McCrum Foyer.

16:50 – 17:50	**Educational Day Talk 7: Special Lecture: *Positive Exposure*: The Spirit of Difference** *Rick Guidotti, New York, USA*

17:50 – 18:00: Closing remarks (Petrus de Vries, Vicky Whittemore & Christopher Howe)

18:30 – 20:30: Closing Reception & Art Exhibition
The closing reception will take place in Michaelhouse Café, Trinity Street. Drinks and nibbles will be served. Michaelhouse is five minutes' walk from Corpus.

Abstracts for Educational Day

Educational Day Talk 1: Tuberous Sclerosis Complex

David N Franz
Cincinnati Children's Hospital, Cincinnati, USA

Tuberous sclerosis complex (TSC) affects approximately 1 of every 6000 live births. Affected individuals are subject to hamartomas in virtually every part of the body, which produce epilepsy, autism, mental handicap, renal and pulmonary disease. These result from activation of the protein kinase mTOR (mammalian target of rapamycin). For this reason, TSC is a model for a growing number of other conditions in which the mTOR pathways is also up regulated, including systemic cancer, autism, and intractable epilepsy not related to TSC. Previously thought to be a "hopeless" disorder, it is now clear that a majority of patients have normal intelligence, and that all benefit from aggressive, pro-active medical management. This often differs from that for epilepsy, neoplasia, cognitive impairments etc. that occur in non-TSC patients. In this talk we will review the basic background to assessment and treatment of TSC. Results of completed and on-going clinical trials involving giant cell astrocytoma, angiomyolipoma, epilepsy, and lymphangioleiomyomatosis with the mTOR inhibitors rapamycin and everolimus (RAD001) conducted at our institution will also be reviewed.

Good clinical practice tips

- Periodic screening for manageable complications of TSC such as giant cell astrocytoma, angiomyolipoma, lymphangioleiomyomatosis, learning and behavior problems.
- Aggressive management of epilepsy with medications specifically known to be effective in the disorder, such as vigabatrin and lamotrigine. Epilepsy surgery should be considered as soon as medical intractability is established, i.e after failure of adequate trials of 2–3 anti-epileptics.
- Angiomyolipomas should be evaluated for embolization when they reach 4–6 cm in maximum diameter. Nephrectomy or resective surgery is fraught with complications and is rarely if ever necessary. Every effort should be made to preserve functioning renal tissue. Advanced imaging such as MRI and PET is valuable in distinguishing angiomyolipomas from lesions such as pericytic endothelial cell (PEC-omas) or epithelioid tumors.
- The hamartomatous lesions of TSC are rarely malignant, and affected persons should not be subjected to unnecessary surgical procedures as might be undertaken in individuals without TSC.

Educational Day Talk 2: Advances in the Assessment and Treatment of Individuals with Fragile X Syndrome

Randi Hagerman

MIND Institute and Department of Pediatrics University of California at Davis Medical Center, Sacramento California

In the last 5 years neurobiological studies of Fragile X syndrome (FXS) and the mouse and Drosophila models for this disorder have revealed significant up – regulation of a number of proteins that are important for synaptic plasticity in the absence of FMRP. In addition, the protein production leading to internalization of the AMPA receptors stimulated by the metabotropic glutamate receptor 5 system (mGluR5) is enhanced in FXS. This leads to enhanced long term depression (LTD) causing weak and immature synaptic connections particularly in the hippocampus in those with FXS. Other systems are also dysregulated including the $GABA_A$ receptors that are down-regulated, cAMP which is lowered and the matrix metalloproteinase 9 (MMP9) which is up-regulated. These neurobiological changes lead to the behavioral and cognitive phenotype of FXS. In additional to behavioral checklists and cognitive testing, psychophysiological measures, such as prepulse inhibition (PPI), eye tracking, papillary dilation and ERPs are new quantitative CNS measures that can be utilized as outcome measures for new targeted treatments for FXS. Some mGluR5 antagonists are undergoing trials currently in Europe and the USA with initial positive responses. In addition, the $GABA_B$ agonist R-Baclofen can down regulate glutamate levels at the synapse leading to improvement in behavioral problems. R-Baclofen is currently in a controlled trial at 6 centers in the US in children and adults with FXS. Minocycline, which can lower the MMP9 level is also undergoing trials in those with FXS. We have entered into a new age of targeted treatment for FXS which will hopefully lead to significant improvements in cognition and behavior in this disorder and in related conditions such as autism.

Good clinical practice tips

- Fragile X DNA testing should be done in all individuals with a diagnosis of intellectual disability and/or autism spectrum disorders with no known etiology.
- Both the premutation and the full mutation of Fragile X can cause autism spectrum disorders albeit through different molecular mechanisms.
- Minocycline which is available now by prescription may become a targeted treatment for individuals with fragileX syndrome – clinical trials are currently under way.
- The use of antioxidants which are available over the counter appear to strengthen synaptic connections in individuals with Fragile X syndrome. These too may become targeted treatments for Fragile X syndrome pending confirmation in clinical trials.
- MgluR5 antagonists are showing encouraging early clinical trial evidence of efficacy in both Fragile X syndrome and in autism.

Educational Day Talk 3: Ageing and Alzheimer's disease in people with Down Syndrome

Anthony J. Holland
University of Cambridge, Cambridge, UK

People with Down Syndrome (DS) have been found to develop changes in the brain early in life that are similar to those found in people without DS but who have the clinical features of Alzheimer's disease (AD). Subsequently clinical studies have found evidence of age-related prevalence rates of AD in people with DS – based on accepted clinical criteria – of 1% in their 30's, 10% to 15% in their 40's, and between 40% and 75% in their 50's. Whilst precise prevalence rates vary across studies all agree that the clinical development of AD is not inevitable but age-related increases in prevalence rates occur at an age that is 30 to 40 years earlier than would be the case for people without DS. More recent studies report that the early clinical changes that precede the development of obvious dementia in people with DS are characterised by behaviour and personality changes. The diagnosis of dementia in people with DS requires careful attention to be paid to retrospective evidence for the loss of functional abilities and deterioration in those cognitive domains that normally deteriorate with the development of AD. This is best obtained from an informant who has known the person well for at least the last six months. One off neuropsychological assessments are of limited diagnostic value but can be helpful when repeated over time and they also help inform as to the nature and extent of specific strengths and weaknesses thus informing support strategies.

Diagnostic assessment is essential to exclude other potentially treatable causes of decline and to provide a clear base line for planning support strategies that can help maintain the person's dignity and quality of life. These will be considered in the talk.

Good clinical practice tips

- The diagnosis of dementia in people with DS is based on evidence of decline in those cognitive and functional domains known to decline with the onset of dementia obtained in structured way from an informant.
- A full assessment is required to exclude other causes of possible decline (some of which may be reversible) and to establish a profile of that person to inform his/her subsequent care plan.
- The support of people with DS who have developed dementia requires a focus on individual and environmental factors that may inform strategies that help compensate for progressive loss of function, and help maintain dignity and quality of life.
- In planning support consideration needs to be given to how that person's wishes and feelings can be recorded in a manner that will help inform future decision-making in the event of the person losing the capacity to make decisions for him/herself.

Educational Day Talk 4: Sleep in Developmental Disorders: Effects on Development and Behaviour.

Helen (Honey) S. Heussler
Mater Children's Hospital, Brisbane & University of Queensland, Australia

In the normal population 20–30% of the paediatric population have a sleep problem at some stage. In children with craniofacial problems, developmental disorders or specific genetic syndromes the rates can be significantly higher.

