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

Petrus De Vries
Developmental Psychiatry Section, University of Cambridge
Email: pd215@cam.ac.uk

Chris Oliver
Professor of Neurodevelopmental Disorders at the University of Birmingham
Email: C.Oliver@bham.ac.uk

Antonio Federico
Professor of Neurology, University of Siena
President, Italian Society of Neurology
Email: federico@unisi.it

Lidia Larizza
Professor of Medical Genetics, Department of Medicine, Polo San Paolo, University of Milan
President of Italian Society of Human Genetics
Email: lidia.larizza@unimi.it

Giovanni Cioni
Professor of Child Neurology and Psychiatry, Department of Developmental Neuroscience,
Stella Maris Scientific Institute and University of Pisa
Email: Gcioni@inpe.unipi.it

Renzo Vianello
Dean of the Faculty of Psychology, University of Padova
Email: renzo.vianello@unipd.it

Orsetta Zuffardi
Professor of Medical Genetics, Department of Human and Hereditary Pathology, University of Pavia,
responsible for the Cytogenetics Services at IRCCS Policlinico San Matteo and of The GenTher Center at National Neurological Institute, IRCCS C. Mondino Foundation
Email: orsetta.zuffardi@unipv.it
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 Neupatologica), 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 Neuropsychological 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

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

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<th>Year</th>
<th>Venue</th>
<th>Type</th>
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<td>1991</td>
<td>Kings Fund, London, UK</td>
<td>Workshop</td>
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<td>1993</td>
<td>Royal Society of Medicine, London, UK</td>
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<td>1996</td>
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<td>2000</td>
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<td>2002</td>
<td>Whistler, Canada</td>
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<td>Newcastle, UK</td>
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<td>2004</td>
<td>Barcelona, Spain</td>
<td>8th International</td>
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<td>2005</td>
<td>Cairns, Australia</td>
<td>9th International</td>
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<td>2006</td>
<td>Dublin, Ireland</td>
<td>11th Annual</td>
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<td>2007</td>
<td>MIND Institute, Sacramento &amp; Lake Tahoe, California</td>
<td>10th International</td>
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<td>2008</td>
<td>Cologne, Germany</td>
<td>11th International</td>
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<td>2009</td>
<td>Cambridge, UK</td>
<td>12th International &amp; 12th Annual</td>
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<td>2010</td>
<td>Pavia, Italy</td>
<td>13th International</td>
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Forthcoming SSBP Meetings

2011
Brisbane, Australia

2012
Europe (City to be confirmed)

2013
South Africa (City to be confirmed)

The SSBP Executive Committee

Elected President
Dr Martin Bax (London) (m.bax@imperial.ac.uk)

Chair
Dr Petrus de Vries (Cambridge) (pdv215@cam.ac.uk)

Hon. Secretary
Professor Leopold Curfs (Maastricht) (curfs@msm.nl)

Hon. Treasurer
Dr Howard Ring (Cambridge) (har28@cam.ac.uk)

Committee
Dr Honey Heussler (Brisbane) (honey.heussler@gmail.com)
Dr Deborah McCartney (Cambridge) (dlm31@cantab.net)

Dr Joanna Moss (London) (j.f.moss@bham.ac.uk)
Dr Raja Mukherjee (London) (raja.mukherjee@ssbp.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)

International Representatives
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)

(brandi.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;
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.
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<tr>
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<tr>
<td>2009</td>
<td>Alcino Silva</td>
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<td>2008</td>
<td>Hans-Christoph Steinhausen</td>
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<tr>
<td>2007</td>
<td>Petrus J de Vries</td>
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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 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 unsheakable 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 (IUSST). 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 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 laude)
- 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 laude)
- Specialization in Medical Genetics in 1994/95 at School of Specialization in Medical Genetics University of Milan (voting 40/40 cum laude)
- From March 1991 until December 1994 Medical Assistant at Cyto genetic 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. Aymé)
- 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-Hirschhorn and AISAC
- From July 2007 he has been the chair of the Scientific Advisory Comittee of the Cornelia de Lange Syndrome Foundation (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 Pathology) 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.
- Assistenzial 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"

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.

