



# 13th SSBP International Research Symposium

*Neurobehavioural variability in genetic disorders*

23rd – 25th October 2010, Pavia, Italy

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# Welcome

Dear colleagues,

On behalf of the SSBP Chair, Dr Petrus de Vries, we are delighted to welcome you to the 13th International Research Symposium in Pavia.

The Symposium represents an important time for on several themes relating to the more recent developments of our knowledge of behavioural phenotypes. Careful observation of behaviour is becoming more important as developments in genetics continue to define new syndromes. It is well known that the study of behavioral phenotypes helps individuals with underlying genetic or neurodevelopmental disorders to understand intellectual and behavioural traits related to the underlying condition. Lombroso, Director of the Mondino Institute in Pavia, was one of the first researchers who tried to correlate the clinical to the behavioral phenotype.

Our special topics this year will be Cornelia de Lange syndrome (CdLS) and Klinefelter Syndrome and X-related disorders. We will have important research to present on the genetics of CdLS, as well as on the treatment of behavioral problems in FXS, including core symptoms of autism.

We welcome you to Pavia and we hope that this University city with Romanesque and medieval buildings with its typical atmosphere will be a beautiful setting. We are hopeful that this conference will lead to new collaborations and new research that will improve the lives of individuals with genetic disorders.

## Local Organizing Committee

Annapia Verri, Fondazione "Istituto Neurologico Nazionale C. Mondino" - Istituto di Ricovero e Cura a Carattere Scientifico, Pavia

Angelo Selicorni, Clinica Pediatrica , Università Milano Bicocca, Fondazione MBBM, A.Ospedale S Gerardo Monza

Luigi Tarani, Clinica Pediatrica La Sapienza Università di Roma.

# Scientific Committee

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National Neurological Institute, IRCCS C. Mondino Foundation  
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# About National Neurological Institute, IRCCS C. Mondino Foundation

## Brief history and mission

The research activity carried out at the Casimiro Mondino National Institute of Neurology Foundation has evolved over a period now spanning almost a century. Ever since the second decade of the twentieth century, research at Mondino has developed along the lines originally laid down by Camillo Golgi (Nobel laureate in 1906 and father of the modern neurosciences) and subsequently consolidated by two of his pupils, both professors at the University of Pavia, Casimiro Mondino and Ottorino Rossi, the latter founder of the Pavia school of neurology. The institute, originally a 'neuropathological clinic' (Clinica Neuropatologica), was established in 1915 through a bequest of Prof. Casimiro Mondino, lecturer in psychiatry at the University of Pavia; in 1917 it was made a non-profit organisation by royal charter. In those early years the treatment of nervous and mental disorders was conducted alongside original research studies inspired by the teachings of Golgi, the institute's true mastermind, but it was thanks to the stimulus of Ottorino Rossi that the University of Pavia Neuropathological Clinic, which had in the meantime become the Mondino Foundation, began to move away from the rigid late-19th-century nosographic systems towards the concept of clinical neurosciences.

This transition continued in the decades that followed, a milestone coming in 1973, when the Italian Health Ministry officially recognised the 'Casimiro Mondino Institute of Neurology' Foundation as a Scientific Institute for Research, Hospitalisation and Health Care (IRCCS), a denomination that confirmed its dual role as a centre both for the treatment of nervous system disorders and, and at the same time, for applied research in the field of neurology. The institute's historical links with the University of Pavia are maintained through special agreements that, regulating the activities and respective roles of the two organisations, guarantee that the provision of highly specialised healthcare services by the foundation as a hospital operating in the field of neurosciences, is properly integrated with teaching and research requirements.

Research work, closely tied in with healthcare provision, is thus the fundamental mission of the institute, which is an independent organisation of national renown and a private legal entity. The Mondino Foundation conducts, in accordance with standards of excellence, mainly clinical and translational research in the biomedical field and in the field of healthcare service organisation and management, as well as providing highly specialised inpatient and outpatient diagnostic and healthcare services. The activity focuses on diseases and disorders, both organic and functional, related to the nervous system and the field of child neurology and psychiatry, both ones occurring frequently in the population and more complex conditions with high healthcare and social costs. These problems are dealt with through a broad-ranging approach which extends from clinical, epidemiological and social-healthcare research to translational-type preclinical research.

Another official purpose of the Mondino Foundation is the organisation of high-level training activities within the disciplines and areas of specific interest to it.



# Sponsors



*SIN – Società Italiana di Neurologia  
Italian Society of Neurology*



*SINPIA – Società Italiana di Neuropsichiatria dell'Infanzia  
e dell'Adolescenza  
The Italian Society of Child and Adolescent Psychiatry*



*Università di Pavia  
University of Pavia*



*Fondazione "Istituto Neurologico Nazionale C. Mondino"  
– Istituto di Ricovero e Cura a Carattere Scientifico  
National Neurological Institute, IRCCS C. Mondino  
Foundation*



*SIMGEPED – Società Italiana Malattie Genetiche  
Pediatriche e Disabilità Congenite  
Italian Society of Genetic Pediatric Diseases and  
Congenital Disability*



*UNIAMO – Federazione Italiana Malattie Rare  
Italian Federation for Rare Diseases*

# 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
2010	Pavia, Italy	13th International

## Forthcoming SSBP Meetings

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

## The SSBP Executive Committee

<b>Elected President</b>	Dr Martin Bax (London) (m.bax@imperial.ac.uk)
<b>Chair</b>	Dr Petrus de Vries (Cambridge) (pd215@cam.ac.uk)
<b>Hon. Secretary</b>	Professor Leopold Curfs (Maastricht) (curfs@msm.nl)
<b>Hon. Treasurer</b>	Dr Howard Ring (Cambridge) (har28@cam.ac.uk)
<b>Committee</b>	Dr Honey Heussler (Brisbane) (honey.heussler@gmail.com)
	Dr Deborah McCartney (Cambridge) (d1m31@cantab.net)
	Dr Joanna Moss (London) (j.f.moss@bham.ac.uk)
	Dr Raja Mukherjee (London) (raja.mukherjee@sabp.nhs.uk)
	Dr Kieran O'Malley (Republic of Ireland) (privatecarr@hotmail.com)
	Dr Sarita Soni (Glasgow) (sarita.soni@ggc.scot.nhs.uk)
	Professor Jeremy Turk (London) (jeremy.turk@slam.nhs.uk)

<b>International Representatives</b>	Europe: Professor Leopold Curfs (Maastricht) (curfs@msm.nl)
	Australia: Professor Stewart Einfeld (Randwick) (s.einfeld.usyd.edu.au)
	Canada: Dr Roger Freeman (Vancouver) (roger_freeman@yahoo.com)
	USA (East Coast): Professor James Harris (Baltimore) (jamesharris@erols.com)
	USA (West Coast): Professor Randi Hagerman (Sacramento) (randi.hagerman@ucdmc.ucdavis.edu)

**Administrative Secretary** Robbie Fountain

For any enquiries about SSBP activities or membership, please contact Robbie Fountain, Administrative Secretary, 2nd Floor, Douglas House, 18b Trumpington Road, Cambridge CB2 8AH, UK; email [ssbprobbie@aol.com](mailto:ssbprobbie@aol.com); telephone +44 (0)1223 746 100; fax +44 (0)1223 746 122.

## 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

2009	Alcino Silva
2008	Hans-Christoph Steinhausen
2007	Petrus J de Vries

# 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 was 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.

# The Tom Oppé Distinguished Lecture

## Randi Hagerman

Professor Randi Hagerman is a Developmental and Behavioral Pediatrician and the Medical Director of the M.I.N.D. Institute at UC Davis. She is internationally recognized as both a clinician and researcher in the fragile X field.

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

Professor Hagerman's research involves genotype-phenotype correlations in fragile X and the association of fragile X and autism. She has written over 200 peer-reviewed articles and 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. Prof. Hagerman has received numerous awards for her research, including the Jerrett Cole Award from the National Fragile X Foundation for unselfish dedication to work with fragile X children and adults, the Bonfils-Stanton Foundation Award for Science including Medicine, the IASSID Distinguished Achievement Award for Scientific Literature, the 2005 Distinguished Scholarly Public Service Award from UC Davis, and the 2006 Dean's Award for Outstanding Mentoring at UC Davis. In 2004, to honor both Randi and Paul Hagerman in recognition of their work in FXTAS, the National Fragile X Foundation established the Hagerman Award. This award recognizes research accomplishments in the field of FXTAS and is given at the bi-annual International Conference on Fragile X. Dr Hagerman received the Lifetime Achievement Award from the National Fragile X Foundation in 2008 and the Dean's Team Research Award from UC Davis in 2010. Dr Hagerman has worked internationally to establish fragile X clinical programs and research programs throughout the world.

Her recent work has focused on targeted treatments for FXS, FXTAS and Autism. She has worked with her husband Paul to establish the Neurotherapeutics Research Institute (NTRI) at UC Davis dedicated to finding treatments for neurodevelopmental and neurogenerative disorders.



# Keynote Speaker Profiles

## Paolo Mazzarello

Paolo Mazzarello took a degree cum laude in Medicine and Surgery at the University of Pavia in 1980, at the University of Milan obtained a postgraduate degree in Neurology in 1984 and a Research Doctorate in Neurological Sciences in 1987.

He has been Professor of History of Medicine at the University of Pavia since 2001 and, since 2004, has been a member of the teaching staff of the Pavia 'Istituto Universitario di Studi Superiori (IUSS)'. He developed his research activity at the Molecular Genetic Institute of the Italian National Council of Research (CNR) at Pavia and at present is working at the Museum of History and at the Experimental Medicine Department in the General Pathology Section of the University of Pavia.

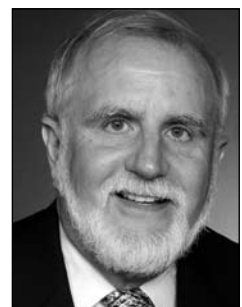
He is author of the following books: *The Hidden Structure: a Scientific Biography of Camillo Golgi* Oxford University Press, Oxford 1999, *Costantinopoli 1786: la congiura e la beffa. L'intrigo Spallanzani*, Bollati Boringhieri, Turin 2004, *Il genio e l'alienista. La strana visita di Lombroso a Tolstoj*, Bollati Boringhieri, Turin 2005, *Il Nobel dimenticato. La vita e la scienza di Camillo Golgi*, Bollati Boringhieri, Turin, 2006 (special prize Cesare Angelini 2006; prize Cesare Cantù 2007), *Una punizione esemplare. Camillo Golgi liceale nel Risorgimento pavese* (Pavia Society of Homeland History, 2007), *Il professore e la cantante. la grande storia d'amore di Alessandro Volta* (Bollati Boringhieri 2009).

He is author of more than 150 publications and notes for journals in science and in medicine history, in molecular biology and in neurosciences. Since 2007 he has been President of the Museum System of the University of Pavia and is secretary member of the executive board of the Center for History of the University of Pavia.



## James Harris

Dr James C. Harris is Professor of Psychiatry and Behavioral Science and Pediatrics and founding Director of the Developmental Neuropsychiatry program at the Johns Hopkins University School of Medicine and the Kennedy Krieger Institute. Dr Harris is the U.S. representative for the SSBP; his research focus is on Lesch Nyhan syndrome. Dr Harris' two-volume single-authored textbook, *Developmental Neuropsychiatry*, received the 1996 "Medical Book of the Year" award in the United States. He is a recipient of the Agnes Purcell McGavin Award for Distinguished Career Achievement from the American Psychiatric Association and is a fellow of the American College of Neuropsychopharmacology, the American College of Psychiatry and the American Psychopathological Association. Dr Harris has published over 200 articles, book, chapters, commentaries and abstracts. Since 2002 he has published over 100 commentaries on the lives of artists, the visual arts, and their relationship to psychiatry.



## Chris Oliver

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



## Angelo Selicorni

- Degree in Medicine in 1987 at Milan University (voting 110/110 cum laudae)
- Statal examination for medical profession in November 1987 at Milan University
- Specialization in Pediatrics in 1990/91 at I School of Specialization in Pediatrics University of Milan (voting 40/40 cum laudae)
- Specialization in Medical Genetics in 1994/95 at School of Specialization in Medical Genetics University of Milan (voting 40/40 cum laudae)
- From March 1991 until December 1994 Medical Assistant at Cytogenetic Laboratory of Mangiagalli Clinic of Milan
- From December 1994 to the present Medical Assistant at I Pediatric Clinic IRCCS Policlinico Foundation Milan
- From December 1994 Director of Ambulatorio di Genetica Clinica within I Pediatric Clinic IRCCS Policlinico Foundation Milan
- From May 2010 Director of Ambulatorio di Genetica Clinica within Pediatric Department Milano Bicocca University S Gerardo Hospital Monza
- Stages: August 1990 at Genetic Service del Kennedy Galton Center, Northwick Park Hospital, Londra (prof. R. Winter) and Hospital for Sick Children, London (prof. M. Baraitser) and from september 1990 till december 1990 at Departement de Genetique Medicale de L'Hôpital des Enfants de la Timone, Marsiglia (prof.ssa S. Aymè)
- Dr Selicorni is member of the Scientific Board of the Associazione Nazionale di Volontariato Sindrome di Cornelia de Lange, Associazione Italiana Sindrome di Williams, Associazione Italiana Sindrome di Wolf-Hirshhorn and AISAC
- From July 2007 he has been the chair of the Scientific Advisory Comitee of the Cornelia de Lange Syndrome Foundation ([www.cdlsworld.com](http://www.cdlsworld.com))
- Dr Selicorni is author of 83 scientific papers.



## Joachim Wistuba

Joachim Wistuba was educated in Münster. He studied biology with a focus on Comparative Zoology at the Faculty of Natural Sciences where he awarded his PhD, before he entered the field of Reproductive Biology and Medicine. He is focussing on animal experimental work to understand testicular organization and development and to find answers and models for translational research aiming at the deeper understanding of infertility and how to overcome those problems.





## Nicole Tartaglia

Dr Nicole Tartaglia completed her medical education at the University of Colorado and completed her residency training in pediatrics at Children's Hospital Los Angeles. She completed subspecialty training in Developmental-Behavioral Pediatrics at the University of California – Davis Medical Center M.I.N.D. Institute. She is currently a subspecialist in Developmental Pediatrics at The Children's Hospital Child Development Unit in Denver, Colorado. She is also the Director of the Fragile X Clinic and the eXtraordinary Kids Clinic at the Child Development Unit. Dr Tartaglia's clinical work and research interests include studying neurodevelopmental disorders in children with genetic syndromes including Fragile X syndrome and X&Y chromosome variations.



## Antonio Radicioni

- Medical Degree at University of Rome "La Sapienza" in 1978.
- Specialist graduation in Endocrinology at University of Rome "La Sapienza" in 1981
- Specialist graduation in Andrology at University of Pisa in 1986
- Assistant Professor in Endocrinology and Andrology at University of Rome "La Sapienza" since 1988
- Confirmed Researcher (Med 05) (Clinical Patology) by Sapienza University of Rome since 1990
- Scientific activities: Clinic and laboratoristic activities in endocrinological and andrological topics. Publications both in Italian and International journals and books. Member of Italian Society of Endocrinology, Italian Society of Andrology and Medicine of Sexuality, Italian Society of Pediatric Endocrinology and Diabetology, International Society of Immunology of Reproduction.
- Didactic Activities: Professor in Endocrinology and Andrology at University of Rome "La Sapienza" of Rome, teacher in "Corso di Laurea Specialistica D", 1st Faculty of Medicine and Chirurgia; Corso di Laurea in Igienista Dentale; Corso di Laurea in Tecnico di Laboratorio Biomedico; Scuola di Specializzazione in Endocrinologia.
- Assistenziat Activities: Chairman of Rare Diseases Center, Dept. of Medical Pathophysiology, Sapienza University of Rome. Director of Laboratory of Endocrinology. The service is accredited by the "European Academy of Andrology" as a section of "Andrology Training Centre". Clinical activity in the ambulatory of Endocrinology and Andrology.



# The 13th SSBP International Research Symposium

## “Neurobehavioural variability in genetic disorders”

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### Programme

#### Day 1 (Saturday 23rd October 2010)

The introductory lecture of the Symposium will follow the presentation of the XXI Ottorino Rossi Award – New Series Founders of Neurology.

15:00 – 15:30	Registration (Pavia Main University Building)
15:30 – 15:45	Welcome and Introductions <i>Petrus de Vries (Chair, SSBP)</i>
15:45 – 16:30	Introductory lecture: <b>Cesare Lombroso: an anthropologist between evolution and degeneration</b> <i>Paolo Mazzarello (University of Pavia)</i>
16:30 – 17:15	<b>The Contributions of Camillo Golgi to Neurodevelopmental studies</b> <i>J. C. Harris (The Johns Hopkins University School of Medicine, Baltimore)</i>
17:30 – 18:00	Visit to the Historical Museum of Pavia University
20:30	Welcome dinner

#### Day 2 (Sunday 24th October 2010)

##### Session 1: De Lange Syndrome Symposium (Chair: Chris Oliver, Angelo Selicorni)

08:30 – 09:00	Set up of Posters (Mondino Institute)
09:00 – 10:00	Talk 1: Keynote: <b>Cornelia de Lange syndrome.</b> <i>Chris Oliver (University of Birmingham)</i>
Invited Lectures	Talk 2: Keynote: <b>Mild CdLS phenotype: clinical and molecular results of an international survey</b> <i>Angelo Selicorni (IRCCS Fondazione Policlinico Magiagalli Regina Elena – Milan)</i>

10:00 – 11:00	<p>Oral Presentation 1: <b>Relevance of large deletions/duplications of the major candidate gene NIPBL as pathogenetic mechanism of the Cornelia de Lange syndrome.</b>  <i>M. Masciadri, C. Gervasini, J. Azzollini, A. Cereda, A. Selicorni, L. Larizza, S. Russo</i></p> <p>Oral Presentation 2: <b>Delineating the Profile of Autism Spectrum Disorder in Cornelia de Lange Syndrome.</b>  <i>J. Moss, S. Hall, L. Collis, K. Arron, C. Burbidge, C. Richards, &amp; C. Oliver</i></p>
11:00 – 11:30	Coffee and poster session
11:30 – 13:00	<p>Oral Presentation 3: <b>Autism, Intellectual Disability, and Molecular-Genetic Aspects Associated with Subtelomeric Rearrangements</b>  <i>G.S. Fisch, P.D. Grossfeld, J. Youngblom, R. Simensen, A. Battaglia</i></p> <p>Oral Presentation 4: <b>Receptive Language and Intellectual Disability in CDLS. Importance of instruments of evaluation in a cohort of 10 patients.</b>  <i>P. Vizziello, P. Ajmone, F. Dall'Ara, C. Rigamonti, F. Monti, M.A. Costantino, A. Selicorni</i></p> <p>Oral Presentation 5: <b>Augmentative and Alternative Communication intervention in Cornelia de Lange Syndrome (CDLS)</b>  <i>M.A. Costantino, S. Anastasia, E. Bergamaschi, L. Bernasconi, G. Zappa, A. Selicorni</i></p> <p>Oral Presentation 6: <b>EEG and clinical polymorphism of Rett Syndrome</b>  <i>N.L.Gorbachevskaya, V.Yu.Voinova, A.V.Budilov, A.B.Sorokin, Yu.B.Yurov</i></p>
13:00 – 14:00	Lunch and poster session
14:30 – 16:15	<p><b>Free Abstract session (Chair: A. Swillen)</b></p> <p>Oral Presentation 7: <b>Prevalence of autistic symptoms in children with ADHD: a clinic-based study</b>  <i>S. Mohiuddin, R. Legrou, M. Ghaziuddin</i></p> <p>Oral Presentation 8: <b>Behavioural Intervention for Challenging Behaviour in Children with Angelman Syndrome</b>  <i>D. Allen, C. Oliver, J. Petty, P. Webster, D. Reid, D. Villa, S. Beaumont, S. Hyland, I. Arowolo, A. Jones, S. Gorniak, M. Radstaake</i></p> <p>Oral Presentation 9: <b>Focus related performance problems (FRPP) among persons with ASD and genetic syndromes</b>  <i>T. Nærland, K. Hildebrand, H. Martinsen, S. Storvik</i></p> <p>Oral Presentation 10: <b>Does cognitive impairment explain behavioural and social problems of children with Neurofibromatosis Type 1?</b>  <i>S. Huijbregts</i></p> <p>Oral Presentation 11: <b>Visual cognitive function in Autism spectrum disorder</b>  <i>D. Pereverzva</i></p>
16:15 – 16:30	Coffee and poster session