Obstructive sleep apnoea is well recognised to cause significant changes to behaviour and learning attributes. Recent evidence also suggests that sleep restriction alone can have a significant effect on daytime performance.

Many groups of children who are affected by specific developmental disorders are known to have sleep difficulties. Prader-Willi, Angelman, Cri du Chat, and CHARGE syndromes, as well as myotonic dystrophies and mitochondrial disorders all have defined sleep problems. Examining the sleep problem can lead to a better understanding of the child's behavioural patterns and can lead to new therapies for example the inverted Melatonin cycle in Smith-Magenis Syndrome. Addressing these issues by a variety of means can make a significant difference to the child's functioning and have a profound impact on the family well-being and functioning.

Good clinical practice tips

- When assessing children with developmental or behavioural problems always remember to assess sleep.
- Formal assessment is required where obstructive sleep apnoea is suspected.
- Those at high risk include those with craniofacial abnormalities or abnormalities of tone.
- Appropriate management should be instituted where possible.
- Management options include NCPAP, behavioural interventions or pharmacological measures.

Educational Day Talk 5: Improving intervention and intervention research for young children with Autism Spectrum Disorders.

Patricia Howlin
Institute of Psychiatry, London, UK

Until recently, intervention research for young children with autism has been strongly criticised because of the paucity of well-controlled comparative studies and particularly the lack of randomised control trials (RCTs). Over the last decade, however, there has been a steady improvement of the quality of research in this area and there is now much better evidence for the effectiveness of a range of different treatment approaches, including those with a focus on parent management style, early, intensive behavioural intervention, social communication, joint attention and play programmes, and augmentative communication systems. Overall, *group* results indicate moderate, but encouraging improvements for children involved in each of these interventions. However, at an individual child level, outcome is much more variable, with some children in each programme showing considerable change, others only minor improvements and some showing no improvement, or even deterioration over time. Identification of the children who respond most to specific types of intervention remains a major challenge for research in this field in the future.

This presentation will focus on an overview of the range of and evidence-base for interventions in ASD, before concluding with a more critical appraisal of future research directions.

Good clinical practice tips

- Detailed assessment of child and family situation necessary before embarking on any specific intervention programme.
- Practitioners should be familiar with the evidence base for the most commonly used interventions (EIBI, Diets, Son-Rise, medication etc) in order to be able to advise parents about known effects and or side effects.
- There are no miracle cures – the question for clinicians is "Which child characteristics, interacting with which treatment characteristics, lead to better outcomes and on which dimensions?"

Educational Day Talk 6: Assessment and management of self-injury and aggression in genetic disorders associated with severe intellectual disability

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

There is robust evidence that the prevalence of self-injury and aggression is raised in some syndromes associated with intellectual disability. Studies of the form and correlates of self-injury and aggression in children and adults who have genetic syndromes show substantial diversity across groups. This diversity alludes to the possibility of different causal pathways. Testing these causal pathways involves making the role of environmental and person variables explicit so that they might be subject to experimental manipulation. In a series of studies we have identified a role for specific biological, cognitive, emotional and motivational variables in the aetiology of self-injury, aggression and temper outbursts across Cornelia de Lange, Cri du Chat, Angelman, Prader-Willi and Smith-Magenis syndromes. These studies have indicated that each of these broad classes of causal variables is more or less important in each syndrome and that intervention that targets the critical class of variable alongside the relevant environmental factors is likely to be effective. We propose a conceptual framework for the study, formulation, assessment and treatment of self-injury and aggression in syndrome groups that would provide a more complete account of the causes of these behaviours in people with intellectual disability and promote generalisation of findings across groups and beyond genetic syndromes. The implications of the model for the possibility of syndrome weighted assessment and treatment protocols and responsive and early intervention are discussed.

Good clinical practice tips

- Pain and discomfort should always be assessed as a possible cause of self-injurious behaviour.
- Functional analysis should be employed to evaluate social/environmental causes of both self-injury and aggression.
- Behavioural interventions should be based on the results of functional analysis but should also take into account cognitive and motivational differences that are associated with syndromes.
- Early advice and monitoring are advisable for high risk syndromes.

Educational Day Talk 7: Special Lecture: *Positive Exposure*: The Spirit of Difference

Rick Guidotti
Positive Exposure, New York, USA

Rick is the founder and director of Positive Exposure, an innovative arts, education and advocacy organization working with individuals living with genetic difference. Positive Exposure utilizes the visual arts to significantly impact the fields of genetics, mental health and human rights.

The first Positive Exposure photographic exhibition was held at the People's Genome Celebration in June 2001, at the Smithsonian National Museum of Natural History in Washington, DC. Positive Exposure continues to exhibit in galleries, museums and public arenas internationally.

Rick's Positive Exposure photo and video presentation explores the social and psychological experiences of people living with genetic, physical and behavioral conditions of all ages and ethno-cultural heritages. The presentation celebrates the richness and beauty of human diversity.

The lecture provides new opportunities to see individuals living with a genetic difference first and foremost as a human being with his/her own challenges rather than as a specific diagnosis/disease entity.

SSBP Syndrome Sheets

Angelman Syndrome

Alternative names

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

First description

In 1965, Doctor Harry Angelman, a general paediatrician in Warrington, described three children with severe developmental delay, ataxia, prolonged bouts of laughter, seizures and similar craniofacial features. He referred to these patients as 'puppet children'. Until the 1980s relatively few patients were reported, when it became apparent that electro-encephalography and cytogenetic testing could greatly contribute to identifying affected patients. Clinical diagnostic criteria rest on physical and behavioural features (Williams et al. 1995).

Incidence/prevalence

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

Genetic aspects

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

Many of the features of the syndrome are thought to result from impaired expression of UBE3A. This gene is found throughout the brain and has a role in proteic scavenging processes. This expression is normally determined epigenetically by a methylation pattern which is specific to the maternally inherited chromosome. Abnormal imprinting in various regions of the brain and the cerebellum are probably responsible for most of the phenotype. Angelman syndrome phenotype has been associated with mutations in the X-linked methyl-CpG-binding protein 2 (MECP2) which has been incriminated in Rett syndrome. According to the mechanism of inheritance, the recurrence risk may be close to 0 or to 50%.

Physical phenotype

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

Cognitive aspects

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

Behavioural aspects

The behavioural phenotype is reviewed extensively by Horsler and Oliver (2006a). Of note are the presence of raised levels of laughing, smiling and happy demeanour, excessive sociability, little or no speech, sleep disturbances, hyperactivity and aggression in 6–10% (Summers, Allison, Lynch, & Sandler, 1995). There is very little literature describing the behavioural phenotype of adults with Angelman syndrome, but it is suggested that many of these behaviours may decrease in frequency as the individual ages. Sixty (94%) out of the 64 studies reviewed by Horsler and Oliver identified elevated levels of laughing and smiling behaviours. Early work suggested that these behaviors were neurologically driven, and therefore environmental factors were not influential (e.g. Dooley, Berg, Pakula, & MacGregor, 1981; Williams & Frias, 1982). However, careful experimental manipulation of the environment identified that both the frequency and duration of these behaviors are related to environmental context (e.g. Horsler & Oliver, 2006b; Oliver *et al.*, 2007).