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<td>15:30 – 15:45</td>
<td>Welcome and Introductions Petrus de Vries (Chair, SSBP)</td>
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| 15:45 – 16:30 | Introductory lecture: Cesare Lombroso: an anthropologist between evolution and degeneration  
                          Paolo Mazzarello (University of Pavia)                        |
| 16:30 – 17:15 | The Contributions of Camillo Golgi to Neurodevelopmental studies  
                          J. C. Harris (The Johns Hopkins University School of Medicine, Baltimore) |
| 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)

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|              | Talk 2: Keynote: Mild CdLS phenotype: clinical and molecular results of an international survey  
                          Angelo Selicorni (IRCCS Fondazione Policlinico Maggiore Regina Elena – Milan) |
10:00 – 11:00
Oral Presentation 1: Relevance of large deletions/duplications of the major candidate gene NIPBL as pathogenetic mechanism of the Cornelia de Lange syndrome.
M. Masciari, C. Gervasini, J. Azzollini, A. Cereda, A. Selicorni, L. Larizza, S. Russo
Oral Presentation 2: Delineating the Profile of Autism Spectrum Disorder in Cornelia de Lange Syndrome.
J. Moss, S. Hall, L. Collins, K. Arron, C. Burbidge, C. Richards, & C. Oliver

11:00 – 11:30
Coffee and poster session

11:30 – 13:00
Oral Presentation 3: Autism, Intellectual Disability, and Molecular-Gene tic Aspects Associated with Subtelomeric Rearrangements
G.S. Fisch, P.D. Grossfeld, J. Youngblom, R. Simensen, A. Battaglia
Oral Presentation 4: Receptive Language and Intellectual Disability in CDLS.
Importance of instruments of evaluation in a cohort of 10 patients.
P. Vizzio, S. Ajmone, F. Dall’Ara, C. Rigamonti, F. Monti, M.A. Costantino, A. Selicorni
Oral Presentation 5: Augmentative and Alternative Communication intervention in Cornelia de Lange Syndrome (CDLS)
M.A. Costantino, S. Anastasia, E. Bergamaschi, L. Bernasconi, G. Zappa, A. Selicorni
Oral Presentation 6: EEG and clinical polymorphism of Rett Syndrome

13:00 – 14:00
Lunch and poster session

14:30 – 16:15
Free Abstract session (Chair: A. Swillen)
Oral Presentation 7: Prevalence of autistic symptoms in children with ADHD: a clinic-based study
S. Mohiuddin, R. Legrou, M. Ghaziuddin
Oral Presentation 8: Behavioural Intervention for Challenging Behaviour in Children with Angelman Syndrome
A. Jones, S. Gornick, M. Radstaak
Oral Presentation 9: Focus related performance problems (FRPP) among persons with ASD and genetic syndromes
T. Næland, K. Hildebrand, H. Martinsen, S. Storvik
Oral Presentation 10: Does cognitive impairment explain behavioural and social problems of children with Neurofibromatosis Type 1?
S. Huijbregts
Oral Presentation 11: Visual cognitive function in Autism spectrum disorder
D. Pereverza

16:15 – 16:30
Coffee and poster session
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<td>16:30 - 17:45</td>
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<td>Oral Presentation 12: Neurobehavioural deficits in 11 children (2-12 years) with 22q11.2 duplication</td>
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<td>Oral Presentation 13: Identification of a de novo distal 22q11.2 deletion in an adult female referred for an anxiety disorder</td>
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<td>W. Verhoeven, J. Egger, H. Brunner, N. de Leeuw</td>
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<td>K.M. Tierny, D.L. McCartney, J.R. Serfontein &amp; P.J. de Vries</td>
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<td>Oral Presentation 15: Epilepsy and Tsc2 haploinsufficiency independently lead to autistic-like behaviors in rats</td>
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<td>17:45 - 18:45</td>
<td>SSBP AGM. Members and non-members welcome.</td>
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<td>20:00</td>
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Day 3 (Monday 25th October 2010)