16:30 – 17:45	<p><b>Free Abstract session (Chair: G.S. Fisch, A. Swillen)</b></p> <p>Oral Presentation 12: <b>Neurobehavioural deficits in 11 children (2–12 years) with 22q11.2 duplication</b> <i>A. Swillen, S. Van Campenhout, K. Devriendt, H. Peeters, H. Van Esch, T. de Ravel.</i></p> <p>Oral Presentation 13: <b>Identification of a de novo distal 22q11.2 deletion in an adult female referred for an anxiety disorder</b> <i>W. Verhoeven, J. Egger, H. Brunner, N. de Leeuw</i></p> <p>Oral Presentation 14: <b>Neuropsychological Attention Skills and Related Behaviours in Adults with Tuberous Sclerosis Complex</b> <i>K.M. Tierney, D. L. McCartney, J. R. Serfontein &amp; P. J. de Vries</i></p> <p>Oral Presentation 15: <b>Epilepsy and Tsc2 haploinsufficiency independently lead to autistic-like behaviors in rats</b> <i>R. Waltereit, B. Japs, M. Schneider, P.J de Vries, D. Bartsch</i></p> <p>Oral Presentation 16: <b>Neurobehavioural profile of Noonan syndrome</b> <i>E. Wingbermühle, J. Egger, I. van der Burgt, W. Verhoeven</i></p>
17:45 – 18:45	SSBP AGM. Members and non-members welcome.
20:00	Social dinner

## Day 3 (Monday 25th October 2010)

### Session 2: Klinefelter Syndrome and X-related disorders (Chair: Lidia Larizza, Orsetta Zuffardi)

09:00 – 10:00	<p>Talk 3: <b>Keynote: Mouse models of Klinefelter Syndrome</b> <i>Joachim Wistuba (University of Muenster)</i></p> <p>Talk 4: <b>Keynote: Evaluation of MAO-A and serotonin transporter polymorphisms in the behavioral phenotypes of males with XXY, XYY, and XXYY syndromes</b> <i>Nicole Tartaglia (University of Denver)</i></p>
10:00 – 11:00	<p>Oral Presentation 17: <b>Expression of sex chromosome genes sybl1, asmt, jarid, il9r, and rps4y in males with sex chromosome aneuploidy</b> <i>F. Tassone, A. Verri, E. Sanchez, V. Destefani, R. Hansen, N. Tartaglia</i></p> <p>Oral Presentation 18: <b>Cognitive control functions and risk for psychopathology in Klinefelter syndrome</b> <i>S. van Rijn, L. de Sonnevile, H. Swaab</i></p> <p>Oral Presentation 19: <b>Language Impairments in Fragile X Syndrome: A Failure to Use Social Cues?</b> <i>L. Abbeduto, R.J. Hagerman, A. McDuffie, S.T. Kover, D. Benjamin, S. Harris, S. Schroeder</i></p>
11:00 – 11:30	Coffee & Poster Session

11:30 – 13:15	<p>Talk 5: <b>Keynote: Endocrinological Treatment in Klinefelter Syndrome</b> <i>Antonio Radicioni (University of Rome)</i></p> <p>Talk 6: <b>Keynote: Targeted Treatment for Fragile X Syndrome: Results of a Randomized Controlled Phase II Trial of Arbaclofen</b> <i>Randi Hagerman (University of California)</i></p> <p>Oral Presentation 20: <b>Parental decision following prenatal diagnosis of Klinefelter syndrome: a proposal for a correct approach</b> <i>L. Tarani, C. Mattiucci, N. Liberati, F. Mancini, F. Colloridi</i></p> <p>Oral Presentation 21: <b>Triple X syndrome ascertained through prenatal diagnosis: characteristics of 42 young Italian girls and parental emotional response to prenatal diagnosis and counselling.</b> <i>F. Lalatta, D. Quagliarini, E. Folliero, U. Cavallari, B. Gentilin, P. Castorina, F. Forzano, S. Forzano, E. Grosso, V. Viassolo, V.G. Naretto, S. Gattone, F. Ceriani, F. Faravelli, L. Gargantini</i></p>
11:30 – 13:00	Lunch & Poster Session
14:30 – 16:15	<p><b>Free Abstracts session (Chair: F. Lalatta, R. Vianello)</b></p> <p>Oral Presentation 22: <b>The parent-of-origin of the extra X chromosome differentially affects psychopathology in Klinefelter syndrome</b> <i>H. Bruining, S van Rijn, H Swaab, M. J. H. Kas, H van Engeland, L de Sonnevile</i></p> <p>Oral Presentation 23: <b>A Comparison of Visual Motor Integration and Motor Skills in Children and Adolescents with Sex Chromosome Aneuploidy</b> <i>S. Martin, S. Davis, N. Tartaglia</i></p> <p>Oral Presentation 24: <b>Emotion recognition problems in boys with Klinefelter syndrome</b> <i>H. Swaab, H. Bruining, S. van Rijn, M. Bierman, H. van Engeland, L. de Sonnevile</i></p> <p>Oral Presentation 25: <b>Narrative skills in Klinefelter Syndrome</b> <i>M. Vernice, A. Cremante, F. Clerici, A. Verri</i></p> <p>Oral Presentation 26: <b>Late diagnosis in multiple X and Y chromosome disorders: role of learning disabilities and behavioural disorders</b> <i>A.Verri, A. Cremante, F. Clerici</i></p>
16:15 – 16:30	Coffee & Poster Session ( <i>Chair: G. Cioni, J. Turk</i> )
16:30 – 17:30	<p>Oral Presentation 27: <b>Molecular and clinical correlations in Fragile X syndrome and in FMR1 related disorders</b> <i>F. Tassone, P.J. Hagerman, R.J. Hagerman</i></p> <p>Oral Presentation 28: <b>Anticonvulsants &amp; SSRIs Improve Psychological Functioning in Fragile X Syndrome</b> <i>J. Turk</i></p> <p>Oral Presentation 29: <b>Females with fragile X syndrome and autism spectrum conditions</b> <i>J. Turk</i></p>
17:30 – 18:00	Closing Remarks <i>Petrus de Vries (Chair, SSBP)</i>

# Abstracts for Oral Presentations

## Introductory Lecture 1: Cesare Lombroso: an anthropologist between evolution and degeneration

**P. Mazzarello**

*Museum for the History of the University of Pavia and Department of Experimental Medicine, University of Pavia.*

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Cesare Lombroso (1835–1909) was a prominent Italian intellectual of the second half of the Nineteenth century. A man of great originality, he began to distinguish himself while he was medical student by publishing in 1855 the essay “On the madness of Cardano” where we already find some of the themes (such as the relationship between madness and genius) that, within a few years, would make him internationally famous. He was born in Verona and enrolled at the University of Pavia Medical School in 1852 but he studied also at the University of Padua and at the University of Vienna. After graduating in 1858 from the University of Pavia, he pursued scholarly studies in psychiatry, hygiene, anthropology, criminology and forensic medicine. He began his teaching career (psychiatry and anthropology) at the University of Pavia in 1863. From 1871 to 1883 he directed the insane asylum of Pesaro, and after another appointment at the University of Pavia he moved as full professor of forensic medicine to the University of Turin. Lombroso became world while famous for his theory that criminality, madness and genius were faces of the same psychobiological reality, expression of *degeneration*, a sort of regression in the phylogenetic scale or a fixation to an early stage of evolution. Degeneration affected especially criminals, in particular the so called “born delinquent”, who had suffered arrested development at an early stage and were therefore the most “atavistic” type of human being. Lombroso also advocated the theory that genius was closely linked with madness. A man of genius was a degenerate, an example of retrograde evolution in whom madness was a form of “biological compensation” for excessive intellectual development. His theories fuelled a heated debate on biological determinism of human behavior.

## **Introductory Lecture 2: The Contributions of Camillo Golgi to Neurodevelopmental studies**

**J. C. Harris**

*The Johns Hopkins University School of Medicine, Baltimore*

Camillo Golgi (1843–1906) was co-recipient of the Nobel Prize in Physiology or Medicine in 1906 for investigation of the structure of the nervous system. He graduated from the University of Pavia in 1865 and subsequently established an internationally recognized experimental pathology laboratory at the University. Throughout his career he emphasized clinico-pathological correlations. In 1873, as chief medical officer in a psychiatric hospital experimenting with metal impregnation of nervous tissue he discovered a method of staining nervous tissue, later known as the Golgi stain (chrome-silver impregnation method), that for the first time allowed the paths of nerve cells in the brain to be visualized. The following year he published the first detailed case report on the neuropathology of chorea. Subsequently he identified the “internal reticular apparatus”, that is known today as the “Golgi apparatus”. Two fundamental types of nerve cells are named after him, Golgi type I (motor) neurons with long axons and Golgi type II (sensory) neurons with short axons. Other findings include his description of the “tendinous sensory corpuscles” that carry his name: “Golgi (proprioceptive sensory receptor) tendon organ”. He described the Golgi–Rezzonico filaments in the nerve fibers. This presentation will review Golgi’s contributions to neuroscience and their pertinence to the study of the neurobiology of behavioral Phenotypes.

## Talk 1: Keynote: Cornelia de Lange syndrome.

### C. Oliver

*Cerebra Centre for Neurodevelopmental Disorders, School of Psychology, University of Birmingham, Birmingham, B15 2TT, UK*

**Abstract:** When William Nyhan first described the concept of a behavioural phenotype nearly 40 years ago he made particular reference to both Lesch-Nyhan and Cornelia de Lange syndromes. At that time descriptions of Cornelia de Lange syndrome (CdLS) focused primarily on physical abnormalities and self-injurious behaviour and it is likely that a mild presentation had not yet been recognised. A review of the literature on the behavioural phenotype of CdLS reveals that since Nyhan's early description was published there has been a broadening of perspective to encompass autism spectrum phenomenology, 'compulsive' and other repetitive behaviours, selective mutism and social anxiety. More recently, studies of more mildly affected individuals have started to reveal specific cognitive impairments that are associated with behavioural presentation and appear to emerge in the teenage years through to early adulthood.

There is much to learn from the history of research in CdLS. The study of the behavioural phenotype has shown how behaviours such as self-injury, that were initially thought to be due to neuroanatomical difference, may be completely unrelated to central nervous system disorder and, in this case, associated with painful health conditions. The genetic causes of CdLS include three different chromosomes with the potential for genotype-phenotype correlational studies allowing differentiation of components of the behavioural phenotype. Finally, the value of applying a standard psychiatric taxonomy to the behavioural phenotypes of genetic syndromes may be called into question if its application masks important differences that might allude to causal mechanisms.



## Talk 2: Keynote: Mild CdLS phenotype: clinical and molecular results of an international survey

**A. Cereda<sup>1,2</sup>, FJ Ramos<sup>3,6</sup>, J. Wierzba<sup>4</sup>, G. Gillessen<sup>5</sup>, M.P. Ribate<sup>3</sup>, M. Ratajska<sup>7</sup>, J. Limon<sup>7</sup>, J. Pie<sup>3</sup>, C. Gervasini<sup>8</sup>, M. Masciadri<sup>9</sup>, A.Selicorni<sup>10</sup>**

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**Background:** Cornelia de Lange syndrome (CdLS) is a multisystemic genetic condition characterized by typical dysmorphisms, prenatal and postnatal growth deficiency, microcephaly, psychomotor/mental retardation, hirsutism and limb malformations. In 60–65% of CdLS patients mutations in the genes NIPBL, SMC1 or SMC3 are found. Since 1993, the existence of a mild phenotype has been recognized, but no clear data are available regarding the natural history of this subgroup of CdLS patients.

**Method:** We collected clinical (growth parameters, age of achievement of the main childhood developmental milestones, presence/absence of major congenital malformations) and molecular data of 69 patients from Italy, Poland, Germany and Spain. All patients had a clinically confirmed CdLS diagnosis according to previously published criteria (Kline et al.) and a neuropsychiatric definition of mild psychomotor/intellectual retardation of borderline/normal development. In Italian cohort we collected data also about main clinical complications.

**Results:** 36% of the analyzed patients showed a mutation in the gene NIPBL, while in 5% the mutation was in the gene SMC1. Within the results of our analysis, the most informative clinical parameters predictive of a mild CdLS phenotype refer to prenatal /postnatal growth values (mean of birth weight 2541g, birth weight > 2500g in 63% of patients) and achievement of the common childhood developmental milestones (mean age of sitting position 10 months, mean age of first walk 19 months, mean age of first words 19 months).

**Conclusion:** Our data demonstrated that mild phenotype, in the meaning of better functional outcome, is relatively common within the large clinical spectrum of CdLS patients. As previously described, a normal birth weight, the absence of severe major malformations, a relatively good postnatal growth and, particularly, a near normal/slightly delayed achievement of the basic psychomotor milestones are features strongly predictive of better neurodevelopmental prognosis. At molecular level, the prevalence of mutations in the gene NIPBL is lower than the overall reported in CdLS, but we didn't find a strong correlation between the mildness of phenotype and type of mutation (missense versus truncating). Regarding the prevalence of the main clinical complications, the analysis of the subgroup of Italian cohort didn't show any significant difference in comparison with the data of the medical literature.

**Keywords:** Cornelia de Lange, mild phenotype, NIPBL gene, SMC1 gene

## Oral Presentation 1: Relevance of large deletions/duplications of the major candidate gene NIPBL as pathogenetic mechanism of the Cornelia de Lange syndrome.

M. Masciadri<sup>1</sup>, C. Gervasini, J. Azzollini<sup>2</sup>, A. Cereda<sup>3</sup>, A. Selicorni<sup>3</sup>, L. Larizza<sup>1</sup>, S. Russo<sup>1</sup>

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**Background:** Cornelia de Lange syndrome (CdLS; OMIM #122470) is a rare multisystem developmental disorder (1:10,000) characterized by mental and growth retardation, congenital heart defects, intestinal anomalies, facial dysmorphisms including cleft palate and limbs' reduction defects.. Mutations in three cohesin proteins, a key regulator of cohesin, NIPBL, (chr 5p13.2) and two structural components of the cohesin ring SMC1A (chr Xp11) and SMC3, (10q25) occur in about 65% of individuals with CdLS. NIPBL is the major candidate gene and is affected in about 50–60% of CdLS patients: genotype-phenotype correlation studies indicate a milder phenotype in patients carrying missense mutations than in those with truncating defects.

**Method:** Mutational screening of NIPBL defects within a large cohort of 180 Italian CdLS patients has been carried on by the two following steps: detection of point mutations by DHPLC and sequencing and search for large deletion/duplications in negative samples by MLPA (multiple ligation probe assay).

**Results:** We found 64/180 among truncating, splicing, missense mutations and small deletions. MLPA allowed to detect whole exons deletions (exons 2, 3, 1–10, 25–27, 32) and one duplication (exon 32) in 5/143 cases negative to sequencing. Thus in our cohort NIPBL mutations account for an overall frequency of 39% ,with the notable fraction of 4,2% of large deletions/duplications. Confirmation of the intragenic imbalances and their boundaries was performed by quantitative Real Time PCR for the duplication and RT-PCR in the deleted patients where RNA was available. This analysis revealed that one deletion was in frame. As regards the 10 exons deletions it involved other 14 genes upstream NIPBL 5'UTR, as assessed by BAC FISH.

**Conclusion:** This study underlines that standard NIPBL sequencing underscores large deletion/duplications which account for a significant fraction of CdLS patients. MLPA is thus an adjunctive tool for diagnosis and management of CdLS patients. To this purpose the characterization of each single case is necessary to highlight the exact extent of the rearrangement and to predict the effect at the protein level.

**Keywords:** MLPA, deletion/duplication, CdLS

## Oral Presentation 2: Delineating the Profile of Autism Spectrum Disorder in Cornelia de Lange Syndrome.

J. Moss<sup>1</sup>, S. Hall<sup>2</sup>, L. Collis<sup>1</sup>, K. Arron<sup>1</sup>, C. Burbidge<sup>1</sup>, C. Richards<sup>1</sup>, & C. Oliver<sup>1</sup>

<sup>1</sup> *Cerebra Centre for Neurodevelopmental Disorders, University of Birmingham, Institute of Psychiatry, King's College London*

<sup>2</sup> *Department of Psychiatry and Behavioral Sciences, Stanford University*

**Background:** To investigate the profile of autism spectrum characteristics in individuals with Cornelia de Lange syndrome (CdLS) and Fragile X syndrome (FXS) compared to individuals with Autism Spectrum Disorder (ASD).

**Method:** The Social Communication Questionnaire (SCQ; Rutter et al., 2003) was employed to evaluate the profile of ASD characteristics in CdLS and FXS. Participants were 116 individuals with CdLS (mean age = 17.12; SD=8.63), 197 individuals with FXS (mean age =17.43; SD = 8.93) and 260 individuals with ASD (mean age =12.04; SD = 5.98).

**Results:** Between groups analysis revealed that the CdLS group scored significantly higher than the FXS group on the communication ( $p<.001$ ) and social interaction domains ( $p=.04$ ) of the SCQ. No significant differences were identified between the CdLS group and ASD group on these subscales ( $p = .55$ ;  $p = .29$ ). The FXS and ASD groups scored significantly higher than the CdLS group on the repetitive behaviour domain ( $p = .002$ ;  $p <.001$  respectively) while the ASD group scored significantly higher than the FXS group on all domains. Odds Ratio item level analysis identified that the ASD group was significantly more likely (99% CI) than the CdLS and FXS to score on a range of items on the SCQ. For the CdLS group this included 3 items in the repetitive behaviour domain, 2 items in the communication domain and 2 items in the social interaction domain. For the FXS group this included 4 items in the repetitive behaviour domain, 5 items in the communicatio domain and 5 items in the social interaction domain.

**Conclusions:** CdLS and FXS are both syndromes that are reported within the literature to show a heightened association with ASD. While domain level analysis reflected the findings in the literature regarding CdLS, this was not found in the FXS group. Item level analysis identified a number of areas of significant difference between both the FXS and CdLS groups compared to the ASD group suggesting that at this fine-grained level of analysis there may be subtle differences in the profile of behaviours between these groups.