Life expectancy

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

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Autism and Asperger Syndrome

Classification

Autism and Asperger Syndrome are the two principal conditions included by DSM-IV & ICD-10 in the category of Pervasive Developmental Disorders (PDD). The others include atypical autism and PDD Not Otherwise Specified (PDD NOS). Rett syndrome and Childhood Disintegrative Disorder are also incorporated within the PDD category although they have very different causes and trajectories. There is continuing debate as to whether autism and Asperger syndrome are distinct conditions within the PDD Classification, or whether Asperger syndrome should be considered as synonymous with high functioning autism (i.e. autism in individuals of normal IQ [i.e. ≥70] with well developed language skills). Current research tends to support the latter view (Mackintosh & Dissanayake, 2004)

First described

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

Aetiology

The risk of ASD in siblings of probands is significantly increased and there is an exceptionally high concordance rate in monozygotic twins. Family studies indicate that the "Broader Autism Phenotype" (i.e. having problems related to social, language and/or cognitive functioning) occurs in up to 20% of first degree family members. Autism is not a single gene disorder and current evidence indicates that between 2 and 15 genetic loci may be involved. Possible candidate sites include chromosomes 2q, 7q and 11q (Autism Genome Project Consortium, 2007) but various other sites, including 17q, have also been implicated. Recent research suggests that many (possibly the majority) cases of autism may be due to de novo mutations occurring first in the parental germ line and which have high penetrance in males (Zhao et al., 2007) There is no evidence that single environmental factors (e.g. MMR or other vaccines) cause autism although more complex environmental risk factors (e.g. abnormalities in the immune system of individuals with ASD, or pre-natal perturbations) cannot be ruled out. The role of gene-environment interaction must also be considered (Rutter et al., 2006).

Associated conditions

There is a significant association between autism and Tuberous Sclerosis and a lesser association with Fragile X. Links with other conditions have also been described (e.g. rubella, cytomegalovirus, phenylketonuria) but the phenotype in these cases tends to be atypical. Epilepsy, often with onset in early teens, occurs in around 20–30% of individuals with comorbid intellectual disability, but in under 19% of those with normal IQ. (Levisohn, 2006)

Prevalence

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

Physical Phenotype

This is usually normal although minor physical anomalies are not uncommon. One of the most consistent

anatomical findings is an enlarged head circumference (Van Engeland & Buitelaar, 2008)

Life expectancy/natural history

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

Behavioural and cognitive characteristics

Autism and Asperger syndrome are identified by a "triad" of impairments: abnormal development of social skills and communication, and the presence of ritualistic and stereotyped behaviours/interests. Onset of language is usually significantly delayed in autism but by definition there are no marked delays in Asperger syndrome. Although frequently associated with cognitive delays, recent studies suggest that up to 50% of individuals with ASD may in fact be of normal intellectual ability. IQ in Asperger syndrome is, by definition, within the normal range (≥ 70). In children with autism, non-verbal IQ is frequently higher than Verbal IQ, although this pattern may be reversed in older, more able individuals.

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

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Patricia Howlin, August, 2008

Cornelia de Lange Syndrome

Alternative name

Cornelia de Lange syndrome (CdLS) is also known as Brachman de Lange syndrome.

Incidence/prevalence

CdLS has an estimated prevalence of 1 in 50,000 live births (Beck 1976, 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, Wang, Lisgo, Bamshad, & Strachan, 2004). Additional mutations on the SMC3 gene on chromosome 10 (Deardorff et al., 2007) and X linked SMC1 gene (Musio et al., 2006) are reported to account for 5% of cases. The NIP-BL gene is expressed in the developing skeleton and soft tissue of the limbs, hands, spinal column, face and head including the ear canal, the atrial and ventricular areas of the heart, oesophagus, trachea and lungs (Tonkin *et al.* 2004).Individuals with NIP-BL mutations show large variability in presentation but a larger proportion of these individuals appear to be more severely affected by the syndrome with more severe intellectual disability and limb abnormalities (Gillis *et al.* 2004; Bhuiyan *et al.* 2006). In contrast, mutations in SMC1A and SMC3 have currently been found to result in a milder presentation of the CdLS phenotype with less severe intellectual disability and fewer physical abnormalities (Deardorff *et al.* 2007).

Physical features

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 (Ireland *et al.* 1993; Jackson *et al.* 1993; Selicorni *et al.* 1993; 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 (Ireland *et al.* 1993; Jackson *et al.* 1993; 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 (Hall *et al.*, 2008; Jackson *et al.* 1993; Luzzani *et al.* 2003). Gastro-intestinal disorders are particularly problematic in CdLS. Luzzani *et al.* (2003) found 65% of individuals with CdLS evidenced various degrees of oesophagitis which was strongly associated with behavioural difficulties such as hyperactivity and self-injurious behaviour.

Life expectancy and age related changes

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

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

Behavioural characteristics

Self-injurious behaviour is generally thought to be more common in people with CdLS than in the general intellectual disability population (Berney *et al*., 1999; Gualtieri, 1990; Hyman *et al*., 2002; Sloneem *et al.* In submission) 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 (Berney *et al*., 1999; Gualtieri, 1990, Hyman *et al*., 2003) and this has led to suggestions that individuals with CdLS may be at risk for self-injurious behaviour to become difficult to regulate (Bryson *et al*., 1971; Shear *et al*., 1971). The increased frequency of compulsive like behaviours within the syndrome such as tidying up and lining up behaviours (Hyman *et al*., 2003; Moss *et al.* In submission) also indicates that individuals with CdLS may be at risk for difficulties with behaviour regulation.

An association between CdLS and autism spectrum disorders has recently been recognised. Berney *et al.* (1999) reported that 53% of 49 individuals with Cornelia de Lange syndrome demonstrated the triad of impairments diagnostic of autism spectrum disorder. For 37% of individuals, this triad was "pronounced." Using the Diagnostic Interview for Social and Communication Disorders, Bhyuian *et al*.(2006) reported that 66.6% of 36 individuals with CdLS scored above cut-off for a diagnosis of autism. Furthermore, 61.1% of participants scored above the diagnostic cut-off for autism on the Autism-Algorithm Scale of the Developmental Behavior Checklist. Similar prevalence figures are reported by Oliver *et al* (In review) and Basile *et al.* (2007) using the Childhood Autism Rating Scale and by Moss *et al.* (2008) using the Autism Diagnostic Observation Schedule. Extreme shyness and social anxiety is thought to be characteristic of many individuals with CdLS and an unusually high number of individuals with CdLS are reported to show characteristics of selective mutism. These difficulties may become more prominent with age (Collis *et al*., 2006)

Cognitive 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 (Goodban 1993; Sarimski 1997; Berney *et al.* 1999; Oliver *et al.*2003).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).

CdLS parent resources:

- CdLS Foundation UK and Ireland: www.cdls.org.uk
- CdLS World: www.cdlsworld.org
- Oliver C., Moss J., Petty J., Arron K., Sloneem J. & Hall S. (2003). *Self-injurious Behaviour in Cornelia de Lange Syndrome: A Guide for Parents and Carers*. Trident Communications Ltd., Coventry. – Available from the CdLS Foundation UK and Ireland.
- CdLS Foundation UK and Ireland (2007). *Facing the Challenges: A Guide for Caregivers to People with the Cornelia de Lange Syndrome* – Book and DVD available from the CdLS Foundation UK and Ireland.

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Moss, J., Collis, L & Oliver, C. updated August 2008.

CHARGE Syndrome

First Description
Hall (1979)

Incidence/prevalence
Most common estimate is 1/12,000 births. Recent surveillance study in Australia found 3.24/100,000 (Williams, 2003).