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

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<td>Talk 4: Keynote: Evaluation of MAO-A and serotonin transporter polymorphisms in the behavioral phenotypes of males with XXY, XYY, and XXYY syndromes</td>
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<td>Nicole Tartaglia (University of Denver)</td>
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<td>Oral Presentation 17: Expression of sex chromosome genes syb, asmt, jard, il9, and rps4y in males with sex chromosome aneuploidy</td>
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<td>F. Tassone, A. Veri, E. Sanchez, V. Destefani, R. Hansen, N. Tartaglia</td>
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<td>10:00 - 11:00</td>
<td>Oral Presentation 18: Cognitive control functions and risk for psychopathology in Klinefelter syndrome</td>
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<td>S. van Rijn, L. de Sonneville, H. Swaab</td>
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<tr>
<td>10:00 - 11:00</td>
<td>Oral Presentation 19: Language Impairments in Fragile X Syndrome: A Failure to Use Social Cues?</td>
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<td>L. Abbeduto, R.J. Hagerman, A. McDuffie, S.T. Kover, D. Benjamin, S. Harris, S. Schroeder</td>
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<td>11:00 - 11:30</td>
<td>Coffee &amp; Poster Session</td>
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11:30 - 13:15

Talk 5: **Keynote: Endocrinological Treatment in Klinefelter Syndrome**
Antonio Radicioni (University of Rome)

Talk 6: **Keynote: Targeted Treatment for Fragile X Syndrome: Results of a Randomized Controlled Phase II Trial of Arbaclofen**
Randi Hagerman (University of California)

Oral Presentation 20: **Parental decision following prenatal diagnosis of Klinefelter syndrome: a proposal for a correct approach**
L. Tarani, C. Mattucci, N. Liberati, F. Mancini, F. Collordi

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.**

11:30 - 13:00

Lunch & Poster Session

14:30 - 16:15

**Free Abstracts session (Chair: F. Lalatta, R. Vianello)**

Oral Presentation 22: **The parent-of-origin of the extra X chromosome differentially affects psychopathology in Klinefelter syndrome**
H. Bruining, S van Rijn, H Swaab, M J H. Kas, H van Engeland, L de Sonnevile

Oral Presentation 23: **A Comparison of Visual Motor Integration and Motor Skills in Children and Adolescents with Sex Chromosome Aneuploidy**
S. Martin, S. Davis, N. Tartaglia

Oral Presentation 24: **Emotion recognition problems in boys with Klinefelter syndrome**
H. Swaab, H. Bruining, S. van Rijn, M. Bierman, H. van Engeland, L. de Sonnevile

Oral Presentation 25: **Narrative skills in Klinefelter Syndrome**
M. Vernice, A. Cremante, F. Clerici, A. Verri

Oral Presentation 26: **Late diagnosis in multiple X and Y chromosome disorders: role of learning disabilities and behavioural disorders**
A. Verri, A. Cremante, F. Clerici

16:15 - 16:30

Coffee & Poster Session (Chair: G. Cioni, J. Turk)

16:30 - 17:30

Oral Presentation 27: **Molecular and clinical correlations in Fragile X syndrome and in FMR1 related disorders**
F. Tassone, P.J. Hagerman, R.J. Hagerman

Oral Presentation 28: **Anticonvulsants & SSRIs Improve Psychological Functioning in Fragile X Syndrome**
J. Turk

Oral Presentation 29: **Females with fragile X syndrome and autism spectrum conditions**
J. Turk

17:30 - 18:00

Closing Remarks Petrus de Vries (Chair, SSBP)
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.