## Oral Presentation 3: Autism, Intellectual Disability, and Molecular-Genetic Aspects Associated with Subtelomeric Rearrangements

G.S. Fisch<sup>1</sup>, P.D. Grossfeld<sup>2</sup>, J. Youngblom<sup>3</sup>, R. Simensen<sup>4</sup>, A. Battaglia<sup>5</sup>

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<sup>5</sup>Dept. of Neurology, University of Pisa

**Background:** Nearly 3% of all neonates are born with Intellectual Disability [ID]. From recent studies, it is now clear that 5–10% of formerly idiopathic ID is produced by subtelomeric rearrangements. Previously undetected by conventional cytogenetic techniques, subtelomeric rearrangements are now considered significant causes of many clinical, behavioral, and developmental disorders that include ID and autism. The purpose of this symposium is to provide a comprehensive overview of the clinical, cognitive, behavioral and molecular-genetic features associated with subtelomeric rearrangements on chromosomes 2q37, 4p16 (WHS), 8p21–3, and 11q25 (Jacobsen Syndrome).

**Methods:** We examined 43 children, ages 4 – 20 years, with del2q37 [n=8], invdupdel8p21–3 [n=7], del11q25 [n=9], or 4p16 [n=19], from 9 sites in the US and Europe, using a neuropsychological battery to evaluate cognitive ability, adaptive behavior, emotionality and temperament, attentiveness/ hyperactivity, and autistic-like features.

**Results:** We found 13/43 (30%) of our sample with CARS scores  $\geq 30$  who could be diagnosed as autistic. Attention deficits and hyperactivity [ADHD] were also noted in 25/43 [58%] of the sample of children assessed. Cognitive ability ranged from lownormal to severe ID. Children with del11q25 had significantly higher cognitive abilities, while those with WHS were significantly lower. Adaptive behavior was also significantly higher among children with 11q25. Cognitive ability and adaptive behavior profiles were statistically significantly different among the groups.

**Conclusions:** We conclude that cognitive-behavioral profiles and the risk of developing autism differ among children with dissimilar subtelomeric deletions. Moreover, differences in cognitive-behavioral profiles support a model of different gene-brain-behavior pathways producing ID.

## Oral Presentation 4: Receptive Language and Intellectual Disability in CDLS. Importance of instruments of evaluation in a cohort of 10 patients.

**P. Vizziello<sup>1</sup>, P. Ajmone<sup>1</sup>, F. Dall'Ara<sup>1</sup>, C. Rigamonti<sup>1</sup>, F. Monti<sup>1</sup>, M.A. Costantino<sup>1</sup>, A. Selicorni<sup>2</sup>**

<sup>1</sup>*UONPIA Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy*

<sup>2</sup>*Ambulatorio Genetica Clinica Pediatrica, Clinica Pediatrica Università Milano Bicocca e Fondazione MBBM, A.O S Gerardo Monza*

**Background:** Language and speech in CDLS are generally severely affected, with a specific pattern. Only 3–4 % of children will become talkers, 40 % are late talkers, 25% are limited talkers and 30 % are non talkers. Receptive language is usually considered more adequate than expressive language, but almost no works analyze in depth receptive components nor try to correlate them (vocabulary and morpho-syntax) with cognitive development and behavior. The aim of this study is to describe the correlations between the cognitive and communication (expressive and receptive components) profiles of a cohort of 10 CDLS patients without hearing loss.

**Method:** Cognitive level has been measured with Leiter Scale when possible; language and communication have been evaluated in their receptive components with Mac Arthur Questionnaire, TVL Scale, TCGB Test and Miceli Scale. Hyperactive, aggressive, and autistic behavior were assessed with CARS Scale, DBC and CBCL Questionnaires.

**Results:** In our cohort there are 4 patients with normal IQ, one mild ID and one moderate ID. In the remaining 4 patients it was not possible to obtain a direct IQ evaluation, and indirect measures had to be used. In most patients, we observed a clearly lower receptive language performance than IQ level. Initial correlations with expressive language and with behavior will be tried.

**Conclusion:** Differently from other syndromes, in CDLS receptive language performance seems to be generally lower than IQ, but with a variable pattern not directly related with IQ level. We suppose that receptive language may be one of the most relevant elements that impact on general functioning of CDLS, frequently underestimated because of the difficulties in appropriate direct evaluation. Interestingly, receptive language is also the area in which parents evaluation differ the most from direct evaluations.

**Keywords:** Receptive language, Intellectual Disability, Behavior, Direct/Indirect Assessment, CDLS

## Oral Presentation 5: Augmentative and Alternative Communication intervention in Cornelia de Lange Syndrome (CDLS)

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**Background:** It is known that only 3–4 % of Cornelia de Lange Syndrome children will become talkers, 40 % are late talkers, 25% are limited talkers and 30 % are non talkers. Children with CdLS may have a very low level of intentional communicative behavior, particularly when compared to that of other genetic syndromes, and this seems to be a very relevant early indicator of subsequent development of speech and of challenging behaviors. Worsening of autistic traits and, more generally, of challenging behaviors in CdLS children may be related to internal stress factors, but also to external stressors, in particular to communication and relational impairment. As for others rare diseases though, the importance of early intervention for communication is not yet widespread.

**Method:** Augmentative and Alternative Communication (AAC) is a well known intervention for complex communication disabilities. Providing a full range of AAC opportunities in the first years of life is of great importance in CDLS, with particular attention on input strategies to support language comprehension, particularly morpho-syntactic. Another area in need of specific attention is adolescence, where the dramatic increase of social anxiety can be managed by the introduction of sequences, agendas and routines that may have not been as much necessary in the years before, and that could permit to reach greater control and independence.

**Results:** The effects of AAC intervention in CDLS on early social interaction, behavior and anxiety will be described, and the constant interaction with families and associations.

**Conclusion:** Knowing the behavioral phenotype of CDLS allows to better personalize AAC interventions, decoding more easily the risk signals that may emerge in single children and focusing immediately on the best strategies to deal with them, or activating ways to prevent critical moments.

**Keywords:** Augmentative and Alternative Communication, receptive language, CDLS

## Oral Presentation 6: EEG and clinical polymorphism of Rett Syndrome

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**Background:** Rett syndrome (RTT)- is a complex progressive neurological disorder- the second most frequent cause of mental disability in females (following Down syndrome). RTT is caused by loss-of-function mutation in the gene MeCP2- transcriptional repressor of brain-derived neurotrophic factor (Bdnf). Reduced Bdnf gene expression has been reported in the frontal cortex of RTT patients. The current study examines phenotype-genotype and EEG correlations in RTT patients.

**Method:** EEGs of 63 children with RTT (54, i.e. 86% of which genetically supported) were obtained (age 3–19 years). EEG logarithm spectral power (LnPower) was calculated for standard and narrow frequency bands in following patient groups: 18 patients with missense mutation, 24 with nonsense mutation, 10 with frame-shift mutation and 2 with deletion. 39% RTT patients had skewed X inactivation.

**Results:** Before Stage 2 the EEG is most probably normal. At Stage 2 the EEG flattened with deterioration of occipital alpha rhythm and sensory motor rhythm, at Stage 3 we observed slowing of background activity with dominant theta rhythm (4–6 Hz) and deterioration of occipital alpha rhythm with accompanying multifocal epileptiform discharges. At Stage 4 marked slowing of background activity (delta activity) is the characteristic pattern in the electroencephalogram. Multifocal epileptiform discharges in the state of waking were observed. There is complex relationship between phenotype severity in RTT and the mutation type and position in MeCP2 gene as well as X chromosome inactivation. The positive correlation of thetaiindex and deterioration of emotional communication and contact was revealed. RTT patients with truncating mutations at the 3 disease stage demonstrated most severe alpha deterioration and greater amount of slow activity than patients with missense mutation. In one girl with extremely skewed X-inactivation (2/98) we observed the clinical form “fruste” and nearly normal EEG.

**Conclusion:** Excessive theta activity correlates with cognitive function and attention level deterioration and may reflect disruptions in synaptic signaling.

**Grants:** Supported by RGNF 09–06–00603a grant.

**Keywords:** Rett syndrome, EEG

## Oral Presentation 7: Prevalence of autistic symptoms in children with ADHD: a clinic-based study

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**Background:** Attention Deficit Hyperactivity Disorder (ADHD), the most common child psychiatric disorder, is characterized by inattention, hyperactivity, and impulsivity. However, these symptoms are non-specific in nature and occur in a wide variety of disorders that can lead to diagnostic difficulties. One such disorder is autism. While studies have examined the occurrence of ADHD in children with autism, information is limited about the prevalence of autistic symptoms in children with ADHD. The purpose of this report is to examine this issue in a group of children referred to a specialist ADHD clinic.

**Method:** The study was conducted at a tertiary ADHD clinic for children and adolescents. Approval was obtained from the IRB for analyzing the collected data. Participants were referred by primary care doctors; school personnel; social agencies and parents. Each participant was examined by a PhD level Neuropsychologist, a Child and Adolescent Psychiatry Fellow, and a Board Certified Child Psychiatrist with over 20 years' experience. The following measures were used: Conner's Parent Rating Scale; Social Communication Questionnaire and Child Behavior Checklist. A final diagnosis was made based on all the available information.

**Results:** Seventy-eight participants received a diagnosis of ADHD; 9 (11.5%) of these received an additional diagnosis of an autistic spectrum disorder. None of these had previously been suspected of having an ASD or received a diagnosis of that disorder. The ADHD+ASD group was found to have a higher mean total score on the SCQ in contrast with the ADHD alone group (12.33 and 6.05 respectively;  $p < 0.001$ ) and also scored higher on the CBCL social scores. Children with mixed ADHD+ASD had more ritualistic behaviors and social deficits than those with ADHD alone.

**Conclusion:** At least 10% of children referred to a specialist ADHD clinic had autistic symptoms. These children scored higher on the SCQ and on the social subscale of the CBCL. In addition, they had a history of ritualistic behaviors. These findings suggest that children referred for an evaluation of ADHD should be routinely screened for autism.

**Keywords:** Autism ADHD Comorbidity



## Oral Presentation 8: Behavioural Intervention for Challenging Behaviour in Children with Angelman Syndrome

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<sup>2</sup>Radboud University Nijmegen, The Netherlands

**Background:** A proof of principle study, designed to evaluate the effect of behavioural intervention on challenging behaviour for young children with Angelman Syndrome (AS), was conducted.

**Method:** Five children with AS, aged between three and seven years, who were anecdotally or empirically reported to present functional and frequent challenging behaviour participated in the present study. Each child participated in standard analogue conditions in order to identify the function of challenging behaviour. If a social function for challenging behaviour was not identified, modified analogues were conducted based on parent / teacher report or researcher observations. Following assessment, all children received functional communication training with the aim of reducing challenging behaviour by replacing it with a functionally equivalent communicative behaviour. Functional communication training included differential reinforcement (positive reinforcement of appropriate communicative behaviour and extinction of challenging behaviour) and physical prompting to activate a switch operated voice output device. The effects of these brief interventions for each child were evaluated by comparing the rates of challenging behaviour during postintervention treatment evaluation sessions to baseline sessions using a single-case reversal design.

**Results:** A social function for challenging behaviour was identified for all five children. The behaviour of three children was maintained by attention. One child's behaviour was maintained by access to a preferred activity and the other child's behaviour was maintained by escape from a task. Rates of challenging behaviour reduced significantly when compared to baseline for four out of five children.

**Conclusion:** These findings provide further evidence that challenging behaviour in children with AS can be maintained by positive and negative reinforcement in their environment. Although based on a small sample, the results also suggest that challenging behaviour can be environmentally manipulated using behavioural intervention. The implications of these results for early intervention and the limitations of the present study are discussed further.

**Keywords:** Angelman Syndrome, Early intervention, Functional Communication training, Challenging behaviour, Behavioural intervention

## Oral Presentation 9: Focus related performance problems (FRPP) among persons with ASD and genetic syndromes.

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**Background:** During a 15 years period it has been gathered data on temperamental and behavioural characteristics of persons with ASD in Norway. From clinical experiences it is known that some persons with ASD have severe dyspractic problems with the execution of voluntary motor acts when their attention are directed to their own performance (FRPP). Persons with FRPP respond poorly to some typical autism interventions.

**Method:** Parents and teachers of 233 individuals diagnosed with ASD (1–60 years of age) completed the “Way of being – questionnaire”, which comprise items on temperamental and personality traits, reaction forms, and somatic and clinical problems. Five items concerns how voluntary movements are carried out and nine how environmental factors influences the movements. Six persons with tuberous sclerosis (TS) and 18 with Down syndrome (DS) are compared to matched control groups in addition to 209 persons with ASD on measures of FRPP.

**Results:** About 10% of the total autism sample showed FRPP. 8/18 in the DS/autism group and 3/6 in the TS/ASD group were found to have FRPP. A FRRP score based on FRPP typical behavioural typography, negative reactions to focus on own performance, and social interaction was significantly different between the control groups and both the DS/autism and the TS/ASD group.

**Conclusions:** FRPP in the ASD groups seems to be a prevalent problem that one needs to identify in order to give suitable interventions. Individuals with autism and DS or TS show disturbingly high incidence of FRPP. When it comes to providing suitable interventions for persons in these co-morbid conditions it is important to investigate whether they also meet criteria for FRPP. It seems likely that both combinations of disorders increase the risk of debilitating movement disorders that require tailored interventions.

**Keywords:** Focus related performance problems, Down syndrome; Tuberous sclerosis; autism; Asperger syndrome

## Oral Presentation 10: Does cognitive impairment explain behavioural and social problems of children with Neurofibromatosis Type 1?

**S. Huijbregts**

*Leiden University*

**Background:** This study's aim was to examine whether social and behavioural problems in children with Neurofibromatosis Type 1 (NF1) could be explained by cognitive impairments.

**Method:** Thirty NF1-patients (mean age 11.7 years, SD = 3.3) and 30 healthy controls (mean age 12.5 years, SD= 3.1) were assessed on social skills, social responsiveness/autistic traits, hyperactivity-inattention, emotional problems, conduct problems, and peer problems. Cognitive control/executive function, information processing speed, and social information processing were measured using 5 computer tasks. GLM analyses of variance were performed to examine age-corrected group differences in social-behavioural outcomes. Cognitive control, social information processing and information processing speed were introduced to these analyses as covariates.

**Results:** Group differences, to the disadvantage of NF1-patients, were observed for social skills [ $F(1,57) = 11.4$ ,  $p = .001$ ,  $\eta^2 = .17$ ], autistic traits [ $F = 64.3$ ,  $p < .001$ ,  $\eta^2 = .53$ ], hyperactivity-inattention [ $F = 7.2$ ,  $p = .010$ ,  $\eta^2 = .11$ ], emotional problems [ $F = 6.7$ ,  $p = .012$ ,  $\eta^2 = .11$ ], conduct problems [ $F = 5.3$ ,  $p = .025$ ,  $\eta^2 = .09$ ], peer problems [ $F = 8.7$ ,  $p = .005$ ,  $\eta^2 = .13$ ], cognitive control [ $F = 12.2$ ,  $p = .001$ ,  $\eta^2 = .18$ ], processing speed [ $F = 5.9$ ,  $p = .019$ ,  $\eta^2 = .09$ ], and social information processing [ $F = 6.7$ ,  $p = .012$ ,  $\eta^2 = .11$ ]. Despite significant reductions of group differences after cognition was controlled for, group differences regarding social skills, autistic traits and peer problems remained significant. Differences regarding hyperactivity-inattention, emotional problems and conduct problems were no longer significant.

**Conclusion:** Social and behavioral difficulties of NF1-patients are partly explained by cognitive difficulties. Unexplained variance regarding social functioning and interactions with peers may be accounted for by environmental factors, aspects of cognition not measured here, disease severity, or specific pathology of the brain that is not necessarily reflected in cognitive dysfunction.

**Keywords:** Neurofibromatosis Type 1; Social Functioning; Cognition; Behaviour

## Oral Presentation 11: Visual cognitive function in Autism spectrum disorder

### D. Pereverzva

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**Background:** Autism is associated with visual cognitive function abnormalities, such a deficit in face recognition, disorder of global perception, attention impairments etc. Nevertheless the question of object recognition in autism isn't currently clear. Poorly defined is also a problem of visual control of movement. According to dual stream (what and where or how) model of visual neuroscience we investigated two aspects of VCF: object recognition and visually guided movement.

**Method:** Method. In the current study 20 children with ASD, 10 children with Down syndrome and 20 typically developing children were assessed with visual cognitive tests battery that included object recognition tasks, visually guided movement tasks and videotaping of free visual behavior.

**Results:** Our results reveal that children with autism were likely to make specific object recognition errors, relying on elementary feature of object, like a shape form, and had a superior ability of identification of abstract high detailed pictures. This kind of errors weren't appropriate for typically developing children and those with Down syndrome and can indicate both pathological and compensatory mechanisms. In addition our study reveals strong deficit in developing of anticipatory action preparation in visually guided motion and problems in "on-line" control of action accordingly to changed visual information.

**Conclusion:** Children with autism have a fragmental object representation, and are likely to use compensatory cognitive strategy for object recognition. Impairments of anticipatory action preparation may reveal a deficit in sensorimotor transformation that is considered a base of attention in the Premotor Theory of Attention.

**Grant:** This study was supported by RGNF grant 09–06–00603a

**Keywords:** Autistic Spectrum Disorder, object recognition, anticipatory action preparation.

## Oral Presentation 12: Neurobehavioural deficits in 11 children (2–12 years) with 22q11.2 duplication.

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**Background:** The clinical phenotype in 22q11.2 duplication is extremely variable (both inter- and intrafamilial) ranging from multiple defects to mild learning difficulties, and sharing features with DGS/VCFS, including heart defects, velopharyngeal insufficiency with or without cleft palate, or hypernasal speech, and urogenital abnormalities. Also behavioural difficulties in individuals with 22q11.2 duplication have been reported.

**Methods:** 11 children (6 males, 5 females) with 22q11.2 duplication (1 detected by FISH, 10 by array GH testing), aged between 2- 12 years, were evaluated. Assessment included cognitive testing (using standardized instruments such as BSID-II, SON-R, WPSSI-R and WISCIII), language development (Reynell language tests, TVK), visual-motor skills (VMI) and behavioral observation using standardized questionnaires (CBCL 1.5–5; CBCL 4–18; ADHD, VABS).

**Results:** The degree of developmental delay in these 11 patients varied from moderate ID, mild developmental delay to low-average intelligence. Delayed language acquisition, speech delay and fine motor impairment were present in a number of children. Also behavioural difficulties including anxiety, attention problems, obsessive traits, and social interaction problems were noted. Psychiatric comorbidity including ADHD, ASD and ODD occurred in 7 children.

**Conclusion:** Several neurobehavioural deficits in this group of children with 22q11.2 duplication were present. However, since most individuals with 22q11.2 duplication were identified by array genomic hybridization (array GH) testing as part of the evaluation of developmental delay or mental retardation, this ascertainment bias makes the (clinical and neurobehavioural) phenotype associated with 22q11.2 duplication difficult to establish.

## Oral Presentation 13: Identification of a de novo distal 22q11.2 deletion in an adult female referred for an anxiety disorder

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**Background:** Velocardiofacial syndrome, nowadays called 22q11 deletion syndrome (22q11DS), involves a common hemizygous ~3 Mb interstitial microdeletion in the 22q11.2 region. The syndrome has a highly variable expression and patients with 22q11DS have an increased risk for psychiatric disorders within the schizophrenic, bipolar and autistic spectrum. During the last decades, a small number of patients with only mild features suggestive for the 22q11DS has been reported in whom atypical deletions were found that do not overlap with the common ~3 Mb deletion.

**Method:** An 18-years-old female patient and only child from non consanguineous parents was referred because of anxious preoccupations with death. At the age of six months she underwent surgical correction of cardiac septal defects and closure of the ductus arteriosus. Her history mentioned, apart from postnatal feeding problems, frequent upper airway infections during childhood, developmental delay and recurrent anxieties starting at the age of 16.