Genetics/aetiology
Study underway at Baylor University (Lalani, 2003). Able to exclude a large part of the genome for microdeletion. Looking at translocation between chromosome 2 and 7 in one child with CHARGE.

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.

CHARGE is asymmetrical. Two recent studies have found the left side to be more often affected than the right. 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.

Cognitive characteristics
There is considerable variability here, with some children very developmentally delayed, and others attending college. One longitudinal study (N. Hartshorne, 2003) found average adaptive behaviour in the low normal range, with little change over four years.

Behavioural characteristics
There is variability in the presence of behavioural difficulties (T. Hartshorne, in press). The behaviours have led to diagnoses of autism, attention deficit/hyperactivity disorder, obsessive-compulsive disorder, and tic disorder. Because these behaviours are frequently found in persons who are deaf-blind it is difficult to identify a behavioural phenotype.

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Tim Hartshorne, 2003

Cri du Chat ("Cry of the Cat") Syndrome

Alternative names
5p – deletion syndrome; chromosome 5 short arm deletion

First description
The syndrome was first described by Lejeune et al (1963)

Incidence/Prevalence
arly research described the prevalence of cri-du-chat syndrome has about I in 50,000 live births (Neibhur, 1978), although more recent estimates suggest a greater incidence of I in 37,000 live births (Higurashi, Masaaki et al 1990).

Genetic Aspects
Cri-du-chat syndrome results from a deletion of chromatin from the short arm of chromosome 5 (5p). A de novo deletion is present in 85% of cases while 10–15% of cases are familial with the overwhelming majority (>90%) due to parental translocations. Neibuhr was the first researcher to identify the specific chromosomal region implicated in the syndrome as 5p15.1–5p15.3 using cytogenetic analysis (Neibuhr 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 cat-like cry has been mapped to the proximal part of 5p15.3 (Gersh, Goodart et al 1994), the speech delay to the distal part of 5p15.3 (e.g. Overhauser, Huang et al 1994) and severe intellectual impairment to 5p15.2 (Overhauser, Huang et al 1994). The importance of careful characterisation of the 5p deletion in a new-born suspected of presenting with cri-du-chat is further highlighted by the growing number of studies that have described individuals with 5p deletions outside the critical region and who often present with the eponymous cat-cry but not severe learning disability (e.g. Cornish, Cross et al. 1999). Such studies highlight the need for accurate differentiation between 5p deletions that result in the typical phenotype and those that result in a milder phenotype and a much more optimistic developmental prognosis.

Physical Aspects
The hallmark cat-cry is a core feature of this syndrome and is still regarded as an important early clinical diagnostic feature in most but not all individuals. Many infants tend to be of low birthweight and show marked hypotonia. Feeding difficulties are common and the associated failure to thrive may be the initial clinical presentation. Some infants may require enteral feeding, a process which may have to continue for several years. Certain facial and head abnormalities are also over represented: microcephaly, micrognathia, rounded face, macrostomia, hypertelorism with downward sloping palpebral fissures, low set ears, broad nasal ridge and short neck. Structural laryngeal abnormality and hypotonia are thought to be responsible for the cat-like cry.The phenotype tends to become less striking with advancing age which may result in diagnostic difficulty in these circumstances; conversely, other features tend to become more apparent long face, scoliosis and macrostomia (Van Buggenhout et al 2000). In addition to the major health problems already described, CDC children are very prone to develop recurrent upper respiratory tract infections, otitis media and dental problems. In contrast, the prevalence of epilepsy is very low compared to heterogeneous samples of severely mentally retarded people (Cornish and Pigram 1996). Once patients manage to negotiate childhood, they can probably expect to live a normal life-span.

Cognitive aspects
The early reports on the syndrome suggested that profound intellectual disability was a cardinal feature of the

syndrome, presenting in all individuals with a 5p deletion. However, recent findings indicate that in children with typical cri-du-chat IQ predominantly falls into the moderate to severe learning disability range but that there is a crucial discrepancy in the pattern of language functioning with children displaying better receptive than expressive language (Cornish, Bramble et al 1999; Comish and Munir 1998). These findings extend previous research that discovered 'language delay" to be a deviant feature of the syndrome by highlighting a particular strength within their cognitive profile. Even in children with very minimal speech, studies have shown that many can use basic sign or gestural language for communication (Carlin 1990).

Behavioural aspects

Self-injurious behaviour appears to be very common in cri-du-chat syndrome (Dykens and Clarke 1997; Collins and Cornish 2001) most notably head banging, hitting the head against body parts, and self-biting all reaching a plateau in late childhood and then remaining constant throughout early adulthood. Clinical hyperactivity is also known to be over represented in children with the syndrome (Dykens and Clark 1997) and is further compounded by a high incidence of chronic sleep problems and restlessness.

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Kim Cornish & David Bramble, January 2000

Down Syndrome

First description

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

Incidence/prevalence

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

Genetics

Three types of abnormality affecting chromosome 21 occur. In about 95% of cases the DS is caused by primary non-disjunction leading to trisomy 21. The origin of supernumerary human chromosome 21 (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 . On the contrary, congenital heart defect occurs only in ~40% and atrioventricular canal in ~16% of patients. Duodenal stenosis/atresia, Hirschsprung disease and acute megakaryocytic leukemia occur 250-, 30 – and 300-times more frequently, respectively, in patients with DS than in the general population. In addition, for any given phenotype there is considerable variability (severity) in expression. DS is also associated with an increased incidence of autoimmune disorders,such as autoimmune tiroiditis,primary sclerosing cholangitis, insulin dependent diabetes mellitus,celiac disease and alopecia areata. On the other hand, DS seems be protective against other conditions, such as multiple sclerosis, Crohn disease, neuroblastoma and the development of solid tumors, which are rarely reported in association with DS.

Most adults with DS are of short stature (70%), with a characteristic facial appearance. The eyes seem to slope upwards and outwards as a result of alterations in the structure of the surrounding tissues. Iris Brushfield spots are present in 55%. The nose has a wide bridge, and the head an unusual shape ("brachycephaly"). Protruding tongue is present in 45%.Limb abnormalities include a single transverse crease on the palm (85%), a large cleft between the first and second toes, and relatively short upper arms. People with DS are prone to abnormalities of the thyroid gland (15% develop hypothyroidism during childhood or adolescence). Ninety percent of all DS syndrome patients have a significant hearing loss, usually of the conductive type.

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

Behavioural characteristics

Fewer behavioural problems compared to controls with cognitive disability have been described in DS but more frequent than in sibling or in controls with normal IQ. 17·6% of individuals with DS aged less than 20 years have a psychiatric disorder, most frequently a disruptive behaviour disorder such as attention deficit hyperactivity disorder (6·1%), conduct/oppositional disorder (5·4%), or aggressive behaviour (6·5%). 25·6% of adults with DS a psychiatric disorder, most frequently a major depressive disorder (6·1%) or aggressive behaviour (6·1%).The dual diagnoses of DS and autism has gained much attention; although the association has always been appreciated, recent reports suggest a frequency as high as 7% and great delays in diagnosis.

The stereotype of people with DS as happy, placid individuals with a gift for mimicry is not borne out by recent behavioural research. "Stubbornness" and obsessional features seem to be over-represented, and many people with DS react adversely in situations involving conflict.

Cognitive characteristics

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

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

Cognitive abilities tend to be greater among people whose DS is caused by mosaicism for 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) may be the cause of dementia in DS.