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 1873 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 international 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 3: Keynote: Mouse models of Klinefelter Syndrome

J. Wistuba
Institute of Reproductive and Regenerative Biology Centre of Reproductive Medicine and Andrology, University Clinics

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

N. Tartaglia, A. Verri, W. Zhang, A. Cremante, R. Hagerman, F. Tassone

1 Department of Pediatrics, University of Colorado Denver School of Medicine, Aurora, CO, USA
2 Child Development Unit, The Children's Hospital, Aurora, CO, USA
3 Fondazione Istituto Neurologico Nazionale Casimiro Mondino - Istituto di Ricovero e Cura a Carattere Scientifico, Pavia, Italy
4 Department of Biochemistry and Molecular Medicine, University of California School of Medicine, Davis, CA, USA
5 M.I.N.D Institute, University of California Davis Medical Center, Sacramento, CA, USA
6 Department of Pediatrics, University of California Davis School of Medicine, Davis, CA, USA

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 15.5±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) (F20.4, 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, il9r, and rps4y in males with sex chromosome aneuploidy

F. Tassone¹³, A. Verri³, E. Sanchez³, V. Destefani³, R. Hansen⁴⁵, N. Tartaglia⁴⁵

¹ Department of Biochemistry and Molecular Medicine, University of California, School of Medicine, Davis, CA, USA
² Fondazione Istituto Neurologico Nazionale Casimiro Mondino - Istituto di Ricovero e Cura a Carattere Scientifico, Pavia, Italy
³ M.I.N.D. Institute, University of California Davis Medical Center, Sacramento, CA, USA
⁴ Department of Pediatrics, University of Colorado Denver School of Medicine, Aurora, CO, USA
⁵ Child Development Unit, The Children's Hospital, Aurora, CO, USA

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, JARID1, IL9R, and RPS4Y. Polymorphisms in SYBL1 have been associated with bipolar disorder, ASMT mutations have been associated with depression and autism, JARID1 mutations have been associated with intellectual disability, IL9R 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 XXXY (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, XXXY<XY), JARID1 (F 12.45, p<0.0001, posthoc Tukey HSD XY, XYY < XYY, XXXY<XY), RPS4Y (F 12.1, p<0.0001, post-hoc Tukey HSD XY, XYY < XYY, XXXY<XY), and IL9R (F 3.27, p=0.024, post-hoc Tukey HSD XY<XXY). There were no statistically significant differences in expression between groups in ASMT expression. For all genes studied except the SYBL1 gene, the XXXY 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 XXY 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

S. van Rijn, L. de Sonnevile, H. Swaab
Department of Clinical Child and Adolescent Studies, Leiden University, The Netherlands

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 dysfunction 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?

L. Abbeduto¹, R.J. Hagerman², A. McDuffie³, S.T. Kover¹, D. Benjamin⁴, S. Harris⁵, S. Schroeder⁶, A. Oakes⁶, A. Mastergeorge⁷, B. Goodlin-Jones⁸, S. Lifson¹, E. Haebig³, C. Hauser¹ & C. Compton¹

¹University of Wisconsin, Madison
²University of California, Davis

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

A. F. Radicioni
Department of Fisiopatologia Medica, Sapienza University of Rome, Italy

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 supernumerous X chromosomes (48,XXXXY, 49,XXXXXY) 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 intervention 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

R. Hagerman¹, B. Rathmell¹, L. Wang¹, R. Carpenter², P. Wang³, E. Berry-Kravis¹

¹MIND Institute and Department of Pediatrics, UC Davis Medical Center, Sacramento
²Seaside Therapeutics, Boston
³Rush University Medical Center, Dept of Neurology, Chicago

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=0.03) 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 ≥18 on the ABC-I scale. Similarly, significantly more subjects were responders with "much improved or very much improved" on the CGH 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

L. Tarani, C. Mattiucci, N. Liberati, F. Mancini, F. Colloidi
Pediatric Department, "Sapienza" University Hospital of Rome, Policlinico Umberto I, Rome, Italy

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.