**Results:** At referral, her somatic phenotype was characterized by nasal speech and minor facial dysmorphisms. Neuropsychiatric examination demonstrated affective instability, severe anxieties accompanied with social withdrawal, perseverations and paranoid ideation. In addition, there were executive dysfunctions, attention deficits, low social and interpersonal skills and a disharmonic intelligence profile. Total IQ was 81. Laboratory analyses and MRI scanning of the brain revealed no abnormalities. A provisional clinical diagnosis of 22q11 deletion syndrome was made. Furthermore, a diagnosis of panic disorder was established. SNP array analysis demonstrated a de novo 738,8 kb distal deletion in 22q11.21q11.22 comprising 14 genes. Treatment with 20mg citalopram daily for 2 years resulted in complete remission of anxiety symptoms.

**Conclusion:** In individuals with a less suggestive phenotype of 22q11DS and in all patients with a truncus arteriosus anomaly, testing for distal 22q11 deletions is warranted. The putative psychopathological phenotype of distal 22q11 deletion syndrome may included anxiety disorders.

**Keywords:** Distal 22q11 deletion, MAPK1, panic disorder

## Oral Presentation 14: Neuropsychological Attention Skills and Related Behaviours in Adults with Tuberous Sclerosis Complex

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**Background:** Children with TSC have significant deficits on neuropsychological attention tasks, particularly dual tasking and speed of processing measures. Very little is known about the attentional phenotype of adults with TSC. Here we investigate neuropsychological attentional skills and attention-related behaviours in daily life in adults with TSC.

**Method:** Adults with TSC who have global intelligence in the normal range and non-TSC control participants matched on age, gender and performance IQ were assessed using the Test of Everyday Attention for Children (TEA-Ch). Attention related behaviours in daily life were examined using the Attention-Deficit Scales for Adults (ADSA).

**Results:** No group differences were demonstrated on visual selective or auditory sustained attention tasks carried out alone. However, adults with TSC performed significantly worse when these tasks were combined in a cross-modal dual task condition. On the ADSA the TSC group had significantly elevated scores on the attention-focus/concentration, behaviour-disorganised activity, academic and emotive domains. Cross-modal dual task decrement scores were significantly correlated with these domains.

**Conclusion:** Normally intelligent adults with TSC have a significant ability correlated with a clear impact on attention-related behaviours in daily life. These findings, alongside findings from similar research with children, suggest that dual task deficits may be a consistent feature of the neuropsychological phenotype of TSC.

**Keywords:** cognition; attention; dual-tasking; neurodevelopmental disorders; test of everyday attention for children; TEA-Ch; attention deficit scales for adults; ADSA

## Oral Presentation 15: Epilepsy and Tsc2 haploinsufficiency independently lead to autistic-like behaviors in rats

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<sup>7</sup> Joint senior authorship

**Background:** There is a strong association between autism spectrum disorders (ASD), epilepsy and intellectual disability, but the nature of these correlations is unclear. The monogenic disorder Tuberous Sclerosis Complex (TSC) has high rates of ASD, epilepsy and cognitive deficits. Here we used the Tsc2+/- (Eker) rat model of TSC and an experimental epilepsy paradigm to study the causal effect of seizures on learning & memory and social behavior phenotypes.

**Method:** Status epilepticus was induced by kainic acid injection at P7 and P14 in wild-type and TSC2+/- rats. At the age of 3–6 months, adult rats were assessed in the open field, light/dark box, fear conditioning, Morris water maze, novel object recognition and social interaction tasks.

**Results:** Learning & memory was unimpaired in naïve Tsc2+/- rats, and experimental epilepsy did not impair any aspects of learning & memory in either wild-type or Tsc2+/- rats. In contrast, rearing in the open field, novel object exploration and social exploration was reduced in naïve Tsc2+/- rats. Seizures induced anxiety, social evade, as well as reduced social exploration and social contact behavior in wild-type and Tsc2+/- rats.

**Conclusion:** This study provides the first evidence of behavioral deficits in naïve Tsc2+/- rats and presents the first evidence that experimental epilepsy can induce autistic-like (social deficit) behaviors in wild-type and Tsc2+/- rats. Our results suggest that epilepsy may induce social, but not necessarily learning & memory deficits in individuals who have or are at risk of ASD.

**Keywords:** Tuberous sclerosis, global intellectual deficit, autism, epilepsy, learning and memory, social interaction



## Oral Presentation 16: Neurobehavioural profile of Noonan syndrome

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**Background:** Noonan syndrome (NS) is an autosomal dominant genetic disorder with an estimated incidence of 1:1,500 live births and characterized by short stature, facial dysmorphism and congenital heart defects. Genetic research has revealed mutations in seven genes. There are indications that NS is associated with affective processing impairments and increased levels of anxiety. This study introduces neuropsychological assessment as an essential tool for studying the contribution of cognition and behaviour in the expression of NS.

**Method:** A group of 40 adult NS-patients, as well as 40 healthy controls matched for age, sex and IQ, underwent extensive neuropsychological assessment. Next to the standard cognitive domains (i.e. intelligence, attention, memory, executive functioning) social cognition was included as a research domain to explore affective information processing. To this end, a theory of mind test, an emotion recognition test (ERT) and two alexithymia questionnaires were administered, and psychopathology was assessed with state of the art interviews and questionnaires. Correlational analysis and repeated measures MANCOVA were used.

**Results:** Mean IQ was just below average, but overall cognitive functioning was intact. However, in the NS group, marked problems were detected in the recognition of own and other's emotions, as well as in the ability to verbally express feelings. Significant main effects were found for group and emotion type on the ERT and alexithymia was significantly more prevalent in the NS group. In addition, NS-patients displayed more mood and anxiety complaints than controls. A tendency was found towards social desirability and agreeableness.

**Conclusion:** Although no specific behavioural phenotype has been described for NS before, these results show that impairments in social cognition are common. Through concise neuropsychological assessment, psychosocial immaturity, alexithymia and amenable traits could be identified as the prerequisites for the development of mood and anxiety disorders in NS.

**Keywords:** Noonan syndrome, neuropsychology, social cognition, alexithymia

## Talk 3: Keynote: Mouse models of Klinefelter Syndrome

### J. Wistuba

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**Background:** Amongst karyotype anomalies, Klinefelter's syndrome (KS) is one of the most frequent genetic disorders, affecting 0.2% of the male population. Characteristic features of the syndrome are germ cell loss, metabolic, and endocrine changes which result in changed body proportions and hypergonadotropic hypogonadism. In addition, the aberration is also suspected to cause various cognitive abnormalities. As the presence of a supernumerary X-chromosome is associated with infertility, the generation of representative animal models of KS has been difficult.

**Method:** Therefore it was a breakthrough when a mouse strain with a mutated Y chromosome (Y\*) was discovered which after a complex breeding protocol resulted in the birth of male mice with a supernumerary X chromosome. This breeding resulted in 41, XXY and 41, XXY\* male mice both of which display similar pathophysiology features to those caused by the supernumerary X-chromosome in KS.

**Results:** Utilizing these models, it was shown that presence of a supernumerary X chromosome caused cognitive deficits in conditional and non-conditional tests, in that the XXY mice exhibited delayed learning in a Pavlovian setting and XXY\* mice showed deficits in memory recognition when exposed to a Novel Object Task. In the latter experiment serum testosterone levels and the ability to perform the task were found to be correlated.

**Conclusion:** These findings support the idea that the presence of a supernumerary X in male mice influences cognitive abilities either by the direct influence of genes escaping from X-inactivation, or changes in the endocrine milieu, or a combination of both. For the mechanisms responsible for these detrimental perturbations to be deciphered, specific experimental strategies will need to be employed in which the KS animal models will no doubt play a pivotal role.

**Keywords:** Klinefelter Syndrome, mouse models, memory recognition, learning behavior, hypogonadism

## Talk 4: Keynote: Evaluation of MAO-A and serotonin transporter polymorphisms in the behavioral phenotypes of males with XXY, XYY, and XXYY syndromes

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**Background:** Genetic factors explaining the significant variability in cognitive and behavioral features of Sexual Chromosome Aneuploidy (SCA) have not yet been identified. Polymorphisms in the serotonin transporter (*SLC6A4*) and monoamine oxidase A (*MAOA*) gene have been associated with behavior and mood symptoms in the general population and in other disorders including fragile X, Alzheimer's and Tourette's syndromes. Here we evaluated polymorphisms in *SLC6A4* and *MAOA* in males with SCA.

**Methods:** This study was conducted in collaboration between the MIND Institute, UC Davis in California, the IRCCS Fondazione C. Mondino in Pavia, Italy, and the University of Colorado Children's Hospital. Assessment of 85 males with SCA (33 XXY, 19 XYY, 34 XXYY) age 4–59 (mean 15.6±10.6) included cognitive testing and standardized behavioral questionnaires (Age 4–18: BASC-2, MASC Childhood Anxiety Questionnaire, Age 19+: SCL-90, All ages: SCQ). Genotyping was carried out by PCR analysis following conditions specific to the polymorphism analyzed.

**Results:** Mean cognitive abilities were significantly higher in the XXY group (102.1±13.6) compared to both XYY (89.2±14.4) and XXYY (79.6±14.0) ( $F_{2,0.4}$ ,  $p < 0.0001$ ). After adjusting for differences in IQ between groups, males who carried one or two copies of the low-activity 3-repeat polymorphism of the MAO-A allele (3,3 or 3,4) showed more symptoms of some domains of anxiety including withdrawal (BASC-2, pediatric group,  $n=42$ ,  $p < 0.01$ ), separation anxiety, (MASC, pediatric group,  $n=38$ ,  $p=0.04$ ) and phobic anxiety (SCL-90, adult group,  $n=25$ ,  $p=0.04$ ). Also, males in the pediatric age group who were homozygous for the short, low-transcribing (S/S) *SLC6A4* allele showed lower stereotyped behaviors compared to those who were heterozygous (S/L) and homozygous (L/L) ( $p=0.02$ ). *SLC6A4* or *MAOA* polymorphisms were not associated with scores in other behavioral domains (depression, aggression, attention, or autism symptoms) in the SCA groups.

**Conclusions:** Polymorphisms in the *SLC6A4* and *MAOA* gene may contribute to the variability of anxiety symptoms and stereotyped behavior in males with SCA, although additional genetic and environmental factors are also involved and yet to be elucidated.

## Oral Presentation 17: Expression of sex chromosome genes *sybl1*, *asmt*, *jarid*, *ilgr*, and *rps4y* in males with sex chromosome aneuploidy

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**Background:** Overexpression of genes on the sex chromosomes is hypothesized to be associated with the physical and behavioral phenotypes of sex chromosome aneuploidy (SCA). This study evaluated expression levels of the candidate sex chromosome genes SYBL1, ASMT, JARID, IL9R, and RPS4Y. Polymorphisms in SYBL1 have been associated with bipolar disorder, ASMT mutations have been associated with depression and autism, JARID mutations have been associated with intellectual disability, IL-9R has been associated with asthma, and RPS4Y is a Y-chromosome specific ribosomal protein. Expression in SCA was compared to XY controls to determine if differences in mRNA expression levels could be detected in peripheral blood samples and be correlated to the clinical phenotype.

**Methods:** Assessment of 100 males with SCA (38 XXY, 27 XYY, 35 XXYY (age 3–59, mean 17.4±12.6) and 19 XY controls (age 3–37, mean 17.7±11.8) included medical history, cognitive testing and standardized behavioral questionnaires. Gene expression mRNA levels were measured using Taq Man real time PCR using primers and probes specific for the target genes. Expression levels were compared between SCA subgroups by ANOVA.

**Results:** Significant differences in gene expression were identified in 4 of the 5 genes studied, including SYBL1 (F 13.78,  $p < 0.0001$ , post-hoc Tukey HSD XXY, XYY, XXYY < XY), JARID (F 12.45,  $p < 0.0001$ , posthoc Tukey HSD XY, XXY < XYY, XXYY  $p < 0.01$ ), RSP4Y (F 12.1,  $p < 0.0001$ , post-hoc Tukey HSD XY, XXY < XYY, XXYY  $p < 0.01$ ), and IL9R (F 3.27,  $p = 0.024$ , post-hoc Tukey HSD XY < XXYY). There were no statistically significant differences in expression between groups in ASMT expression. For all genes studied except the SYBL gene, the XXYY group had the highest mean expression level. Expression levels were not significantly correlated with co-morbid medical diagnoses (asthma, seizures, tremor), cognitive level, or behavioral symptoms within each SCA subgroup or across the entire cohort.

**Conclusions:** Differences in expression levels of some sex chromosome genes were detected in peripheral blood leukocytes of males with SCA, although not always consistent with what would be expected based on known patterns of X-inactivation in the general population. Study of expression differences in tetrasomy conditions such as XXYY may show more significant differences compared to XY controls than the trisomy conditions, leading to identification of genes associated with the phenotype in SCA.

## Oral Presentation 18: Cognitive control functions and risk for psychopathology in Klinefelter syndrome

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**Background:** Approximately 1 in 700 boys are born with an extra X chromosome, also known as Klinefelter syndrome (KS). Because of the risk for development of psychopathology, it has been suggested that studying individuals with KS may help in the search for cognitive, neural and genetic mechanisms underlying psychopathology. Understanding the brain mechanisms and cognitive systems involved in dysregulation of thought, emotion and behavior is a crucial step in understanding why some individuals with KS, but not others, struggle in adapting to complex and dynamic environments. Here, executive functions allow us to organize our thoughts and actions in a goal-directed way. The importance of impairments in executive functioning is illustrated by the range of psychiatric disorders characterized by impairments in this domain, such as autism spectrum disorders, psychotic disorders or ADHD. Our aim was to study cognitive regulation functions and relation with risk for psychopathology in KS.

**Method:** Our database consists of 52 adults (the majority recruited through endocrinology and infertility clinics) and 58 boys (half of them prenatally diagnosed, the other half recruited through pediatricians and endocrinologists). Using a cross-sectional design, we examined executive functioning in children, adolescents and adults with KS as compared to non-clinical controls. We also assessed autism traits and schizotypal traits in these groups and the relation with executive functioning, i.e. attention, inhibition and mental flexibility.

**Results:** Overall, our findings point to executive dysfunctions and increased levels of autism and schizotypal traits in KS. Executive dysfunctioning correlated with autism and schizotypal traits. We observed developmental effects in areas of attentional control and schizotypal traits.

**Conclusion:** Our results underscore the importance of studying the role of executive dysfunctions, particularly from a developmental perspective, as a vulnerability factor in developing both autism features as well as schizotypal traits in individuals with KS.

**Keywords:** Klinefelter syndrome, XXY, executive functions, autism, schizotypy

## Oral Presentation 19: Language Impairments in Fragile X Syndrome: A Failure to Use Social Cues?

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**Background:** This study is focused on language impairments and fragile X syndrome (FXS). Research on typical development suggests that language impairments arise partly from problems in using social cues (e.g., a conversational partner's eye gaze) to learn the meanings of words. We tested three hypotheses: (1) use of social cues in word learning is a special challenge for FXS; (2) use of social cues is correlated with language growth; and (3) within-syndrome variation in using social cues is explained by autism symptoms and social anxiety.

**Method:** Participants were 25 5- to 10-year-old boys with FXS and 21 typically developing 2-to 5-year-old boys matched on nonverbal mental age. More participants will be tested by the conference. In the word learning task, the child saw two novel objects per trial. In the follow-in condition, a novel word was spoken while child and Examiner (E) looked at Object 1. In the discrepant condition, a novel word was spoken while the child looked at Object 1 and E at Object 2. Comprehension probes determined whether the child correctly mapped the word to Object 1 in the follow-in condition and to Object 2 in the discrepant condition. Language growth was assessed with the Peabody Picture Vocabulary Test-4 (PPVT), autism severity with the Autism Diagnostic Observation Schedule (ADOS), and anxiety with the Anxiety, Depression, and Mood Scale (ADAMS).

**Results:** Boys with FXS tended to do more poorly in the word learning task than their typical matches. Word learning and PPVT scores were correlated for boys with FXS. Word learning scores were not predicted by ADOS or ADAMS scores for FXS.

**Conclusion:** Language impairments in FXS can be traced to problems in using social cues. Problems in social cue use are not related to autism symptoms or anxiety. Implications for clinical practice will be discussed.

**Keywords:** fragile X syndrome, language

## Talk 5: Keynote: Endocrinological Treatment in Klinefelter Syndrome

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Klinefelter Syndrome (KS) is a condition characterized by gynaecomastia, small, firm testes, hypogonadism and raised FSH (Klinefelter *et al.*, 1942). It is the most common chromosomal disorder, affecting 1/660 men (Lanfranco *et al.*, 2004), and is a frequent cause of hypogonadism and infertility. In 1959 Jacobs and Strong demonstrated the presence of an extra X chromosome in the karyotype of patients with KS (47,XXY). The most frequent karyotype is 47,XXY (80–90% of cases). Other cases involve supranumerous X chromosomes (48,XXXY, 49,XXXXY) or different mosaicisms. KS is often not diagnosed until adulthood due to its highly varied clinical presentation, with milder forms very often lacking any clear signs. This variability could depend on the extent and timing of androgen deficiency, hypothalamic-pituitary function, androgen receptor (AR) function and inactivation, potential androgen resistance, expression and inactivation status of X-chromosome genes, and the activity of genes located in the pseudo-autosomal regions of the sex chromosomes, as well as any mosaicism and the number of supernumerary X chromosomes. Puberty in these patients is usually spontaneous with onset at the expected age, but from Tanner stage 2/3 hypergonadotropic hypogonadism becomes evident, with small, firm testes, raised FSH and LH and initial drop in T. There is a critical time during pubertal development when adequate androgen levels are necessary for normal bone mineralization. During puberty, it is considered rational to start T replacement therapy when a pathologically high gonadotropin level is found, in order to allow the regular development of secondary sexual characteristics and muscles and achieve a normal peak bone mass. Literature data show that androgenic replacement treatment during puberty enhances muscle strength, improves mood and ability to concentrate and is useful in developing relational skills (Nielsen *et al.*, 1988). In young hypogonadal patients with KS, treatment resulted in significant positive effects such as reduced fat mass and increased lean mass, improved muscle strength, intensified sexual activity and improved mood (Wang *et al.*, 2000). In 65–85% of adult KS patients, serum T concentrations progressively fall below the normal reference range, although some cases may retain normal values. Early diagnosis and careful follow-up permits the earlier recognition of possible co-morbidities and the implementation of interventional strategies counteracting late-onset complications. Several cross-sectional studies have found a strong correlation between circulating T and cardiovascular risk factors due to the effects of androgens on adipose tissue, insulin sensitivity, endothelial function, vascular tone, atherosclerosis and left ventricular dysfunction. Sex hormones play an important role in the development of muscle, bone and joint mass. KS patients have increased body fat mass and decreased muscle mass (Bojesen *et al.*, 2006), in addition to an increased risk of osteoporosis and a precocious onset of bone diseases. T replacement therapy should be begun early and considered as lifelong, in order to prevent hypogonadism complications such as osteoporosis, obesity, diabetes and metabolic syndrome and gain probable cardiovascular benefits (Simm *et al.*, 2004). Treatment has a positive effect on erectile function, mood, behaviour and quality of life, improves goal-directed thinking and self-esteem and reduces fatigue and irritability (Nielsen *et al.*, 1988). Treatment of older KS patients also improves cognitive ability (Cherrier *et al.*, 2001). Finally, from current pharmacogenetic knowledge of T and T receptor sensitivity (Zitzman *et al.*, 2004), we consider that restoration of normal blood T and LH levels should be the aim of replacement treatment, even though this point is controversial.