Clinical signs and symptoms of Alzheimer's disease are noted in 75% of DS individuals over 60 years of age, and are most frequently seizures (58%), change in personality (46%), focal neurological signs (46%), apathy (36%), and loss of conversational skills (36%).

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

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Annapia Verri, 2005

Fragile X Syndrome

First described by

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 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, with 80% of males with a full mutation (>200 CGG repeats) have learning disability and the rest having learning problems. In full mutation females, approximately 25% have learning disability, and an additional 60% have learning difficulties particularly in math, attention and impulsivity. 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 sometimes intellectual disability or autism can occur in carriers. Carriers have an elevation of their *FMR1* – mRNA level of 2 to 8 times the normal. 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% of older female carriers. Brain atrophy and white matter disease are seen on MRI in those with FXTAS. The premutation disorders including FXTAS and POI do not occur in those with a full mutation because they 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 characteristics

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 with 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.

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 ummethylared 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. 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, whereas atypical antipsychotics help to stabilize mood and decrease aggression.

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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

Randi Hagerman, August 2008

Klinefelter Syndrome

Incidence/prevalence
Between 1:500 and 1:1000 live male births. Two-thirds have a 47XXY pachromosomal complement.

Genetics
Surplus of X chromosomes in phenotypic males (e.g. XXY, XXXY, XXYY and mosaicism). The phenotype described is 47 XXY.

Physical phenotype
Height, weight and head circumference below average at birth. Increased growth (especially of legs) from 3 years of age onwards. Affected males are usually taller than their fathers. Head size remains small. Puberty normally occurs, but testosterone production falls in early adult life. Affected adults have a normal sized penis but small testes. About 60% have some breast enlargement.

Life expectancy
Thought to be normal.

Behavioural and emotional characteristics
Boys with XXY are typically introverted and less assertive and sociable than other children, with poorer school performance. Adults may have increased rates of antisocial behaviour and impulsiveness.

Cognitive characteristics
The IQ distribution is skewed downwards, although measured full scale IQs range from the 60s to the 130s. Performance scores usually exceed Verbal scores. Most affected children receive speech and language therapy, and expressive language deficits are often more pronounced than problems with receptive language.

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Lesch-Nyhan Disease (LND)

Alternative names

Historically, Lesch-Nyhan syndrome has been used. Lesch-Nyhan Disease (LND) and hypoxanthine-guanine phosphoribosyl transferase (HPRT) deficiency are most commonly used to describe this disease.

First description

It is interesting to speculate that the first description of Lesch-Nyhan Disease may very well have been in the year 1267. Beck (Eur J Ped Surg 1991) identified an original description of what is most probably LND when he uncovered cases of self-injury, gout, and mental retardation in individuals living in a small village in England where St. Thomas, Archbishop of Canterbury, had been killed. The original account was written by Jacobus de Voragine from secondary sources (Golden Legend). Incidentally, de Voragine thought the origin of the disease might somehow be related to the murder of St. Thomas and the "wrath of God".

More recently, in 1959, two physicians, Catel and Schmidt, described what has turned out to be the first variant of the disorder of partial HPRT deficiency (Kelley-Seegmiller syndrome) which, in turn, involves a variable degree of neurological symptoms without the self-injurious behavior of LND. The enzyme defect was discovered by Seegmiller in a patient with partial deficiency of HPRT in 1967. In 1960 Riley described gout and cerebral palsy in a 3 year old that appears to be the first classic case of LND to be described in the literature. Riley, a pediatrician in Glasgow, cared for children with developmental disabilities at a time when such clinics were not common. Commonly accepted as the first description of the familial nature of the disease was by Nyhan and Lesch 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. 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 was the first of many different nucleotide changes identified in this gene.

Incidence/prevalence

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

Genetic aspects

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

Physical phenotype

The motor syndrome found in LND is best described as dystonia superimposed upon hypotonia, although chorea, spasticity and athetosis have been described. During volitional movements, the examiner may believe increased tone is present, yet when the movement is over or when the patient is relaxed, hypotonia is clearly evident. Anxiety often confuses the clinical picture, as it does with other aspects of the disorder, especially when the patient is examined by a physician unfamiliar with the patient. The question of the presence of athetosis vs dystonia and the presence of hypotonia vs spasticity is often difficult to distinguish on exam by a physician who is not familiar with the behavioral manifestations of LND. LND presents in the first few months of life as a developmental delay and may be diagnosed initially as cerebral palsy. Interestingly, if CP is defined as a non-progressive movement disorder, LND could then be classified as a dystonic form of cerebral palsy with hypotonia. Affected individuals are generally non-ambulatory. The basal ganglia is now known to be involved in the regulation of areas other than the motor circuits. Personality, cognition, emotion as well as movement are all potentially regulated by the basal ganglia. Visser, Bar, and Jinnah have reviewed in depth the involvement of the basal ganglia in LND.

Cognitive characteristics

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

Behavioural characteristics

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

Treatment

Treatment for the behavioral manifestations of LND is multi-modal and should include: 1) judicious use of protective devices, 2) utilization of a behavioral technique commonly referred to as selective ignoring with redirection of activities, and 3) occasional use of medications. The use of medications for treating the behavioral component of this disorder is controversial yet most children and adults with LND are treated with different medications. No medication has been found to reverse the so-called 'Lesch-Nyhan behaviors', either motor or behavioral. Selective ignoring is a methodology that is designed to extinguish self-destructive emotional or physical behavior in the LND patient. It requires the caretaker to ignore such behavior by the LND patient

towards said caretaker so that the behavior decreases or ceases. Along with selective ignoring, the use of redirection is also found to be helpful. At times controversial, the use of protective devices is essential, yet often problematic for patients and institutions not familiar with the care of LND patients. Professionals unfamiliar with LND may perceive the use of these protective devices from a traditional paradigm of restraints – which is to say, the use of these devices against a patient's will. When protective devices are requested by the patient – and used to safeguard the patient from him or herself – the outcome is an extraordinary feeling of comfort and safety. Not allowing the use of protective devices would violate the autonomous rights of the patient. In Lesch-Nyhan Disease self-injury far exceeds that associated with other developmental disabilities and is a consequence of the neurotransmitter abnormality characterizing the disorder. Although not all individuals with this condition demonstrate severe behavioral manifestations, it is reasonable to say that all benefit from the use of protective devices at some point during their lifetime.

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

Life expectancy

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

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Gary E. Eddey

Neurofibromatosis Type 1 (NF1)

Incidence/prevalence

About 1 in 3,000 births.

Genetics

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

Physical features

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

Life expectancy

Depends on nature and severity of clinical features.

Behavioural characteristics

Many patients experience social and behavioural difficulties (Barton & North, 2004). These include communication difficulties and difficulties forming and maintaining friendships. More than half of children with NF1 show significant scholastic difficulties and more than 30% meet criteria for ADHD. NF1 is associated with autism spectrum disorder but no robust epidemiological data are available to indicate the exact rates of ASD in NF1.

Cognitive characteristics

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

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Prader-Willi Syndrome (PWS)

Alternative Names
Prader-Labhart-Willi syndrome, RHO syndrome.

First Description
Prader et al in 1956

Incidence/ prevalence
Incidence estimated at 1 in 22,000 live births. Birth incidence in Australia and in Belgium found to be 1 in 25,000, from genetics clinics reports.