F. Lalatta 1, D. Quagliarini 2, E. Folliero 1, U. Cavallari 3, B. Gentilin 1, P. Castorina 1, F. Forzano 4, S. Forzano 5, E. Grosso 6, V. Vlassolo 6, V.G. Naretto 6, S. Gattone 4, F. Ceriani 3, F. Faravelli 4, L. Gargantini 8

1 UOD Genetica Medica, Dipartimento Area Salute della Donna del Bambino e del Neonato Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milano, Italy
2 Clinica Ostetrico-Ginecologica, Dipartimento Area Salute della Donna del Bambino e del Neonato Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Italy
3 Centro Malattie Rare Cardiologiche, UO Cardiologia AO Sacco, Milano, Italy
4 SSD Genetica Medica E.O. Ospedali Galliera, Genova, Italy
5 Genetica Medica, AOU San Giovanni Battista di Torino and Dipartimento di Pediatria, Università di Torino, Italy
6 Genetica Medica AO San Giovanni Battista di Torino, Italy
7 Centro Tumori Ereditari IST Genova
8 U.O. Pediatria, A. O. Treviglio, Treviglio, Italy

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 malformations 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.

H. Bruining 1, S van Rijn 2, H Swaab 2, M. J. H. Kas 3, H van Engeland 1, L de Sonneville 2

1 Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Centre Utrecht, the Netherlands
2 Institute of Social Sciences, Department of Developmental disorders, University of Leiden, the Netherlands
3 Rudolf Magnus Institute of Neuroscience, Department of Neuroscience and Pharmacology, University Medical Centre Utrecht, Utrecht, the Netherlands

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=33) 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

S. Martin\textsuperscript{1,2}, S. Davis\textsuperscript{1}, N. Tartaglia\textsuperscript{1,2}

\textsuperscript{1} The Children's Hospital, Aurora, Colorado
\textsuperscript{2} San Jose State University, Department of Occupational Therapy, San Jose, California
\textsuperscript{3} University of Colorado Denver School of Medicine, Department of Pediatrics, Aurora, Colorado

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±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 XYYY syndromes, and describe detailed motor skills assessment in a subset of participants.

Methods: 121 participants with SCA (34 XXY, 24 XYY, 24 XXX, 39 XYYY) 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±14.56), with a profile of significantly higher scores in visual perception (95.00±15.92) and significant weaknesses in fine motor coordination (81.49±16.06) (F(2134, p<0.0001). Comparing SCA subgroups, mean total VMI scores were: XXY 96.69±12.4, XYY 88.78±14.82, XXX 87.17±16.82, XYY 84.29±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=0.00005) and positively correlated with cognitive scores (R=.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±7.1), upper limb coordination (13.1±5.2), and fine motor integration (16.8±5.7), while they were impaired in domains of manual dexterity (9.3±3.2), bilateral coordination (11.9±6.6), running speed and agility (11.4±6.8), and strength (11.4±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. Swaab¹, H. Bruining², S. van Rijn³, M. Bierman⁴, H. van Engeland⁵, L. de Sonneville⁶

¹Department of Clinical Child and Adolescent Studies, Leiden University, Leiden, the Netherlands
²Department of Child and Adolescent Psychiatry, University Medical Centre, Utrecht, the Netherlands

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. Vernice¹, A. Cremante², F. Clerici³, A. Verri⁴
¹Department of Psychology, University of Milano-Bicocca, Milano, Italy
²National Neurological Institute, IRCCS Mondino Foundation, Pavia, Italy

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 focused 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, IQQ=92; IQP=88] and 8 controls matched for gender and age (±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

A. Verri, A. Cremante, F. Clerici
Fondazione Istituto Neurologico Nazionale Casimiro Mondino - IRCCS - Pavia, Italy

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.

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 behavioral 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.
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 in not known.

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

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

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

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

**References**


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