## Talk 6: Keynote: Targeted Treatment for Fragile X Syndrome: Results of a Randomized Controlled Phase II Trial of Arbaclofen

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**Background:** A number of targeted treatments are emerging which demonstrate efficacy in treatment of the mouse model of fragile X syndrome (FXS). Arbaclofen is a GABA-B agonist which has demonstrated efficacy in the mouse model of FXS. Here we present the results of a randomized double-blind crossover phase II trial of arbaclofen, for the treatment of behavioral symptoms in children and adults with FXS.

**Method:** This trial took place at multiple centers across the US and included 63 subjects with FXS, age 6–40 yrs, and who met severity criteria on the Aberrant Behavior Checklist-Irritability (ABC-I) subscale. Subjects were randomized to Arbaclofen or placebo for the first treatment period, followed by flexible titration over 2 weeks, then continued to 4 weeks total dosing, followed by down titration, a washout period, and repetition of the same treatment period with the other blinded treatment.

**Results:** In those who completed the full protocol without deviations (n=49), clinicians (p=0.05) and parents (p<0.10) both reported a blinded preference for arbaclofen vs. placebo. These results were more robust (p<0.01) among subjects who met criteria for Autism, or who had baseline Irritability scores  $\geq 18$  on the ABC-I scale. Similarly, significantly more subjects were responders with “much improved or very much improved” on the CGI-I scale when receiving arbaclofen vs. placebo. The ABC-I scale was not significantly sensitive to these treatment effects. However, a post-hoc analysis showed that subjects with higher baseline scores on the ABC-Social Withdrawal scale showed significant improvement on that scale, consistent with parent reports that subjects showed improved socialization and communication. Arbaclofen was very well tolerated and full safety data will be presented.

**Conclusion:** Arbaclofen shows excellent potential for the treatment of behavioral problems in FXS, including core symptoms of autism, such as social deficits.

**Keywords:** fragile X syndrome, targeted treatments, GABA, arbaclofen



## Oral Presentation 20: Parental decision following prenatal diagnosis of klinefelter syndrome: a proposal for a correct approach

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**Background:** It has been estimated that prenatal diagnosis identifies 10% of cases of Klinefelter Syndrome (KS), and it's evident that genetic counselling at the moment of prenatal diagnosis is fundamental to inform the parents and to help their decision about continuation of pregnancy. We report parental decisions regarding pregnancy termination following the prenatal diagnosis of Klinefelter Syndrome (KS) and propose a personal approach to the problem.

**Method:** Retrospective collection of data from records of 31 families receiving genetic counseling after prenatal diagnosis of the sex chromosome abnormality in the fetus: 47,XXY (KS) in our division during the time period 2002–2010.

**Results:** Among 31 couples with a prenatal diagnosis of KS, 2 couples (6,5%) decided to terminate pregnancy. None of the terminated pregnancies presented a fetal abnormality seen on ultrasound, but one was a couple with previous therapeutic abortion for prenatal diagnosis of Down syndrome and the other one was informed by the gynecologist, that KS presents mental retardation and congenital anomalies. Maternal age and year of test did not influence parental decisions.

**Conclusion:** Parental decision to terminate a pregnancy for a fetus with KS is less probable if first counsels a geneticist, especially if expert of children. In the literature, pregnancy termination rates for KS, range from 23% to 87,5%, while in our experience is only 6,5% because we use an approach that reduces anxiety of the parents. Useful information to provide includes the follow up studies on newborns that show mental retardation isn't a characteristic sign of KS, but carries the same incidence found in the general population, that there is a moderate but not high risk of language deficits, problems with learning, and with motor skills, that can recover with physiotherapy, that the facial and physical appearance of children with KS is normal.

**Keywords:** prenatal diagnosis-klinefelter syndrome

## Oral Presentation 21: Triple X syndrome ascertained through prenatal diagnosis: characteristics of 42 young Italian girls and parental emotional response to prenatal diagnosis and counselling.

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**Background:** 47,XXX karyotype is present in about 1/1000 females, often diagnosed incidentally. Clinical features are subtle and can include tall stature, increased incidence of speech delay, mild learning disabilities, poor motor coordination. Behavioural problems have been reported but not fully confirmed. The diagnosis during pregnancy can represent a dilemma for the prospective parents. An unresolved anxiety might adversely alter their psychological relationship to their pregnancy and their child. Purpose of our study was to gather clinical data from the carrier girls and to analyze the psychological outcomes of the families on a large Italian cohort, which is represented by 42 triple X prenatal diagnoses between 1998 and 2006 in three Italian Centres.

**Method:** Clinical assessment included: personal history, physical evaluation, auxological measurements and, in a subset, the formal Italian Temperament Questionnaire assessment test. To analyze how parents coped with the diagnosis in the prenatal and postnatal periods we conducted a structured interview with 35 item designed to elicit judgements on prenatal communication, present and future worries, needs and expectations.

**Results:** Girls with triple X in our cohort showed: median age for the firsts words at 12 months, slight delay in language skills, increased growth in the pre-puberal age, average incidence of congenital malformation and health needs. Parental responses to the interview demonstrated residual anxiety but with a satisfactory adaptation to and a positive recall of the prenatal counselling session.

**Conclusion:** Girls of our cohort do not present significant differences in physical development compared with their siblings and with other children of the same age. The assessment of the temperament in our paediatric cohort showed a normal functional adaptation in most girls. An integrated approach to prenatal counselling is the best way to manage the anxiety and false expectations which parents feel after being told that their foetus bears this chromosomal abnormality.

**Keywords:** 47,XXX, prenatal diagnosis, genetic counselling, parental adaptation.

## Oral Presentation 22: The parent-of-origin of the extra X chromosome differentially affects psychopathology in Klinefelter syndrome.

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**Background:** Several genetic mechanisms have been proposed for the variability of the KS phenotype such as the parent-of-origin of the extra X chromosome. Parent-of-origin marks on behavior in KS can possibly provide insights into X-linked imprinting effects on psychopathology that may be extrapolated to other populations. Here, we investigated whether the parent-of-origin of the supernumerary X chromosome influences autistic and schizotypal symptom profiles in KS.

**Method:** Parent-origin of the X chromosome was determined through analysis of the polymorphic CAG tandem repeat of the androgen receptor. Autistic symptoms (Autism Diagnostic Interview-revised) were measured in a sample of boys (n=35) with KS and schizotypal traits (Schizotypal Personality Questionnaire) was assessed in a sample of adolescents/adults with KS (n=43). Scale scores on these questionnaires were entered in statistical analyses to test parent of origin effects.

**Results:** The results show that parent-of-origin of the X chromosome is reflected in autistic and schizotypal symptomatology. Multivariate and univariate differences were shown in the degree of both schizotypal and autistic symptoms between the parent-of-origin groups. Furthermore, the parent-of-origin could be correctly discriminated in more than 90% of subjects through ADI-R scales and in around 80 % of subjects through SPQ scales. Conclusion: These findings point to parent-of-origin effects on psychopathology in KS and indicate that imprinted X chromosomal genes may have differential effects on autistic and schizotypal symptom profiles. Further exploration of imprinting effects on psychopathology in KS is needed to confirm and expand on our findings.

**Keywords:** Klinefelter syndrome, Genetics, autism, schizotypy, schizophrenia, imprinting, epigenetics

## Oral Presentation 23: A Comparison of Visual Motor Integration and Motor Skills in Children and Adolescents with Sex Chromosome Aneuploidy.

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**Background:** Sex chromosome aneuploidy (SCA) conditions can be associated with delays in visual motor integration (VMI) and motor skills that affect functional skills. Previous studies of VMI and motor skills in SCA have included small sizes, except for a 2008 study by Ross et al. of 50 males which showed low-average mean VMI scores ( $89.1 \pm 13.5$ ) and most domains of motor skills  $>1$  s.d. below the mean. Here we evaluate and compare VMI skills in a large cohort of children with XXY, XYY, XXX, and XXYY syndromes, and describe detailed motor skills assessment in a subset of participants.

**Methods:** 121 participants with SCA (34 XXY, 24 XYY, 24 XXX, 39 XXYY) age 5–19 were evaluated at The Children's Hospital in Colorado or University of California Davis MIND Institute. All participants were assessed using the Beery Test of Visual Motor Integration (VMI), including the Visual Perception and Motor Coordination subtests. A subset of patients ( $n=25$ ) was also evaluated using the Bruininks-Oseretsky Test of Motor Proficiency – 2nd Edition (BOT-2). Standard scores were compared for the entire cohort and between SCA subgroups by ANOVA.

**Results:** For the entire cohort, mean visual motor integration performance was decreased ( $89.22 \pm 14.56$ ), with a profile of significantly higher scores in visual perception ( $95.00 \pm 15.92$ ) and significant weaknesses in fine motor coordination ( $81.49 \pm 16.06$ ) ( $F_{21,34}$ ,  $p < 0.0001$ ). Comparing SCA subgroups, mean total VMI scores were: XXY  $96.69 \pm 12.4$ , XYY  $88.78 \pm 14.82$ , XXX  $87.17 \pm 16.82$ , XXYY  $84.29 \pm 12.16$  ( $F_{4,98}$ ,  $p = .0027$ , post-hoc Tukey HSD XXY > XXYY). In the male SCA subgroups, motor coordination was significantly lower than VMI and visual perception ( $p < 0.0001$ ), however in XXX there were no significant differences between subtest scores ( $p = 0.61$ ). Total VMI scores negatively correlated with age ( $R = -.32$ ,  $p = 0.0005$ ) and positively correlated with cognitive scores ( $R = 0.76$ ,  $p < 0.0001$ ). In the subset of participants assessed by the BOT-2, mean scores were in the average range in domains of balance ( $15.2 \pm 7.1$ ), upper limb coordination ( $13.1 \pm 5.2$ ), and fine motor integration ( $16.8 \pm 5.7$ ), while they were impaired in domains of manual dexterity ( $9.3 \pm 3.2$ ), bilateral coordination ( $11.9 \pm 6.6$ ), running speed and agility ( $11.4 \pm 6.8$ ), and strength ( $11.4 \pm 5.3$ ).

**Conclusion:** VMI skills are impaired in children with SCA, with results supporting that deficits are more likely associated with fine motor coordination delays compared to visual perceptual skills, except in the XXX group. While mean overall motor scores were impaired, there was considerable variability within each subgroup. Interventions for motor skills are important for academic, functional, and self-care skills.

## Oral Presentation 24: Emotion recognition problems in boys with Klinefelter syndrome.

H. Swaab<sup>1</sup>, H. Bruining<sup>2</sup>, S. van Rijn<sup>1</sup>, M. Bierman<sup>1,2</sup>, H. van Engeland<sup>2</sup>, L. de Sonneville<sup>1</sup>

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**Background:** Apart from a variety of phenotypes, like hypogonadism, androgen deficiency and infertility, cognitive and behavioral dysfunctions are recognized to be associated with Klinefelter syndrome. Especially social dysfunction is reported. Shyness, high levels of social anxiety, social impulsiveness and social withdrawal have been found in Klinefelter man. Recent studies revealed high levels of autism in boys with Klinefelter, findings that draw even more attention to the vulnerability for social dysfunctions associated with Klinefelter syndrome. In the present study we address the question whether social problems in children with Klinefelter syndrome are related to problems in social cognition and disabilities in executive function (EF).

**Methods:** 56 boys with Klinefelter syndrome (mean age 10,7) were included in the present study, as well as 112 normal control boys, matched on age. Social dysfunction was indicated by the Autism Diagnostic Interview (ADI). Recognition of faces as well as recognition of facial emotions were assessed, as well as the ability to regulate thought and behavior, by evaluation of several domains of executive function.

**Results:** The Klinefelter boys were less accurate than controls ( $p=.001$ ) with respect to face recognition. They also had much more difficulty in fast and accurate recognition of emotional facial expression ( $p=.000$ ). In addition, attention regulation was less well developed in Klinefelter boys ( $p=.000$ ), they showed much difficulty in inhibition of responses ( $p=.000$ ) and in mental flexibility ( $p=.000$ ).

**Conclusion:** It appears that social adaptive problems in Klinefelter boys are associated to disabilities in social cognition, like problems in facial emotion recognition. In addition, executive dysfunctions might be essential in regulation of social behavior. In conclusion, social adaptive problems in Klinefelter syndrome, might be associated to an interaction between difficulty in understanding social relevant information and difficulty in regulation of attention, inhibition and mental flexibility.

## Oral Presentation 25: Narrative skills in Klinefelter Syndrome

**M. Vernice<sup>1</sup>, A. Cremante<sup>2</sup>, F. Clerici<sup>2</sup>, A. Verri<sup>2</sup>**

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**Background:** Klinefelter Syndrome (KS) has often been considered as a genetic model of language impairment (Geschwind et al., 2000). Although cognitive abilities appear to be within the normal range, KS show consistent impairment on verbal tasks. The present study was designed to evaluate narrative skills of KS adults. To relate a series of events involves not only the use of memory and attention mechanisms to represent the characters and actions involved, but also a general ability to judge the attention and the knowledge of the interlocutor (Arnold et al., 2009). For instance, the choice of an adequate referential expression (whether a full noun phrase, a null or overt pronoun, etc.) to refer to an entity, is modulated by considerations about the hearer's internal knowledge.

**Method:** The present work focus on KS speakers' ability to report a story based on a Sylvester and Tweety cartoon (Canary Row, McNeill, 1992). Mean Length of Utterance (MLU), Lexical Diversity and Referential choices (e.g., whether a full NP, a null or overt pronoun were appropriate) were examined in 8 KS participants [mean age 18;2 (years; months); IQT=90, IQV=92; IQP=88] and 8 controls matched for gender and age ( $\pm 3$  months). Additionally, we administered to each participant a full battery of cognitive, adaptive and linguistic tests.

**Results:** The utterances of KS participants were found to be shorter and less lexically diverse than participants matched for age, but this difference did not result significant. Regression analyses revealed that MLU was modulated by the general cognitive level of the speakers, whereas the correct use of referential expressions and Lexical Diversity did not appear to be significantly predicted by the cognitive level of the speakers. **Conclusion:** Our results suggest that, whereas receptive vocabulary and comprehension skills are significantly lower in KS, narrative skills are more similar to controls.

**Keywords:** Klinefelter Syndrome, Narrative Skills

## Oral Presentation 26: Late diagnosis in multiple X and Y chromosome disorders: role of learning disabilities and behavioural disorders

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**Background:** Sex chromosome aneuploidies (SCAs) are the most frequently occurring chromosomal abnormalities with an incidence of 1 in 400 births. Males with SCA are known to have variability in their developmental profile. Sixty-four percent of males with 47,XXY are never diagnosed, 10% of these cases are diagnosed prenatally by amniocentesis, and 26% are diagnosed postnatally when they show developmental delay, behavioral problems, hypogonadism, gynecomastia, or infertility. Aim of this paper is to evaluate how often developmental delay and behavioural problems can induce an early suspicion of this conditions.

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**Method:** The sample was composed by 48 subjects (mean age=23,5 yrs, range:1–55) 47, XXY/48,47, XYY (4,1%), 48, XXXY (2%), 49, XXXYY (2%). Primary caregiver completed a comprehensive questionnaire detailing birth, medical, developmental and psychological history (Tartaglia, 2008).

**Results:** Five subjects had a prenatal diagnosis (10,4%), 15 (31,2%) had a diagnosis before 10 yrs and 28 subjects (58,3%) had a late diagnosis (after 10 yrs). In the postnatal diagnosed group, patients were diagnosed for genital anomalies/dysmorphisms 32,5%; learning disabilities/ attention disorders, behavioural disorders were diagnosed in 32,5%, hypogonadism/puberal delay 13,9 %, epilepsy 9,3%, recurrent infections 6,9%, infertility 2,3 %.

**Conclusion:** Boys exhibiting developmental delay with learning and behavioural disorders should be considered for chromosomal analysis early in life. An early identification of the social and behavioral phenotypes in SCA may enhance the clinical treatment, anticipatory guidance, and care throughout the lifespan.

**Keywords:** Late diagnosis; SCA

## Oral Presentation 27: Molecular and clinical correlations in Fragile X syndrome and in FMR1 related disorders

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**Abstract:** A (CGG)<sub>n</sub> repeat expansion located in the 5' untranslated region of the FMR1 gene is the cause of both Fragile X (FXS, >200 CGG) and FMR1 related disorders (FXTAS, FXPOI, 55–200 CGG). Recently, it has been shown that mGluR signaling regulation is disrupted by the lack of FMRP and could possibly leads to abnormal neurodevelopment in FXS. mGluR are expressed on immune cells, where they can modulate immune development, activation, function, duration and extent of response, and cell survival. In addition, differences in mGluR signaling may lead to abnormal immune activation and by extension altered cytokine profiles. Thus, abnormal mGluR signaling may affect immune responses and could influence clinical phenotypes of FXS. Indeed an abnormal immune profile in addition to altered phosphorylation of mTOR substrates and their effectors have also been observed in FXS. Alterations of components of various pathways could represent putative biological markers of cognitive impairment in FXS and the assessment of their levels could complement existing molecular testing and be markers of improvement in targeted treatment protocols. The molecular/clinical implications and findings will be discussed. One of the FMR1 related disorders is the Fragile X-associated tremor/ataxia syndrome, an adult-onset neurological disorder that affects older adult carriers of premutation alleles. The mouse model for FXTAS displays biochemical, phenotypic and neuropathological characteristics of FXTAS including the presence of intranuclear inclusions in neural cells and presents altered patterns of growth, dendritic complexity and synaptic architecture. These alterations, among others, including an dysregulation of the GABAergic system, disruption of the lamin "A/C" nuclear architecture and the sequestration of the RNA binding protein, Sam68, by the CGG repeats with consequent loss of its splicing-regulatory function, reflect a cellular basis for the developmental and aging components of premutation involvement. New advances in FXTAS research and correlations with the clinical phenotype will be discussed.

**Grants and supports:** This work was supported by the National Institutes of Health through a research awards, R01 HD02274 (FT), R01 HD040661 (PJH), R01 HD36071 (RJH); and a Roadmap Interdisciplinary Research Consortium (IRC) (UL1 DE019583, RL1AG032119; RL1AG032115).



## Oral Presentation 28: Anticonvulsants & SSRIs Improve Psychological Functioning in Fragile X Syndrome

**J. Turk**

*St George's & Institute of Psychiatry, University of London & South London & Maudsley Foundation NHS Trust*

**Background:** Social and linguistic disabilities are some of the most functionally impairing of the consequences of having fragile X syndrome. Early evaluation and initiation of multimodal interventions improve language and social as well as other developmental abilities. However, there is very little evidence regarding currently available medications for these developmental difficulties, with few reports on psychotropics for social, speech, emotional, behavioural and cognitive issues. Novel pharmaceuticals remain at early stages of development and evaluation, their efficacy and safety are uncertain and substantial cost implications are likely.

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**Method:** We report on the long-term follow-up of a cohort of boys with fragile X full emotional and behavioural improvements on regular oral carbamazepine or sertraline, initial clinical indications for treatment having been erratic mood and behaviour swings, aggression, lack of social understanding, language delay and anxiety. There had been no history of epilepsy. The boys had received a range of various intensive medical, psychological, educational and social interventions over many years commencing from early in their lives, including language, psychological and behavioural assessments and strategies, but with no clinically significant positive shifts in social, linguistic, cognitive or other abilities.