Genetic Aspects
Approximately 70% of people with PWS have a deletion of the long (q) arm of chromosome 15 at q11q13 of paternal origin, 29% (but more when proportion of older mothers in the general population increases) maternal uniparental disomy (two number 15 chromosomes from mother) and about 1% an imprinting error (apparently altering methylation within 15 ql 1q13 and silencing gene expression). Deletions may (rarely) occur in association with translocations, giving rise to an increased risk of recurrence. All subtypes have in common a lack of paternally expressed imprinted genes in the 15q11-q13 region.

Physical Aspects
Short stature, hypogonadism, hypotonia, small hands and feet, dysmorphic faces. May be obese, but this is not an invariable feature (dietary management is now often started early in life). Increased prevalence of scoliosis and other orthopaedic abnormalities.

Cognitive Aspects
Summarised data from 57 studies including 575 people with PWS show that about 5% have an IQ above 85, 27% IQs between 70 and 85, 34% mild, 27% moderate, 5% severe and 1% profound mental retardation. Deficits in sequential processing, verbal information processing and short-term memory have been found. Deletion subtypes tend to have higher non-verbal IQ, disomy subtypes have higher verbal IQ.

Behavioural Aspects
Neonates feed poorly (often tube fed) and are hypotonic ("floppy"). Overeating becomes apparent in childhood. Adults have delayed satiation of appetite. Food stealing and consumption of 'unpalatable' (pet, frozen, rotting) food is not uncommon. Outbursts of temper, mood abnormalities, self-injury through skin-picking and some other maladaptive behaviours occur more frequently than among people of the same age and sex with equivalent cognitive impairments. Repetitive speech and persistent questioning may reflect relative deficits in processing information presented aurally. Affective disorders and psychotic symptoms have been reported, sometimes with a clinical picture resembling cycloid psychoses with much greater frequency among the older disomy subtype. Obsessional and compulsive behaviours similar to those of normal childhood occur relatively frequently.

Life Expectancy
Life expectancy depends on the extent to which the individual is over-weight for height. Heart failure or diabetes may result from obesity. A 71 year old woman with a deletion of 15q11q13 has been reported. Sudden and unexpected deaths can occur at any age.

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Rubinstein-Taybi Syndrome

Incidence/prevalence

Incidence estimated at 1 in 125,000 live born infants. One of the 25 most common multiple congenital anomaly syndromes in genetic clinics in the USA.

Genetics

Recent studies have found small deletions in about 25% of cases at 16p13.3 that affect at least some part of the CREB-binding protein (CBP) gene. A few apparently familial cases have been reported, and 4 sets of concordant monozygotic (identical) twins have been reported.

Physical features

Thumbs and first toes have broad terminal phalanges, often with an angulation deformity. Short stature, a small head, a beaked or straight nose, downward slanting eyes and high arched palate are commonly present. The gait is stiff with joint hypermobility. Other congenital anomalies like heart defects are not uncommon.
Life expectancy: Inadequate weight gain in infancy, congenital heart defects, urinary tract abnormalities and severe constipation contribute to morbidity reflected in a hospitalisation rate 10 times higher than the general population. There is an increased tumour risk, particularly neural crest derivatives such as medulloblastoma and oligodendroglioma. Affected people can live to the seventh decade.

Behavioural characteristics

Findings from postal questionnaire surveys in the USA and UK indicate a friendly, happy disposition, a propensity to self-stimulatory activities such as rocking as well as an intolerance of loud noises and mood instability. Rocking, spinning and hand flapping were common in the UK survey. Social competence depends on the level of intellectual disability. Systematic studies with contrast groups do not appear to have been performed.

Cognitive characteristics

A survey of non-institutionalised children reported an average IQ of 51. Another report stated that 75% had an IQ below 50. Carers reported a short attention span in 90% of 41 people with the syndrome in the UK.

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Tuberous Sclerosis Complex (TSC)

Incidence/prevalence
About 1 in 6,000 live births.

Genetics and Molecular Biology
Occurs as a spontaneous mutation in 70% of cases. Autosomal dominant inheritance pattern in familial cases. The disorder is associated with mutations in one of two genes, *TSC1* (on 9q34) or *TSC2* (on 16p13.3). The TSC1–2 protein complex acts as a heterodimer linking a number of intracellular signaling pathways including the AMPK pathway, the MAPK pathway and the PI3K pathway. The TSC1–2 complex functions upstream of mTOR (mammalian Target Of Rapamycin).

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

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

Behavioural characteristics
Tuberous Sclerosis is associated with high rates of developmental disorders including autism and autism spectrum disorders (25–50%), ADHD (about 50%) and attention-related disorders. There are high rates of disruptive behaviours, sleep problems and occasionally self-injurious behaviours. In adolescents and adults very high rates of anxiety (>60%) and mood-related disorders are reported. Psychotic disorders should raise the possibility of seizure-related psychopathology.

Cognitive characteristics
Global cognitive abilities show a bimodal distribution. 30% of individuals with TSC have profound global intellectual disability and do not show significant developmental gains over time ('Profound' phenotype). The remaining 70% fall on a normal distribution curve, shifted to the left ('Normal Distribution' phenotype). In clinical practice, more than 50 % of individuals with TSC will have global cognitive abilities in the normal range. There are, however, high rates of specific neuropsychological deficits in those with normal global intellectual abilities. Specific deficits are most prominent in attentional, executive and visuo-spatial skills. These specific cognitive deficits may lead to significant scholastic difficulties and impair functional abilities in daily life. International consensus guidelines recommend regular assessment of cognitive and behavioral problems in TSC (see references).

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Websites for further information:

- www.tuberous-sclerosis.org
- www.tsalliance.org

Petrus de Vries, September 2004, revised July 2009

Velo-Cardio-Facial Syndrome

Alternative names

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

Incidence / prevalence

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

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).

Physical phenotype

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

Psychiatric/behavioural disorder

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

Neuropsychological deficits

Early reports of children with VCFS described language abnormalities including immature language usage, poor development of numerical skills and significant impairments in reading and spelling (14). In a study of 37 VCFS children, Swillen and colleagues (1997) reported a wide variability in intelligence ranging from moderate learning disability to average intelligence with a mean full-scale IQ (FSIQ) of approximately 70 (15). 45% of individuals (n=17) had a learning disability, the vast majority (82%) of which was mild. Similarly, Moss and colleagues (1999) reported that the mean FSIQ of their sample of 33 children and adults was 71, with 17 (52%) of their sample demonstrating learning disability (16). VCFS individuals with a familial deletion are found to have a lower mean FSIQ than individuals with a de novo (non-inherited) deletion (15).

A specific neuropsychological profile has also been described in children with VCFS with verbal IQ exceeding

performance IQ on tests of general intellectual functioning (15–16). This discrepancy may relate to difficulties in planning ability, visuospatial ability and non-verbal reasoning in addition to deficits in novel reasoning and concept formation.

More recently, deficits have been highlighted in memory regulation and VCFS individuals are more likely to demonstrate false recognition deficits in the suppression of irrelevant content. Trait-like deficits of memory regulation may also occur in VCFS and can be observed during the retrieval stage, while selective encoding remains intact (17).

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

Brain structural abnormalities

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

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Kieran C Murphy & Frederick Sundram, September 2008

WAGR Syndrome (11p13 Deletion Syndrome)

Classification

WAGR syndrome is a rare genetic disorder caused by heterozygous contiguous gene deletions of variable size in the chromosome 11p13 region (Fischbach, 2005). The term "WAGR" is an acronym for the clinical features commonly associated with this condition:

Wilms tumor – Approximately half of individuals with WAGR syndrome develop this cancer of the kidney during early childhood (Jones, 2006).