**Results:** Commencement of regular oral medication coincided in all instances with dramatic clinical improvements in all above psychological domains. The initial longstanding unchanged stationary natures of emotional and behavioural functioning, and their subsequent dramatic improvements on carbamazepine and sertraline were reflected objectively through parent and teacher developmental disability behavioural checklists, strength and difficulties questionnaires, quality of life ratings and Child Global Assessment Scales. Improvements continue to increase and to be maintained on regular medication. **Conclusion:** Possible mechanisms for these beneficial responses are discussed. These medications hold the potential to provide substantial remediations of fragile X associated developmental and psychiatric disabilities in cost-effective, evidencebased, readily available and clinically safe fashions.

**Keywords:** fragile X syndrome, treatment, psychopharmacology

## Oral Presentation 29: Females with fragile X syndrome and autism spectrum conditions

**J. Turk**

*St George's & Institute of Psychiatry, University of London & South London & Maudsley Foundation NHS Trust*

**Background:** Females with fragile X syndrome experience an extremely wide range of cognitive, social, linguistic, imaginary, adaptive behaviour, motoric and sensory impairments. However, as with the autism spectrum conditions as a group of diagnoses, clinical affectedness is usually associated in peoples' minds with male gender. A range of theories have evolved in the autism arena to explain this paradox including Baron-Cohen's notion of autism being a naturalistic model of excessive mental maleness, and the hypothesis that because of a resilience-bestowing aspect of femaleness, extreme affectedness is required to manifest the necessary diagnostic criteria.

**Method:** Our academic and clinical services have explored these phenomena over almost two decades, from both the aetiological perspective of how having fragile X pre and full mutations affects females, mindful of the myriad of genetic variables that influence their clinical presentation, and from the clinical-phenomenological perspective regarding just how much or little veracity there may be to the notion that debilitating neuro-developmentally determined social and communication disorders are so much rarer in females.

**Results:** We present data from: - our intellectual disability and epilepsy research programmes to illustrate the frequent reality of a far more even gender ratio for autism disorders, at least in certain populations -our females with fragile X pilot study that demonstrates the common occurrence of marked social and communicatory difficulties, even in those with permutations -our exploration of undiagnosed autism spectrum disorders in adult females eating disorder populations -initial findings from our females with autism study.

**Conclusion:** Emerging data from all four sources converge and are consistent in suggesting that autism spectrum conditions may be far commoner in females than previously thought and that they present in a range of clinically masked ways. However, it may well be the profile and nature of the autistic features rather than their presence versus absence which is the hallmark of females with fragile X and/or autism spectrum disorders.

**Keywords:** fragile X syndrome, autism, females

# Abstracts for Poster Presentations

## Poster 1: Long term memory profile of disorders associated with dysregulation of 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. 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 LEOPARD (LS) syndrome. In our study we evaluate long term memory in 21 patients with NS/LS syndrome.

**Method:** The profile of long term memory abilities of 21 patients, with molecularly confirmed diagnosis of NS/LS syndrome, was investigated using the subtest of explicit/declarative long term memory of PROMEA, a battery of tests specifically designed for assessing memory and learning in verbal, visual and spatial domains.

**Results:** Six patients (29%) had poor performances or borderline results on immediate recall and 9 patients (43%) on the delayed recall of verbal task memory. Seven patients (33%) had poor performances or borderline results on immediate recall and 4 patients (19%) on the delayed recall of visual memory task. High results were obtained in spatial memory task where 17 patients (81%) obtained scores above the 75 percentile in immediate recall and 10 (48%) above the 75 percentile in delayed recall.

**Conclusion:** Our data support that can be a memory involvement in patients with dysregulation of the RAS/MAPK cascade. The patients shown an impairment in verbal and visual long term memory, major in the first domain, while surprisingly obtained scores in spatial memory higher than normal.

**Keywords:** RAS/MAPK cascade, Noonan/LEOPARD syndrome, cognition, long term memory

## **Poster 2: A case of Smith-Magenis syndrome due to *rai1* gene mutation with a predominant psychiatric and behavioural phenotype**

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**Keywords:** Smith-Magenis syndrome; 17p11.2; *RAI1* gene

## Poster 3: Dissecting the Clinical Heterogeneity of Autism Spectrum Disorders through Defined Genotypes

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**Background:** The etiology of autism spectrum disorders (ASD) is largely determined by different genetic factors of variable impact. This genetic heterogeneity could be a factor to explain the clinical heterogeneity of autism spectrum disorders. Here, a first attempt is made to assess whether genetically more homogeneous ASD groups are associated with decreased phenotypic heterogeneity with respect to their autistic symptom profile.

**Methodology:** The autistic phenotypes of ASD subjects with 22q11 deletion syndrome (22q11DS) and ASD subjects with Klinefelter Syndrome (KS) were statistically compared to the symptom profile of a large (genetically) heterogeneous ASD sample. Autism diagnostic interview-revised (ADI-R) variables were entered in different statistical analyses to assess differences in symptom homogeneity and the feasibility of discrimination of group-specific ASD-symptom profiles.

**Principal Findings:** The results showed substantially higher symptom homogeneity in both the genetic disorder ASD groups in comparison to the heterogeneous ASD sample. In addition, a robust discrimination between 22q11-ASD and KS-ASD and idiopathic ASD phenotypes was feasible on the basis of a reduced number of autistic scales and symptoms. The lack of overlap in discriminating subscales and symptoms between KS-ASD and 22q11DS-ASD suggests that their autistic symptom profiles cluster around different points in the total diagnostic space of profiles present in the general ASD population.

**Conclusion:** The findings of the current study indicate that the clinical heterogeneity of ASDs may be reduced when subgroups based on a specific genotype are extracted from the idiopathic ASD population. The current strategy involving the widely used ADI-R offers a relatively straightforward possibility for assessing genotype-phenotype ASD relationships. Reverse phenotype strategies are becoming more feasible, given the accumulating evidence for the existence of genetic variants of large effect in a substantial proportion of the ASD population.

## Poster 4: Preliminary investigation of an early intervention strategy to reduce temper outburst behaviour in Prader-Willi syndrome

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**Background:** Individuals with Prader-Willi syndrome (PWS) can show temper outbursts following unexpected changes in the environment. We aim to evaluate the extent to which the level of exposure to a routine without change affects a person's behavioural reaction to an unexpected change to that routine.

**Method:** Data from ten individuals with PWS will be presented. Individuals' reactions to unexpected changes will be investigated to determine whether the level of exposure to a particular routine/expectation without change is a critical factor affecting a person's behavioural reaction to an unexpected change. Five novel activities were administered to participants for varying amounts of time before unexpected changes to the routines/expectations that had been established during the game were introduced.

**Results:** One-way repeated measures ANOVAs revealed significant main effects: increased behavioural response to changes occurred when the routines had been established for longer.

**Conclusion:** It is possible that an early intervention strategy that encourages carers of people with PWS not to allow routines to become established from an early age may reduce later behavioural difficulties in response to changes.

**Keywords:** Prader-Willi syndrome, intervention, temper outbursts, routines, change

## Poster 5: Age related changes in autism spectrum phenomenology and repetitive behaviour in Cornelia de Lange, Fragile X and Cri du Chat syndromes.

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**Background:** There is an increasing awareness within the behavioural phenotypes literature that many individuals with genetic syndromes experience age related changes in the presentation of associated behavioural phenomenology. In this study we will evaluate the course of autism spectrum phenomenology with age in Fragile X (FXS), Cornelia de Lange (CdLS) and Cri du Chat (CdCS) syndromes.

**Method:** Participants were individuals with CdLS (N=67; mean age=17.33, SD=9.22), CdCS (N= 42; mean age=17.65, SD=11.75) and FXS (N=142; mean age=17.23, SD=8.84) who participated in a longitudinal questionnaire survey. Parents and carers completed the Social Communication Questionnaire (SCQ; Rutter et al., 2003) and the Repetitive Behaviour Questionnaire (RBQ; Moss et al., 2008) at two time points (T1 and T2). Participant groups were split according to age (under 15 vs. over 15) in order to further evaluate the effect of age on these behaviours.

**Results:** At T1, between group analysis revealed that the FXS group scored significantly higher than the CdLS and CdCS groups on the repetitive behaviour subscale of the SCQ ( $p < .01$ ). On the RBQ, the FXS group also scored higher on insistence on sameness and repetitive use of language ( $p < .01$ ) than these groups. FXS and CdLS scored significantly higher than the CdCS group on the communication and social interaction subscales and on total score of the SCQ ( $p < .01$ ). Within syndrome analysis revealed that at T1, over 15s with CdCS scored significantly higher on the communication domain of the SCQ compared to under 15s with CdCS ( $p = .003$ ). Over 15s with CdLS scored significantly higher on the social interaction domain ( $p = .011$ ) and under 15s with FXS scored significantly higher on the repetitive behaviour domain compared to over 15s with FXS ( $p < .001$ ). Specifically, stereotyped behaviour on the RBQ was more frequent in under 15s with FXS ( $p = .001$ ). There were no significant differences on scores on the SCQ between T1 and T2 in the CdCS and CdLS groups. The FXS group showed significantly lower scores on repetitive behaviour ( $p = .02$ ) and social interaction ( $p = .008$ ) at T2. There were no significant differences on the RBQ between T1 and T2.

**Conclusion:** In FXS a difference in the severity of ASD phenomenology with age was identified between T1 and T2. Changes were not observed in the CdCS or CdLS groups however, over 15s with CdLS were more likely to show ASD characteristics than those under 15 suggesting changes with age may also be evident in this group.

**Keywords:** Autism Spectrum Disorder, Repetitive behaviour, Fragile X syndrome, Cornelia de Lange syndrome

## Poster 6: The association between gastro-oesophageal distress and challenging behaviour

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*University of Birmingham*

**Background:** The association between pain and challenging behaviour is attracting increasing interest. High prevalence of gastro-oesophageal reflux disease, and the associated pain and discomfort (Gastro-oesophageal Distress (GD)), has been reported in several syndromes and in individuals with profound intellectual disabilities. This study investigates the association between GD and challenging behaviour in Autism Spectrum Disorder (ASD) and Cri du Chat (CDC) syndrome.

**Method:** Participants were aged 3-47 years, with a confirmed diagnosis of ASD or CDC syndrome. Parent report questionnaires were used; the Gastro-intestinal Distress Questionnaire assessed frequency of behavioural indicators of GD. The Challenging Behaviour Questionnaire evaluated the presence of self-injury, physical aggression and destruction of property over the last month. Estimates of level of intellectual disability were derived from the Wessex Questionnaire, which comprises of a Social and Physical Incapacity scale and a Speech, Self Help and Literacy scale.

**Results:** After controlling for degree of intellectual disability, there were significantly higher rates of self injurious behaviour (SIB), aggression and property destruction in individuals with ASD who had significant GD compared to those without significant GD. Within the CDC group, there were significantly higher rates of SIB in individuals with significant GD. When SIB was present, it was more severe in individuals with clinically significant levels of GD, meaning it occurred more frequently, lasted for longer and required higher levels of intervention.

**Conclusion:** These results highlight the importance of identifying and treating GD with the aim of influencing challenging behaviour. The association between GD and challenging behaviour is particularly pronounced in ASD. It is possible that stronger associations between challenging behaviour and GD were not found in the CDC group because there was insufficient power due to a small sample size.

**Keywords:** Pain, Challenging behaviour, self-injury, gastro-oesophageal reflux disease.



## Poster 7: Mosaicism in CdLS: an explanation for the phenotypic variability

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**Background:** Cornelia de Lange (CdLS, MIM #122470, #300590, #610759) is a rare, congenital neurodevelopmental syndrome characterized by growth/mental retardation, dysmorphic face and limb reduction defects. Wide phenotypic variability is common in the CdLS patients. Mutations in NIPBL, SMC1A and SMC3 genes, encoding for a regulator and two subunits of the cohesin complex respectively, are found in 60-65% of CdLS patients.

**Method:** A CdLS patient with a severe and typical phenotype was screened for the major genes NIPBL and SMC1A by DHPLC and direct sequencing. The ERCC8 gene, responsible for Cockayne syndrome which has a few clinical signs overlapping with CdLS, was also screened as plausible candidate. Finally FISH analysis with a BAC clone encompassing the NIPBL region and genome-wide aCGH were performed to search for targeted and genome-wide imbalances.

**Results:** Screening of NIPBL, SMC1A and ERCC8 did not reveal any point mutations. By contrast FISH analysis targeting the NIPBL gene showed an asymmetric signal in a fraction of cells, suggesting a genomic deletion in mosaic condition. aCGH analysis confirmed the large deletion covering exons 3-23 in a high fraction (80%) of cells. Consistent with the molecular analysis the patient displays a severe phenotype, characterized by all CdLS clinical signs at the extreme level, as attested by his premature death.

**Conclusion:** This case provides the second evidence of mosaicism in CdLS. We have recently reported on a CdLS patient with a mild phenotype imputed to the low level mosaicism for an usually drastic truncating mutation. The large intragenic deletion identified in this case represents a very rare type of mutation in CdLS which is poorly tolerated, although in this case the NIPBL haploinsufficiency is slightly mitigated by the mosaic condition. Further evidence of mosaicism could explain the clinical heterogeneity of CdLS, highlighting the likely underestimated mutation rate of known genes.

**Keywords:** CdLS, mosaicism, NIPBL deletion

## Poster 8: Temperamental and behavioural characteristics of individuals with the co-morbid condition of Tuberous sclerosis and ASD

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**Background:** During a 15-year period data has been gathered on temperamental and behavioural characteristics of persons with ASD in Norway. In the present paper, the characteristics of 6 individuals with both TS and autism are compared with individuals with only ASD.

**Method:** Parents and teachers of 233 individuals diagnosed with ASD (1 to 60 years of age) completed the Norwegian 'Way of being' questionnaire, comprising items on temperamental and personality traits, forms of reaction, and somatic and clinical problems. 6 persons with both Tuberous sclerosis and autism (TS) are compared with the whole ASD sample and an age and gender matched ASD sample (n =24).

**Results:** Comparison of personality traits showed the TS group to be shyer and less active. Further, there was a strong tendency that they were less social and less often in a positive mood than the ASD controls. 11 reaction forms differed in prevalence between the double diagnosis and ASD groups. The TS group had stronger negative reaction of newness, lack of sameness, and being in focus of others. Furthermore, the TS group had more motor and executive problems related to attention being focused on their performance (FRPP). Few somatic problems differed significantly between the groups.

**Conclusion:** Individuals with the double diagnosis of tuberous sclerosis and autism constitute a highly vulnerable subgroup of the autism population. Generally, the TS group was found to be 'more autistic' than the group with ASD only. Clinicians need to be aware of the high likelihood of adjustment problems and FRPP in tuberous sclerosis, which makes it a serious challenge to tailor suitable interventions.

**Keywords:** Tuberous sclerosis; autism; temperament; reactions forms; emotional problems; movement disorder

## Poster 9: Functional assessment and behavioral treatment of skin-picking in a female with Prader-Willi syndrome

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**Background:** Skin-picking (SP) is common in individuals with Prader-Willi syndrome (PWS). Treatment studies for SP have seldomly been published (see Lang et al., 2009; Lang et al., in press). This study reports on outcomes of functional assessment and effects of a treatment package for SP in C., a 16-year-old female with PWS who lived in a residential facility.

**Methods:** During two weeks, staff, teachers and her mother were asked to record instances of SP. Antecedents and consequences of the SP as well as the time and situation wherein SP occurred were noted by staff, teachers and her mother. The treatment package was implemented in all natural settings (school, facility and home) and consisted of antecedent control measures, habit reversal (squeezing a stress ball and playing with a puzzle book) and differential reinforcement of incompatible behavior (e.g., requesting for and applying body lotion when she feels an itch on her skin). Pictures of her wounds were taken and the number of open and closed wounds were counted. If there were less wounds or they appeared healed compared to the previous visit, she received a self-chosen reward. The adverse consequences of SP and antecedents for this behavior were discussed with C. in order to raise her awareness. Pictures of the previous and current visit were also shown to and discussed with C. to make her see the change in her open and closed wounds. C. was given a minor reward every session to praise her for cooperating to the treatment.

**Results:** Findings concerning the antecedents and consequents of her SP indicated that this behavior primarily occurred in situations wherein she had to wait or was otherwise unoccupied, and was often followed by a verbal reprimand by staff or others. Differential reinforcement and habit reversal training may be effective in the treatment of SP (see Lang et al., 2009), and were implemented in the treatment package. A total of 18 sessions were carried out, with an average of approximately two per week. Treatment effectiveness was calculated using Chi-square. Fifteen randomly picked pictures from the first and the last six sessions were shown in a random order to sixteen individuals, blind to the purpose and outcome of this treatment. A significant effect was found ( $df=1, p<0.001$ ), indicating that treatment was effective in reducing the severity of the SP.

**Discussion:** This case study adds to the very small literature on treatment of SP in people with PWS.

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## Poster 10: Apathy: key element of the behavioural phenotype in 9q Subtelomeric Deletion Syndrome

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**Background:** Submicroscopic deletions of the distal long arm of chromosome 9q are relatively common and give rise to a clinically recognizable phenotype referred to as the 9q Subtelomeric Deletion Syndrome (9qSTDS; OMIM 610253). Although the deletions may vary in size, it was shown that haploinsufficiency of the EHMT1 (Euchromatic Histone Methyltransferase 1) gene is responsible for the core phenotype of 9qSTDS. The key features of the syndrome are mental retardation, childhood hypotonia and a characteristic facial appearance. In addition, congenital heart and renal defects, microcephaly, epilepsy, obesity, and behavioral problems are frequently present.

**Method:** In one female and one male patient, aged 53 and 59 years respectively and both institutionalized for many years because of severe intellectual disabilities and challenging behaviours with so far unknown etiology, renewed genetic evaluation was performed. In addition their behavioural, cognitive and neuropsychiatric profile was investigated.

**Results:** Routine cytogenetic investigation showed normal karyotypes. MLPA subtelomere deletion testing demonstrated a submicroscopic deletion of the long arm of chromosome 9 (9q24.3), confirming the diagnosis of 9qSTDS. In both patients the deletion comprised, apart from the EHMT1 gene, 4 other genes. With respect to their neuropsychological profile, both patients showed deficiencies in performing daily activities, a clear dependency on others and a marked decrease of emotional and social responsiveness. In addition, a characteristic behavioural phenotype could be delineated that comprised an absence of motivational behaviours and a peculiar dysomnia with frequent and enduring nocturnal awakenings accompanied by non-goal directed behaviours and daytime sleepiness.

**Conclusion:** The 9qSTDS is constituted, in addition to its distinct phenotypic features, by a specific behavioural phenotype that encompasses, apart from the absence of speech development and aggressive behaviours in the first decades of life, a specific sleep disturbance and severe apathy from the third decade on.

**Keywords:** 9qSTDS, apathy, sleep disturbances, intellectual disability

## Poster 11: An adult female with ring chromosome 21 syndrome (r(21)) and cognitive alexithymia

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**Background:** Ring chromosome 21 syndrome is a rare condition that may occur on a de novo basis or via parental transmission. In about half of cases, the syndrome is accompanied by developmental delay and/or intellectual disabilities. Major characteristics of the phenotype are vulnerability to infections, mild facial dysmorphisms, infertility and kyphosis. In addition there may be congenital malformations of nearly all organ systems.