Aniridia – The eyes fail to develop normally leading to partial or complete absence of the irises and other ocular problems, including cataracts, nystagmus, and glaucoma (Fischbach, 2005).

Genitourinary anomalies – Hypospadias, cryptorchidism, microphallus, and genital ambiguity may be observed in males. Streak ovaries and malformations of the uterus, fallopian tubes, and/or vagina may be observed in females. The risk for gonadoblastoma is increased in both sexes (Clericuzio, 2005).

Mental **R**etardation – Cognitive impairment and developmental delay are common, with the severity ranging from mild to severe mental retardation. However, some children may have normal intelligence (Clericuzio, 2005).

First described

An association between aniridia and Wilms tumor was observed over 50 years ago (Brusa & Torricelli, 1953) and was confirmed a decade later by Miller et al. (1964) who reported six cases of aniridia observed in 440 patients with Wilms tumor, three of whom also had mental retardation. In 1978, Riccardi et al. reported a deletion of chromosome 11p13 in three individuals, proving WAGR syndrome to be a chromosomal deletion syndrome.

Aetiology

Nearly all cases of WAGR syndrome are sporadic with the chromosome 11p13 deletion arising *de novo*, having developed spontaneously during gametogenesis or embroyogenesis. Familial cases have been reported in which one parent carries a balanced translocation. Over 100 genes can be involved in the region of deletion. Some of the clinical symptoms of WAGR syndrome have been attributed to specific gene deletions, including *WT1* (kidney and genitourinary abnormalities), *PAX6* (eye abnormalities), and *BDNF* (hyperphagia and obesity). Differences in individuals' deletion sizes may account for observed phenotypic variability and differences in degree of developmental and mental delay (Jones, 2006).

Associated conditions

There is a significant association between hyperphagia and obesity and the *BDNF* deletion in individuals with WAGR syndrome (Han et al., 2008). Other conditions associated with WAGR syndrome include neurocognitive and behavioral disorders, such as autism spectrum disorders, attention deficit disorder, obsessive compulsive disorder, anxiety disorders, and depression (Fischbach, 2005). Lastly, individuals with WAGR syndrome may also exhibit seizure disorders, chronic pancreatitis, congenital heart defects, and chronic renal failure due to focal segmental glomerular sclerosis (Clericuzio, 2005).

Prevalence

WAGR syndrome is rare in the general population with only a few hundred cases reported thus far. From these cases there is a greater prevalence of the syndrome in males with a male to female ratio of 3:2. A survey of 54 WAGR patients predicted that there was 50% risk of developing Wilms' tumor with a 62% chance in males and a 40% chance in females (Clericuzio, 2005). It is estimated that Wilms' tumor develops in a third of aniridia patients and in half of the patients with aniridia, genitourinary anomalies, and mental retardation. The risk of Wilms' tumor increases to 60%, however, if aniridia patients have a detectable deletion of 11p13 (Jones, 2006).

Physical Phenotype

Common craniofacial features among individuals with WAGR syndrome include prominent lips, micrognathia, and poorly formed ears. In addition to aniridia, some patients with WAGR syndrome exhibit congenital cataracts, nystagmus, ptosis, and blindness. Genitourinary anomalies include cryptorchidism and hypospadias, and about half of WAGR patients have Wilms' tumor, growth deficiency and microcephaly (Fischbach, 2005). Other traits include glaucoma, anterior segment anomaly, microthalmia, kyphoscholiosis, inguinal hernias, obesity, ambiguous external genitalia, cystic lesions of the kidney, streak gonads, gonadoblastoma, fifth finger clinodactyly, and ventricular septal defects (Jones, 2006).

Life expectancy/natural history

Life expectancy in individuals with WAGR syndrome has not been researched, but well-timed and appropriate medical intervention can improve survival and quality of life for these individuals (Fischbach et al., 2005).

Behavioral and cognitive characteristics

Cognitive impairment and developmental delay are common, with the severity ranging from mild to severe mental retardation. However, some children may have normal intelligence. A MedQuest survey found that in addition to mental retardation, many children with WAGR syndrome also exhibited behavioral and psychiatric disorders. A commonly reported diagnosis is attention deficit disorder. Other reported diagnoses include autism, pervasive developmental disorder, anxiety, and obsessive-compulsive disorder (Clericuzio, 2005).

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Williams Syndrome (also known as Williams-Beuren Syndrome)

First described

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

Genetic aspects

Williams syndrome is a genetically determined neurodevelopmental disorder that is caused by a deletion of 21 – 30 genes on one copy of chromosome 7. Research is beginning to identify phenotypical manifestations of some of the commonly deleted genes. A deletion of ELN (occurring in > 99% of individuals with WS) is associated with congenital heart disease and connective tissue expressions, e.g. hernias and premature ageing of the skin (Tassabehji et al., 1999). Several genes have been associated with the intellectual disabilities and cognitive deficits observed in WS, including GTF2I, LIMK1 and CYLN2 (Tassabehji et al., 1999; Van Hagen et al., 2007). 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 in one recent study.

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). 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); 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

Typical behavioural characteristics include overfriendliness, generalized anxiety, attentional problems and over sensitivity to noise (Davies, Udwin & Howlin, 1998). Most individuals have moderate to mild intellectual impairments, although some may be of low-average to average IQ (Howlin, Davies & Udwin, 1998). Although visuo-spatial skills are often thought to be more severely impaired than language skills, 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 (Ansari *et al*., 2003; Bellugi *et al*., 2000). In contrast to these deficits, 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 all delayed (e.g. Martens *et al*., 2008).

Individuals with WS often display particular patterns of emotions and behaviours. In some cases, these may be viewed as positive aspects of the syndrome, e.g. friendliness, sociability and empathetic nature (Doyle, Bellugi, Korenberg & Graham, 2004). Yet, emotional and behavioural difficulties are common, e.g. hypersociabilty, preoccupations and obsessions, impulsivity and distractibility (Einfeld, Tonge & Rees, 2001). Recently, emotional and behavioural problems have been investigated in terms of diagnosable psychiatric disorders (e.g. Dykens, 2003; Leyfer *et al*., 2006). These have demonstrated high rates of anxiety disorders, including specific phobia (12 – 54%), GAD (1 – 24%), separation anxiety (4 – 7%), panic disorder (1 – 5%), agoraphobia (1 – 5%), OCD (2 – 5%) and social phobia (2%). The second most frequently identified mental health problem is depression (9 – 14%). Other affective disorders include bipolar disorder (5%) and hypomania (3%). A small number of cases of psychotic disorders has also been identified (1 – 2%).

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Further information

- www.williams-syndrome.org.uk

Patricia Howlin, 2005, revised 2008

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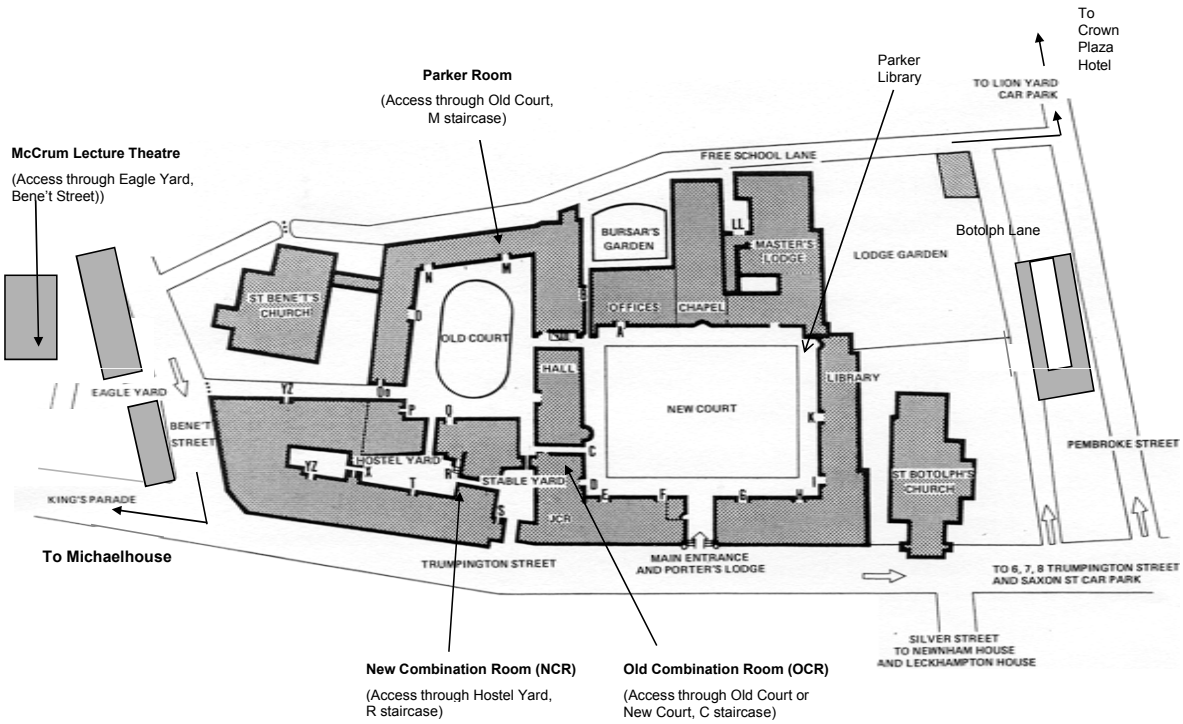
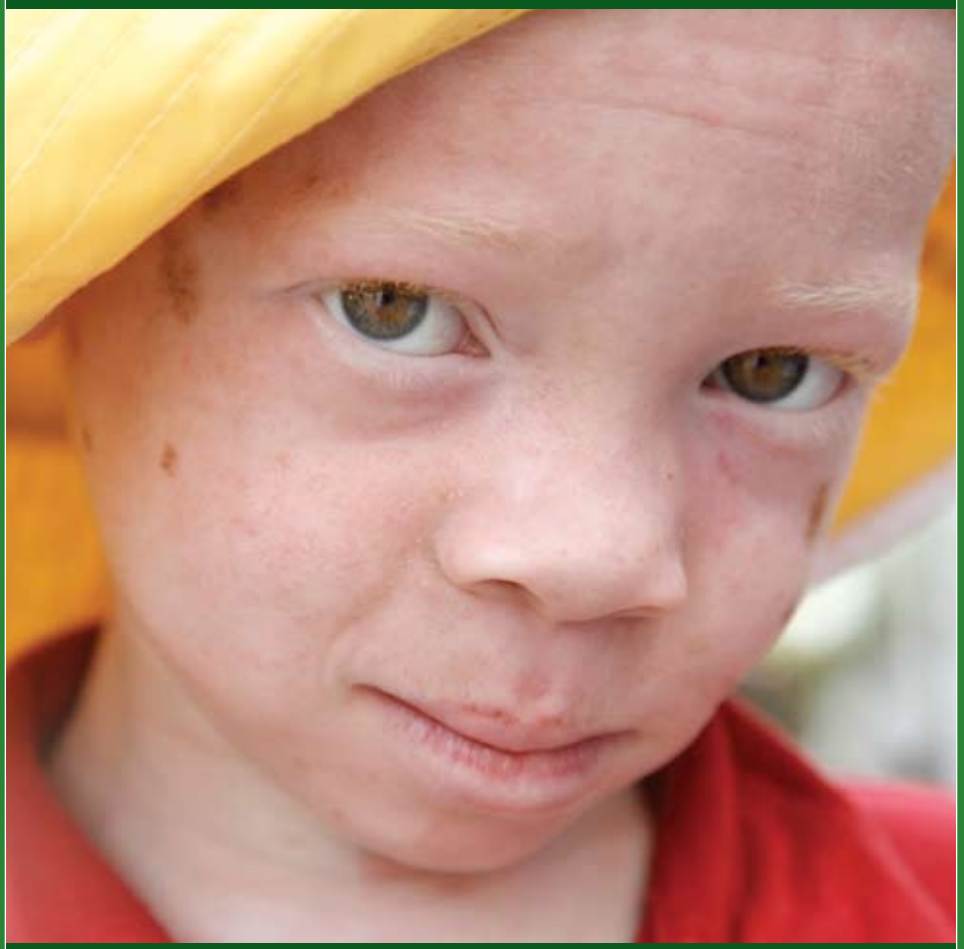
Map of Corpus



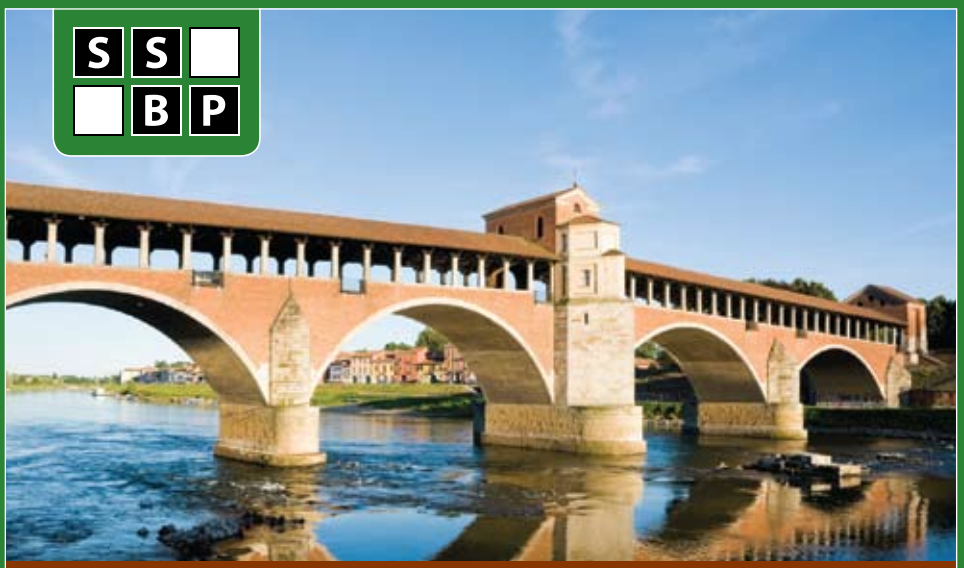
Positive Exposure

An exhibition of photographs celebrating the uniqueness of individuals with genetic difference

14th–25th October 2009
Michaelhouse, Trinity Street, Cambridge, UK



The Society for the Study of Behavioural Phenotypes is an international organisation and a registered charity (No. 1013849). SSBP, Developmental Psychiatry Section, University of Cambridge, Douglas House, 18b Trumpington Road, Cambridge CB2 8AH, UK. Picture courtesy Rick Guidotti (www.positiveexposure.org).



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