**Method:** A 30-year-old female patient with moderate mental retardation and minor dysmorphisms was referred for neuropsychiatric examination because of psychotic and autistic symptoms and impulsivity. She was born dysmaturally after an uncomplicated pregnancy. Postnatally, she developed cyanosis, feeding problems and recurrent urinary tract infections. Her developmental trajectory showed delayed milestones, speech retardation and restricted peer interactions resulting in special education from age 9. From the age of 18, behavioural problems became increasingly apparent that appeared to be caused by her sensory impairments and that had also led to paranoid ideation due to social misinterpretations.

**Results:** At referral, physical investigation revealed mild dysmorphisms, severe hearing loss and visual impairment, oestrogen deficiency, kyphoscoliosis, mild hypotonia and hyperlaxity of joints. Neuropsychological examination disclosed a disharmonic intellectual and social cognitive profile (total IQ: 50) with adequate performal capacities and marked cognitive alexithymia. No formal psychiatric diagnosis could be established. Karyotyping showed a de novo ring chromosome 21: 46,XX,der(21)r(21)(p11q22.3). High resolution array analysis of chromosome 21 demonstrated one interstitial duplication (21q22.1) that did not comprise any genes, two interstitial deletions (21q22.2q22.3 and 21q22.3) and one terminal deletion (21q21.3).

**Conclusion:** This case description demonstrates the importance of targeted high resolution micro array analysis in order to substantiate the genotype-phenotype correlation in patients with r(21). Moreover, the importance of cognitive alexithymia as a potential cause for behavioural problems and psychiatric symptoms in patients with intellectual disabilities in general is stressed.

**Keywords:** Ring chromosome 21, deletion, mental disorder, intellectual disability

## Poster 12: The behavioural phenotype of Smith Magenis syndrome; social functioning

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**Background:** Descriptions of the behavioural phenotype of Smith Magenis syndrome (SMS) include behaviours such as attention seeking and preference for adult attention and strong attachment to specific people is reported anecdotally. This suggests there may be an atypical pattern of social behaviour associated with the syndrome. To evaluate this suggestion this study examined social features of the behavioural phenotype of SMS.

**Method:** From an existing database 22 individuals with SMS were matched with participants with Down syndrome (DS) and Autism Spectrum Disorders (ASD). Sociability (with caregivers, familiar adults, familiar peers, unfamiliar adults and unfamiliar peers, measured using items from the Sociability Questionnaire for people with Intellectual Disabilities), attachment to particular people (measured using items from the Repetitive Behaviour Questionnaire) and ASD phenomenology (using the Social Communication Questionnaire; SCQ) was compared across groups.

**Results:** No differences in sociability were found between SMS and DS groups for any target people; as expected individuals with ASD were less sociable than those with SMS with the majority of people. Individuals with SMS had higher levels of attachment to people than DS or ASD group, who did not differ – a pattern not replicated for attachment to objects or restricted conversation indicating high specificity in SMS. No differences were found between SMS and DS group on either the communication or reciprocal social interaction subscales of the SCQ; ASD participants were more impaired on both domains. On the restricted, repetitive and stereotyped behaviours subscale the DS group was less impaired than those with SMS and ASD, who did not differ.

**Conclusion:** Findings support suggestions of a strong drive to interact with particular people in SMS but generalised hypersociability was not evident. ASD behaviours were limited to restricted, repetitive and stereotyped behaviours, suggesting a need to explore repetitive behaviours as a potential common feature of SMS and ASD.

**Keywords:** Smith Magenis syndrome, sociability, repetitive behaviour, autism

# SSBP Syndrome Sheets

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

## Angelman Syndrome

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### Alternative names

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

### First description

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

### Genetic aspects

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

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

### Incidence/prevalence

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

### Physical phenotype

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

### Behavioural aspects

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

### Cognitive aspects

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

### Life expectancy

Probably close to normal, as health is generally good, except 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). There has been continuing debate as to whether autism and Asperger syndrome are distinct conditions and lack of consistency in differentiating between Asperger syndrome and high functioning autism, or between PDD-NOS and atypical autism have resulted in the draft proposals for DSM-V suggesting an over-arching classification of Autism Spectrum Disorder in which there will be no differentiation between these categories. In addition, whereas current diagnostic criteria require specific impairments in 3 domains (Social, Communication, and Restricted, Repetitive and Stereotyped behaviours/interests [RRSB]) the proposed criteria will be based on just 2 domains, Social –Communication impairment and RRSB. Additionally, a dimensional rating of severity of disorder is also proposed.

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### First described

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

### Associated conditions

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

### Genetics

The risk of ASD in siblings of probands is significantly increased and there is an exceptionally high concordance rate in monozygotic twins. Family studies indicate that the "Broader Autism Phenotype" (i.e. having problems related to social, language and/or cognitive functioning) occurs in up to 20% of first degree family members. However, although ASDs are clearly highly heritable, attempts to identify specific susceptibility genes have thus far met with limited success. Genome-wide association studies have identified regions of suggestive and significant linkage on a number of different chromosomes including 5p,15q, 16p, and 22q but various other sites have also been implicated (Abrahams & Geschwind, 2008; Weiss et al., 2009) Recent research suggests that many (possibly the majority) cases of autism may be due to de novo mutations occurring first in the parental germ line and which have high penetrance in males (Zhao et al., 2007) There is no evidence that single environmental factors (e.g. MMR or other vaccines) cause autism although more complex environmental risk factors (e.g. abnormalities in the immune system of individuals with ASD, or pre-natal perturbations) cannot be ruled out. The role of gene-environment interaction must also be considered (Rutter et al., 2006).

### Prevalence

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

### Physical Phenotype

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

### Life expectancy/natural history

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

### Behavioural and cognitive characteristics

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

### Outcome

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

### Websites

[www.nas.org.uk](http://www.nas.org.uk)  
[www.researchautism.net](http://www.researchautism.net)

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Patricia Howlin, April 2010

## Coffin-Lowry Syndrome

### First description

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

### Genetics and molecular biology

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

### Incidence / Prevalence

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

### Physical features and natural history

The typical facial aspect in adult male patients includes a prominent forehead, orbital hypertelorism, downward-slanting palpebral fissures, epicanthic folds, large and prominent ears, thick everted lips, and a thick nasal septum with anteverted nares. Orodonal findings include typically a high narrow palate, a midline lingual furrow, hypodontia, and peg-shaped incisors. Patients show hyper-extensible, soft, and fleshy hands with lax skin and joints and tapering stubby fingers. Other reported findings include a short horizontal crease in the hypothenar region and fullness of the forearms owing to increased subcutaneous fat. Skeletal malformations appear progressively in most patients and may include delayed bone development, spinal kyphosis/scoliosis, and pectus carinatum or excavatum. Radiographic changes include cranial hyperostosis, abnormal shape and end plates of the vertebral bodies, delayed bone age, metacarpal pseudoepiphyses, and tufting of the distal phalanges. Uncommonly associated manifestations include epileptic seizures and sensorineural hearing loss, which can be profound. Stimulus-induced drop episodes, with onset typically from mid-childhood to the teens (unexpected tactile or auditory stimuli or excitement triggers a brief collapse but no loss of consciousness), and cardiac involvement, usually in the form of mitral valve dysfunction, are often present. Reduced total brain volume, with a particular effect on cerebellum and hippocampus, has been reported in some patients.

Affected newborn males often show only hypotonia and hyperlaxity of joints. However, broad, tapering fingers may also be present at birth. The typical facial appearance is usually apparent only by the second year of life and shows progressive coarsening thereafter with increasing prominence of the glabella and protrusion of the lips. Retardation of growth and psychomotor development become apparent gradually in the first years of life. Other possible early signs are sensorineural hearing deficit and microcephaly. The age of walking is delayed, and

difficulties in ambulating may persist with a clumsy gait.

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

Although accurate information is not available the paucity of reports of older affected males suggests that their life expectancy is reduced in contrast to that of females who can survive well into old age. Reported causes of death in affected males include myocarditis, pneumonia and inhalation during a convulsion. Several males have succumbed to complications following general anaesthesia for correction of orthopaedic problems or dental extraction (Hanauer & Young, 2002, Hunter, 2002).

### Behavioural characteristics

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

Cognitive function of female carriers may be variably affected: it can range from normal intelligence to moderate mental retardation. Frequently, they are reported to have learning difficulties at school. Obesity and psychiatric illness (depression, psychotic behavior, and schizophrenia) have been described in few female carriers. Epilepsy may occasionally develop.

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

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

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André Hanauer, June 2010

## Cornelia de Lange Syndrome

### First description and alternative names

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

### Incidence/prevalence

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

### Genetics

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

### Physical features and natural history

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

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

### Behavioural characteristics

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

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

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

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

### Neuropsychological characteristics

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

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

Kline AD, Krantz ID, Sommer A, Kliwer M, Jackson LG, FitzPatrick DR, Levin AV, Selicorni A. (2007) Cornelia de Lange syndrome: Clinical review, diagnostic and scoring systems, and anticipatory guidance. *American Journal of Medical Genetics, Part A* 143A:1287–1296.

### Useful websites/associations for more information

CdLS Foundation UK and Ireland: [www.cdls.org.uk](http://www.cdls.org.uk)

CdLS World: [www.cdlsworld.org](http://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.

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J Moss & C Oliver, July 2010.

## Cri du Chat Syndrome

### First description and alternative names

First described by Lejeune in 1963, Cri du Chat Syndrome (CdCS), which takes its name from the 'cat-like cry', is often referred to as Deletion 5p- syndrome and chromosome five short arm deletion.

### Incidence/prevalence:

The prevalence of CdCS has been estimated at 1 in 50,000 live births and although the exact gender ratio is unknown, the syndrome is thought to be approximately twice as prevalent in females as in males (Niebuhr, 1978; Van Buggenhout et al., 2000; Dykens et al., 2000).

### Genetics and Molecular Biology

CdCS is predominantly caused by a partial deletion on the tip of the short-arm of chromosome 5 (with a critical region of 5p15). The size of the deletion ranges from the entire short arm to the region 5p15 (Overhauser et al., 1994). A de novo deletion is present in 85% of cases; 10 to 15% are familial with more than 90% due to a parental translocation and 5% due to an inversion of 5p (Van Buggenhout et al., 2000). Niebuhr first identified the specific chromosomal region implicated in the syndrome as 5p15.1–5p15.3, using cytogenetic analysis (Niebuhr, 1978). More recent work has mapped specific critical areas within this region as being responsible for the expression of the core clinical features of the syndrome. For example, the characteristic high pitched 'cat-like' cry from which the syndrome derives its name has been mapped to the proximal part of 5p15.3, the speech delay to the distal part of 5p15.3 and severe intellectual impairment to 5p15.2 (Overhauser et al., 1994). This distinctive cry is considered the most prominent clinical diagnostic feature of the syndrome (Mainardi et al. 2006). Though relatively rare, CdCS represents the most common deletion syndrome in humans (Cornish et al., 2001).

### Physical features and natural history

The distinctive cat-cry is a core feature of the syndrome and is still regarded as an important early clinical diagnostic feature in most but not all individuals (Mainardi et al. 2006). The cry is thought to be caused by anomalies of the larynx (small, narrow and diamond shaped) and of the epiglottis that is usually small and hypotonic (Niebuhr, 1978). Many infants tend to be of low birth weight and low weight usually persists in the first two years of life for both sexes (Marinescu et al., 2000). Feeding difficulties are common and the associated failure to thrive may be the initial clinical presentation. Some infants may require tube feeding, a process which may have to continue for several years. Gastroesophageal reflux is common in CdCS during the first years of life. Other health problems include respiratory tract infections, otitis media and dental problems. Many individuals with CdCS are prone to developing a curvature of the spine (congenital scoliosis) and this can become more apparent with advancing age. Some of the most frequently cited physically defining features of CdCS are facial characteristics including microcephaly, rounded face, widely spaced eyes, downward slanting of palpebral fissures, low set ears, broad nasal ridge and short neck (Dykens et al., 2000; Marinescu et al., 1999). Studies indicate that facial features change over time, specifically, lengthening of the face and coarsening of features (Mainardi et al. 2006).

### Behavioural characteristics

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

as it is typically focussed on one specific item (as opposed to a class of items) and the item may change over time. Additionally, the behaviour tends to become less marked with age.

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

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

### **Neuropsychological characteristics**

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

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

#### **[www.criduchat.org.uk](http://www.criduchat.org.uk)**

Oliver, C., Moss, J., Petty, J., Tunnicliffe, P., Hastings, R., Howlin, P., Griffith, G., Bull, L., Villa, D. and Yip, M. (2009).

*Understanding and Changing Challenging Behaviour in Cri du Chat Syndrome*. Aerocomm Ltd: Essex -Available from the CdLS Foundation UK and Ireland.

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

## Fragile X Syndrome

### First described

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

### Genetic aspects

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

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

### Incidence/Prevalence

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

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

## Physical

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

## Life expectancy/Natural history

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

## Behavioural characteristics

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

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

## Social impairments, autism and ADHD

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

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

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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

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

Randi Hagerman, September 2010



## Klinefelter Syndrome (49,XXY)

### First description and alternative names

"Klinefelter Syndrome" or "Klinefelter's Syndrome", sometimes abbreviated as KS, was first described by Dr Hans Klinefelter in 1942 as an endocrine disorder characterized by small firm testes, hypogonadism, gynaecomastia, and increased levels of follicle-stimulating hormone. Patricia Jacobs determined in 1959 that the clinical phenotype was due to a 49,XXY genotype.

### Genetics and molecular biology

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

### Incidence/prevalence

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

### Physical features and natural history

Although 47,XXY is associated with a characteristic pattern of physical differences, the degree to which an individual is affected can vary widely. Prior to puberty physical differences can be minimal, including increased height and proportional leg length. These are thought likely related to dosage effects of the additional chromosome. Studies of testosterone levels during the perinatal period have had mixed results. During adolescence and adulthood physical features related to hypogonadism become more prominent, including small, firm testes; gynaecomastia, low testosterone levels and other abnormalities in endocrine response. Testicular histology may appear normal until puberty, but then demonstrates increasing hyalinization of the seminiferous tubules, disappearance of Sertoli cells, hyperplasia of Leydig cells, with loss of spermatogenesis. Islands of normal testicular tissue may remain in some individuals. Other areas of increased risk developing over adulthood include low energy and libido; osteoporosis; thromboembolic disease, obesity, and diabetes mellitus. Individuals with a mosaic form are usually less affected and may have normal fertility.

### Behavioural and psychiatric characteristics

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

### Neuropsychological characteristics

The effects on neurocognitive function widely, with many 47,XXY individuals having normal or above average cognitive capacity. On a group level mean IQ values fall within the normal to low normal range, and are depressed approximately 10 points below what would be expected based on siblings. Verbal ability may be more severely affected than nonverbal. 70–80% of 47,XXY individuals across several studies have had identified

language problems. Some studies have reported relatively more pronounced deficits in verbal IQ than performance IQ, although this is not universal. Executive function capacities such as attention and impulse control may be impaired, although available studies are sparse. Several studies have reported impairments in both fine and gross motor skills.

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

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

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

The American Association for Klinefelter Syndrome Information and Support (AAKSIS), [www.aaksis.org](http://www.aaksis.org)

Klinefelter's Syndrome Association UK, [www.ksa-uk.co.uk](http://www.ksa-uk.co.uk)

KS & A (Knowledge, Support and Action), [www.genetic.org](http://www.genetic.org)

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Rhoshel K Lenroot, 2010

## Lesch-Nyhan Disease (Lnd)

### Alternative names

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

### First description

It is interesting to speculate that the first description of Lesch-Nyhan Disease may very well have been in the year 1267. Beck (Euro J of Ped Surg 1991) identified an original description of what is most probably LND when he uncovered cases of self-injury, gout, and mental retardation in individuals living in a small village in England where St Thomas, Archbishop of Canterbury, had been killed. The original account was written by Jacobus de Voragine from secondary sources (Golden Legend). Incidentally, de Voragine thought the origin of the disease might somehow be related to the murder of St Thomas and the "wrath of God". Commonly accepted as the first description of the familial nature of the disease was by Nyhan and Lesch who published data in 1964.

### Incidence

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

### Genetic aspects

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

### Physical phenotype

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

### **Cognitive aspects**

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

### **Behavioral aspects**

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

### **Treatment**

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

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

### Life expectancy

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

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## Neurofibromatosis Type 1 (Nf1)

### Genetics

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

### Incidence/prevalence

About 1 in 3,000 births.

### Physical features

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

### Life expectancy

Depends on nature and severity of clinical features.

### Behavioural characteristics

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

### Cognitive characteristics

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

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## Noonan Syndrome

### First description

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

### Associated conditions

Noonan syndrome is – incorrectly – also referred to as 'Male Turner syndrome', 'Female pseudo-Turner syndrome', 'Turner phenotype with normal karyotype', 'Ullrich-Noonan syndrome' and 'Pterygium Colli Syndrome, included'.

Although the NS phenotype has resemblance to the phenotype of (Ullrich-)Turner syndrome, the genotypes differ. Other examples of distinct syndromes with partially overlapping phenotypes include Cardio-Facio-Cutaneous (CFC) syndrome, Costello syndrome, and LEOPARD syndrome (Van der Burgt, 2007).

### Genetics and molecular biology

NS may occur on a sporadic basis or in a pattern consistent with autosomal dominant inheritance with a predominance of maternal transmission. In approximately 50% of the patients, a missense mutation is found in the *PTPN11* gene on chromosome 12 (12q24.1). The mutations associated with NS result in a gain of function of SHP-2 (Tartaglia et al., 2001). Recently, activating mutations in other genes of the Ras-MAPK pathway (*SOS1*, *KRAS*, *RAF1*, *MAP2K2*, *NRAS*, *SHOC2*) were found as the causative mutations in NS. These findings establish hyperactive Ras as a cause of developmental abnormalities seen in NS (Schubbert et al., 2006).

### Incidence/prevalence

The incidence of NS is estimated as 1 in 1000 to 1 in 2500 live births (Mendez & Opitz, 1985).

### Physical features and natural history

Key characteristics are 1) short stature, 2) typical facial dysmorphology (hypertelorism with down-slanting palpebral fissures, ptosis and low-set, posteriorly rotated ears with a thickened helix) and 3) congenital heart defects (pulmonary valve stenosis, hypertrophic cardiomyopathy, atrial septal defect). Some additional features are pectus carinatum/excavatum, cryptorchidism, lymphatic dysplasia and a webbed neck. There is substantial variability in expression, and improvement of the physical phenotype occurs with increasing age. The diagnosis is made on clinical grounds, by observation of key features. The most widely used scoring system has been developed by Dr Ineke van der Burgt (1994). In 2010, this scoring system was updated by adding a few features (Dyscerne, Noonan Syndrome Guideline Development Group, 2010). Neural complications that have been described more frequently in NS are Arnold-Chiari malformations and hydrocephaly. Life expectancy for patients with NS is fairly normal, unless there are major complications of heart disease. Premature delivery is the main source of morbidity.

### Behavioural and psychiatric characteristics

A distinctive pattern of behavioural characteristics can not be recognized, although there are indications for an increased risk for behavioural problems in children, characterized by social problems, stubbornness, restlessness, and impulsivity. Classical psychiatric syndromes have only incidentally been described for NS and mainly concern cases of anxiety disorders, obsessive-compulsive disorders and mood disorders. In adults, alexithymia seems to be present more often and with respect to personality, friendliness, agreeableness and a tendency to a socially

desirable attitude have been noted. Because of this combination of problems in expressing emotions and amenable traits, psychopathology may remain underreported (Verhoeven et al, 2008; Wingbermühle et al, 2009).

### Neuropsychological characteristics

Neuropsychological findings show intelligence scores in a wide range, with only a mildly lowered average intelligence. In about one-third of the patients mild mental retardation is found (Allanson, 2005). Verbal and performal capacities are divided more or less equally. Language and motor development are often delayed, but are in general no longer dysfunctional in adulthood. Mild attention problems have been found, as well as problems in executive functioning (i.e. slightly diminished organization skills and compromised abilities to structure complex information). As a result, learning difficulties may be present, requiring special educational attention. As described above, social cognitive functions (recognizing and expressing emotions) may be impaired as well (Wingbermühle et al, 2010).

### Available management guidelines

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

### More information

**www.dyscerne.org**. For the 2010 NS guideline PDF-document as developed by the Dyscerne Network of Centres of Expertise for Dismorphology.

**www.ncbi.nlm.nih.gov/omim/163950**. For the information on NS in OMIM, an online database of human genes and genetic disorders.

**www.noonansyndrome.org** For the Noonan syndrome support group.

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## Prader-Willi Syndrome (PWS)

### First description

Prader-Willi syndrome (PWS) was first described in 1956 by Prader, Labhart and Willi.

### Genetics and molecular biology

PWS results from the absence of expression of the paternal allele of paternally expressed/maternally imprinted genes at the chromosomal locus 15q11-q13 (the PWS critical region). The commonest genetic mechanisms leading to PWS are: a) a *de novo* deletion at the PWS critical region on the chromosome of paternal origin (~70% of cases) and b) maternal uniparental disomy (mUPD) of chromosome 15 where both chromosomes are derived from the mother (~25% of cases). Other rarer causes of PWS include imprinting centre defects and unbalanced translocations. A number of paternally expressed/maternally imprinted genes have been identified within the PWSCR of which the largest is *SNRPN* (containing the imprinting centre) which codes for a small nuclear ribosomal protein involved in the control of synthesis of proteins related to hypothalamic function. Other paternally expressed/maternally imprinted genes in this region include *Necdin*, *MAGEL2*, *MKRN3*, *IPW*, *PAR-1* and snoRNAs including *HBII-85* and *HBII-438*. As yet, no single gene mutation has been identified as a cause of PWS, other than a mutation of the imprinting centre which itself influences the expression of several genes.

### Incidence/prevalence

The estimated birth incidence is 1 in 29,000 and the prevalence is 1 in 52,000 (Whittington *et al.* 2001).

### Natural history

The early phenotype is characterised by severe hypotonia after birth, which affects the infant's ability to suck, resulting in feeding problems and consequent failure to thrive which may necessitate gavage feeding. Hypothalamic dysfunction leading to growth hormone and steroidal sex hormone deficiency may account for several features of PWS (Goldstone 2004), including the control of birth processes, short stature, hypogonadism, aberrant body temperature control and daytime hypersomnolence. Characteristic facial features include dolichocephaly, narrow bifrontal diameter, almond shaped palpebral fissures, small down turned mouth and thin upper lip (Holm *et al.* 1993).

The onset of the striking characteristic of hyperphagia separates the early and late phenotype. Between the ages of 1 and 6 years, the child develops a propensity for eating which, if left unaddressed, can result in obesity and medical problems. The hyperphagia is considered to be hypothalamic in origin, and caused by failure of the normal satiety response following food intake (Holland *et al.* 1993; Hinton *et al.* 2005). Infertility remains almost universally present although there are rare reports of children being born to females with PWS.

### Behavioural and psychiatric characteristics

Aside from the over-eating, the most common problem behaviours are temper tantrums, usually arising out of frustration or change to a familiar routine, and which can result in extreme aggression; mood swings which do not fulfil criteria for a defined psychiatric disorder; and self-mutilation in the form of skin-picking. Relative to others with intellectual disability, people with PWS are more likely to exhibit severe problem behaviours (Dykens *et al.* 1997). Obsessional traits occur commonly, in particular needing to ask or tell, requiring routines, hoarding and repetitive questioning (Clarke *et al.* 2002).

The mUPD genetic subtype of PWS is strongly associated with the development of affective psychosis (Boer *et al.* 2002). In a UK-wide sample of 119 adults with PWS, 62% of those with mUPD had a diagnosis of psychotic illness compared with 17% of those with a deletion (Soni *et al.* 2008). Atypical symptoms such as hypersomnia and confusion were seen, and those with mUPD had a more severe, difficult-to-treat illness with a poorer outcome

compared to those with a deletion (Soni *et al.* 2007). Dementias are now being documented as individuals survive into old age (Sinnema *et al.* 2010). Autism has been reported (Veltman *et al.* 2004); candidate genes for autism have been located within the 15q11-q13 region.

### Neuropsychological characteristics

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

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

Growth hormone supplementation can increase height and the rate of growth, decrease mean body fat, improve respiratory muscle function and physical strength and improve facial dysmorphism. Supplementation of the sex hormones assists the development of secondary sexual characteristics and improves bone mineral density and content.

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

Many features of the behavioural phenotype are thought to be serotonin mediated e.g. skin picking, mood swings, obsessional symptoms. Selective serotonin reuptake inhibitors (SSRIs) may be useful in addressing these problems. Antipsychotic, antidepressant and mood stabilising medications have all been shown to be of benefit in those with severe psychiatric disorders.

### Useful websites/associations for more information

PWS Association UK <http://pwsa.co.uk/main.php>

PWS Association USA: <http://www.pwsausa.org/>

Online Mendelian Inheritance in Man (OMIM): <http://www.ncbi.nlm.nih.gov/entrez/dispmim.cgi?id=176270>

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Sarita Soni, April 2010

## Rett Syndrome/ Rett Disorder / RTT

The first full description of the disorder, by the Viennese neurologist Andreas Rett, was published in 1966.

### Genetics and Neurology

The disorder is due to mutations on *MECP2*, (Xq28), a gene which appears to control the activities of other genes. It is expressed throughout the body but particularly in neurones during early brain development and in maturity. The first neurones to be affected, at 10–14 weeks gestation, are those in the brain stem and the Cajal-Retzius neurones which appear to have a role in determining the later function of pyramidal neurones. Since female cells acquire two X chromosomes but use only one in each cell, a wide range of clinical severity is to be expected, according to the proportion of cells using the affected gene. In affected XY males, severe disease is to be expected. The mutation commonly occurs in a sperm, less often in an ovum of an apparently healthy adult and rarely in the zygote leading to mosaic expression. For these reasons the disorder is much more often seen in females than males. Family recurrences are unusual. A figure of 1 in 300 has been proposed. Prenatal diagnosis is possible and mutation testing of parents and female siblings of affected people is advisable. The brain is reduced in size, the cortex being particularly affected with neurones smaller and more closely packed than normal with poor dendritic development but no evidence of degeneration. There is early disturbance of the neurotransmitters serotonin, glutamate and acetylcholine.

### Incidence/prevalence

The disorder occurs worldwide with female childhood prevalence at least 1 in 10,000. It has seldom been found in males in whom early deaths have been reported.

### Life expectancy/ mortality

The annual death rate in rate in the UK is 1.2% with the most physically disabled at increased risk and the most able commonly surviving into adulthood in good health. A number of sudden deaths (probably at least 20%) are thought to be related to the central autonomic dysregulation. Some deaths are related to epilepsy, to aspiration pneumonia or nutritional difficulties but less severely affected people are likely to die from causes unrelated to the Rett disorder.

### Physical features and natural history

Gestation and birth are usually unremarkable and the infant looks normal and makes initial developmental progress. Smiling, sitting, reaching, self-feeding, walking and a little speech may develop although the later milestones tend to be delayed and poorly accomplished. However signs of the disease may also be detected from birth. These are placidity, disturbance of spontaneous movements and reduced exploration by the child. An experienced parent will often recognise a difference as compared with other children. Head circumference, although commonly within the centiles at birth, fails to increase at a normal rate. Developmental stagnation is common around 9–10 months and regression in hand use and communication follows, usually around 1–2 years but occasionally months or even years later. Sleep disturbance and hyperactivity are common. A relatively stable state is then reached and some developmental progress possible. About half of the children can walk and communication and voluntary hand use may improve. Facial appearance is pleasant and not frankly dysmorphic. The fourth metatarsals and metacarpals may be short. Stature is reduced. Epilepsy is present in over 50% and this may be generalised or focal. Early hypotonia gives way to hypertonia with the risk of contractures. Scoliosis develops in most people. Episodes of dystonia are common. Abnormal oral movements may make feeding difficult. Gastric reflux, aerophagy and constipation are common. Poorly regulated central autonomic function leads to disturbed cardio-respiratory control with episodes of breath-holding, shallow breathing, hyperventilation and valsalva breathing, It is important to appreciate the wide range in severity of this disorder, such that all the above features may appear soon after birth, proving rapidly lethal or may appear late and remain mild.

### Cognitive and Behavioural characteristics

Babies are quiet and placid unless in pain. Sleep disturbance, crying spells and withdrawal are usual during the regression period and may persist. After regression there are periods of agitation associated with the labile respiratory rhythm, hyperventilation and breath-holding and aerophagy. The non-epileptic vacant spells may be accompanied by altered attention, specific movements, pallor, cyanosis or fainting. A range of involuntary movements includes stereotyped movements of the hands with squeezing or patting finger action and voluntary hand use is commonly absent or poor. Bruxism and head banging occur in some people. Injury may result to the individual or to others, from these repeated movements. Although speech is uncommon, non-speech communication is enjoyed, as is quiet face-to-face contact. Intellectual disability is usually severe or profound but the range of severity is wide with a few people only mildly affected and others very severe from birth. A few people can speak, write and draw. Typically people with Rett disorder have charm and show interest and enjoyment of the company of familiar people. Music is particularly enjoyed and the choice of music is often personal and emphatic.

### Differential Diagnosis

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

In the very early stages there may be confusion with the degenerative disorders of infancy.

The repetitive movements of the hands has sometimes led to confusion of Rett disorder with Autism and some have recommended classification within the 'autistic spectrum'. However the sociability of people with Rett disorder and their highly characteristic genetic and physical features should make the distinction.

Mutations in the genes *CDKL* or *FOXP1* have been separately reported as leading to very severe developmental disorders, still to be fully characterised but with similarities to Rett disorder.

### Management

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

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

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Alison M Kerr, 2010

## Triple-X Syndrome (47,XXX)

### First description and alternative names

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

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

### Genetics and molecular biology

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

In 46,XX females one X chromosome is silenced. The extra X chromosome in triple-X women is also silenced through Lyonization. In 46,XX females one-third of the genes on the X chromosome escape silencing (Migeon 2007).

The so-called ‘late-replicating’ X chromosome is found on the second X chromosome. In cases of an extra X chromosome there is another late-replicating chromosome, so replication time increases during each cell division (Barlow 1973).

The extra X chromosome might also have some influence on the nuclear architecture and on epigenetic processes (Kelkar and Deobagkar 2010).

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

### Incidence/prevalence

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

### Physical features and natural history

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

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

### Behavioural and psychiatric characteristics

Low self-esteem seems to be the most common feature, and shyness is also common in triple-X females. Receptive and expressive language disorders are common. These language disorders may be responsible for social problems, as is challenging behaviour, although this behaviour is less common. Both individuals living in a stable family and controls in unstable families function better than triple-X girls do (Netley 1986). The triple-X girls

seem to be less able to cope in a stressful environment. After leaving school, most of the girls will find a job that reflects their non-verbal abilities (Robinson *et al.* 1990).

There seems to be a higher prevalence of psychiatric illness in general, especially in cases of less severe global intellectual disability. More specifically, there is a higher prevalence of psychotic disorders and adjustment disorders (Olanders 1975). Newborn-screening studies have not continued to the age at which psychotic disorders could have become noticeable. Further psychiatric research with standardised psychiatric diagnostic tools is warranted in these females.

### Neuropsychological characteristics

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

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

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

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

### Useful websites/associations for more information:

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

<http://www.rarechromo.org/information/Chromosome%20X/Triple%20X%20FTNW.pdf> provides a syndrome sheet with information on physical and behavioural developmental issues.

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

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Maarten Otter, summer 2010

## Tuberous Sclerosis Complex (TSC)

### First description and alternative names

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

### Genetics and Molecular Biology

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

### Incidence/prevalence

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

### Physical features and natural history

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

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

### Behavioural and psychiatric characteristics

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

### Neuropsychological characteristics

Global cognitive abilities show a bimodal distribution. 30% of individuals with TSC have profound global intellectual disability and do not show significant developmental gains over time. The remaining 70% fall on a normal distribution curve, shifted to the left. In clinical practice, more than 50% of individuals with TSC will have global cognitive abilities in the normal range. There are, however, high rates of specific neuropsychological

deficits in those with normal global intellectual abilities. Specific deficits are most prominent in attentional, executive and visuo-spatial skills. These specific cognitive deficits may lead to significant scholastic difficulties and impair functional abilities in daily life (Prather & de Vries, 2004; Kwiatkowski et al., 2010).

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

International consensus guidelines were drawn up for the assessment of cognitive and behavioural problems in TSC (de Vries et al., 2005).

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

Targeted treatments using mTOR inhibitors are currently in clinical trials for the neurocognitive and neurodevelopmental features of TSC (de Vries, 2010), but these should not be used outside formal trials.

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

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

**www.tsalliance.org** [USA user/carer organization]

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Petrus de Vries, August 2010

## Turner Syndrome

### First description

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

### Genetics and molecular biology

In humans, partial or complete loss of either of the sex chromosomes results in the condition. A phenotype arises because of haploinsufficiency for genes that are normally expressed from both X-chromosomes in females (or the Y in males). Early degeneration of the ovaries leads to oestrogen insufficiency. Knowing the genetic sequence of the X chromosome should lead to identification of susceptibility genes; so far, the only 'Turner' gene identified (*SHOX*), influences growth in stature.

### Incidence and prevalence

The prevalence of the syndrome is 4 per 10,000 live female births. Whilst this is the most common chromosomal aneuploidy, the vast majority of affected conceptuses (95% or so) are spontaneously aborted. In ~70% of X-monosomy, there is loss of all or part of the paternal sex chromosome; the single normal X is maternal in origin. In 50% of all clinically identified Turner syndrome there is more than one obvious cell line. One is usually monosomic, the other contains either the full complement of 46 chromosomes, or some other complex structural variation. These so-called mosaics may have either a more mild, or a more severe, phenotype than X-monosomy, depending on the genetic abnormality.

### Physical features and natural history

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

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

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

Other common problems include renal anomalies (30%) associated with an increased risk of urinary tract infections and hypertension. Hypothyroidism is associated with an autoimmune thyroiditis. One of the most serious, but often overlooked, complications is otitis media, exacerbated by anatomical anomalies of the Eustachian tube. This is extremely common in girls with Turner syndrome, particularly in infancy and early childhood. Aggressive treatment of infections is appropriate. The majority (50–90%) of women with Turner syndrome will also develop early sensorineural (nerve) hearing loss and may require hearing aids earlier than the general population.

Because of the small stature, which is almost invariably relative to the height of the parents, it has become

usual to treat with human growth hormone. The average stature after treatment is increased by a few centimeters, although the condition is not associated with growth hormone insufficiency and high doses are needed to achieve any significant benefit.

### **Behavioural and psychiatric characteristics**

Social integration is usually good until adolescence. The normal adolescent growth spurt is then lacking, and secondary sexual characteristics may be delayed (by endocrine management). These factors combine with specific deficits in social cognitive competence, which is severe in at least 30% of cases. Forming and maintaining peer relationships are often problematic, especially as these become more complex in later life. As adults, many women cannot function effectively in complex work environments, and a substantial minority chooses to take jobs focused on child-care (especially nursery nursing, in the UK). This choice is not motivated by their (usual) infertility but by their subtle and superficially mild autistic symptomatology, which may not be obvious to the paediatricians or endocrinologists who manage the syndrome in childhood and adulthood.

Many females with Turner syndrome have poor self-esteem. This is largely due to their difficulty in establishing satisfactory social relationships, the latter being misattributed to associated short stature or infertility. This is rarely the true explanation, and undermines the possibility of effective treatment, but it is the prevailing view in the United States, where the attribution of social maladjustment to fundamental problems with social-cognitive processing is strongly resisted by both women with Turner syndrome and their doctors.

### **Neuropsychological characteristics**

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

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

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

Bondy C.A. (2007) Turner Syndrome Study Group. Care of girls and women with Turner syndrome: A guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab* **92(1)**, 10–25.

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

**<http://np.netpublicator.com/netpublication/n75088268>**

### **Useful websites/Associations for more information**

Turner syndrome support society (UK): **<http://www.tss.org.uk/>**

National Institute of Child Health and Human Development (USA): **<http://turners.nichd.nih.gov/>**

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David H Skuse, 2010

## Velo-Cardio-Facial Syndrome

### Alternative names

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

### Genetics / aetiology

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

### Incidence / prevalence

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

### Physical phenotype

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

### Psychiatric/behavioural disorder

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

### Neuropsychological deficits

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

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

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

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

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

### Brain structural abnormalities

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

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Kieran C Murphy & Frederick Sundram, September 2008

## XYY Syndrome

### First description and alternative names

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

### Genetics and molecular biology

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

### Incidence/prevalence

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

### Physical features and natural history

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

### Behavioural and psychiatric characteristics

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

### Neuropsychological characteristics

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

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

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

### Useful websites/associations for more information

KS & A (Knowledge, Support and Action), [www.genetic.org](http://www.genetic.org)  
[www.rarechromo.org](http://www.rarechromo.org)

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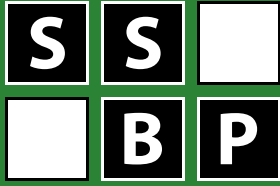
Rhoshel K Lenroot, 2010

# Acknowledgments

We are extremely grateful to the wide range of people who contributed to this conference. A few specific acknowledgements are warranted:

- The Scientific Director of National Neurological Institute, IRCCS C. Mondino Foundation – Prof. Giuseppe Nappi
- The SSBP Chairman – Dr. Petrus J De Vries
- Silvia Molinari – Coordinator of Training & Information Services, National Neurological Institute, IRCCS C. Mondino Foundation
- Robbie Fountain, SSBP Administrator and her team
- Hamish Symington for graphic design ([www.hamishsymington.com](http://www.hamishsymington.com))
- Deborah McCartney for her collaboration
- Members of the Scientific committee for review of abstracts
- All keynote speakers for their time
- Historical Colleges of Pavia for hospitality
- Conference Team
- Café team
- The Editor C.S.H. srl.
- The SSBP Executive committee
- The Staff of the Laboratory of Cognitive Behavioural Psychology - National Neurological Institute, IRCCS C. Mondino Foundation – Valeria Destefani, Anna Cremante, Federica Clerici





## 14th SSBP International Research Symposium

*Translating Genetics to Phenotype: Implications for Management*  
5 – 7 October 2011, Brisbane, Australia

The Society for the Study of Behavioural Phenotypes (SSBP) is pleased to announce that the 14th SSBP International Research Symposium will be held in Brisbane, Australia.

There will be a focus on the genetic and molecular aspects of neurocognition and behaviour in genetic syndromes. Sessions will also focus on evolving therapies. The Symposium will run on 5th and 6th October, and the Educational Day on 7th October.

For more information and details of how to submit an abstract for an oral or poster presentation, visit [www.ssbp.co.uk](http://www.ssbp.co.uk).

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