



FUNDACIÓ CATALANA SÍNDROME DE DOWN

# *PROGRAMME AND ABSTRACTS*

## **III INTERNATIONAL CONFERENCE ON CHROMOSOME 21 AND MEDICAL RESEARCH ON DOWN SYNDROME**

*March 18-19, 2005  
Barcelona - Spain*

# III INTERNATIONAL CONFERENCE ON CHROMOSOME 21 AND MEDICAL RESEARCH ON DOWN SYNDROME

Barcelona, March 18-19, 2005

Auditorium HOTEL GALLERY,  
C/ Rosselló, 249, Barcelona

ORGANIZED BY:

FUNDACIÓ CATALANA SÍNDROME DE DOWN

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SCIENTIFIC ADVISOR FOR THE CONFERENCE:  
NATIONAL DOWN SYNDROME SOCIETY –NDSS- NEW YORK -USA

With the support of:  
Departament de Sanitat Generalitat de Catalunya

**friday, March 18, 2005**

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**MORNING SESSION**

- 08.30-09.15: Registration
- 09.15-13.00: PLENARY SESSION  
Chairperson: F. BALLESTA
- 09.15: Obstructive sleep apnea syndrome: should all children with Down syndrome be tested? Evaluation and treatment options  
S.R. SHOTT
- 10.00: Updating the health care guidelines for Down syndrome  
W. COHEN
- 10.30: The Down syndrome critical region is not critical for Down syndrome  
R.H. REEVES
- 11.00-11.30: Coffee break - poster view
- 11.30: Welcome and Opening Ceremony  
The Ceremony will be Presided by Hble. Mrs. Anna Simó, Minister of Social Welfare of the Catalan Government.
- IX Ramon Trias Fargas Award Presentation  
Presentation of the book "Síndrome de Down. Aspectos médicos actuales" Prof. M. CRUZ HERNANDEZ
- OPENING LECTURE  
Exploring the neurobiology of Down syndrome: new insights suggest new treatment strategies.  
W.C. MOBLEY
- 12.30: Oxidative stress markers in Down syndrome  
(IX Ramon Trias Fargas Award)  
A. CASADO
- 13.00-15.30: Lunch - poster view

**friday, March 18, 2005**

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**AFTERNOON SESSION**

15.30-18.30: Concurrent symposia

*auditorium 1*

A - CYTOGENETICS , EPIDEMIOLOGY AND HEALTH CARE

Chairperson: W. COHEN

15.30: Meiotic prophase features, pairing and recombination, in  
Down syndrome oocytes.  
M. GARCÍA

16.00: Cardiac problems on the Down syndrome during adult life  
Q. FERRER

16.30: Torticollis in Down syndrome.  
J. PUIG GALY

17.00-17.30: Break - poster view

17.30-19.00: Cytogenetics, Epidemiology and Health Care  
Free oral presentations

**friday, March 18, 2005**

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**AFTERNOON SESSION**

*auditorium 2*

**B - MOLECULAR STUDIES ON CHROMOSOME 21**

Chairperson: R. GONZÁLEZ

- 15.30: Characterization of the genes in the DSCR2 – SH3BGR region of chromosome 21.  
R. OLIVA
- 16.00: Phenotypic description and modeling of murine models overexpressing HSA 21 genes.  
JM. DELABAR
- 16.30: DYRK1a and neuronal alterations in murine models of Down syndrome  
X. ESTIVILL
- 17.00-17.30: Break - poster view
- 17.30-19.00: Molecular studies on chromosome 21  
Free oral presentations

**saturday, March 19, 2005**

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**MORNING SESSION**

09.00-13.00: Concurrent symposia

*auditorium 1*

C - CLINICAL ASPECTS

Chairperson: S.R. SHOTT

- 09.00: Updated growth charts for the spanish children with Down syndrome  
X. PASTOR
- 09.30: Complementary and alternative treatments for Down syndrome  
W. COHEN
- 10.00: External auditory canal size in DS. Relationship with ear pathology in children and adolescents.  
J. DOMÈNECH
- 10.30: Compensatory responses in the brains of adults with Down syndrome.  
E. HEAD
- 11.00-11.30: Coffee break - poster view
- 11.30-13.00: Clinical aspects  
Free oral presentations

**saturday, March 19, 2005**

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*auditorium 2*

D - MOLECULAR STUDIES OF DOWN SYNDROME

Chairperson: X. ESTIVILL

- 09.00: The cerebral cortex in Down syndrome murine models  
M. DIERSSEN
- 09.30: Foundations for therapy of neuronal deficits in Down  
syndrome  
R.H. REEVES
- 10.00: Protective effect of green tea on brain alterations in  
murine models overexpressing dyrk1a.  
JM. DELABAR
- 10.30: Gene expression profiles in Down syndrome and  
in mouse models  
M. SULTAN
- 11.00-11.30: Coffee break - poster view
- 11.30-13.00: Molecular studies of Down syndrome  
Free oral presentations

**saturday, March 19, 2005**

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**AFTERNOON SESSION**

15.00-16.30: Concurrent symposia

*auditorium 1*

C - CLINICAL ASPECTS

Panel on Alzheimer disease and Down syndrome

Chairperson: M. BOADA

Dementia and Down syndrome: neuropathological substrates of clinical variability.

LEVERENZ, JAMES B.

Cognitive and behavioural effects of donepezil in adults with dementia associated with Down syndrome

M. BOADA // M. BUENDÍA

*auditorium 2*

D - MOLECULAR STUDIES OF DOWN SYNDROME

Panel on toward understanding the molecular basis of Down syndrome

Chairperson: M. DIERSSEN

Members: JM. DELABAR      RH. REEVES  
                  J. ESTIVILL      M. SULTAN

16.30-17.00: Break - poster view

**saturday, March 19, 2005**

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*auditorium 1*

PLENARY SESSION

Chairperson: J. FLÓREZ

17.00-19.00:

17.00:

Behaviour and learning in the ts65dn mice, a model for Down syndrome: new contributions.

J. FLÓREZ

17.40:

The pyramidal neuron in cognition and mental retardation

R. BENAVIDES-PICCIONE

18.20:

Reducing oxidative damage and providing behavioural enrichment may promote successful aging in Down syndrome: evidence from a longitudinal study in a canine model of human aging.

E. HEAD

18.45:

Vitamin D supplements and exercise are related to the increase of mineral bone density in people with Down's syndrome.

(IX Ramon Trias Fargas Second Prize)

LL. ROSSELLÓ AUBACH

19.00:

CLOSURE

## **OFFICIAL SPEAKERS**

### **BENAVIDES-PICCIONE, RUTH**

I received my Doctoral degree from the Complutense University, Madrid in 2004. Since 1999, I have been working in the laboratory of Dr J. DeFelipe at the Cajal Institute on the microorganization of the cerebral cortex. My particular expertise lies at understanding the neurochemical and microanatomical characteristics of the human neocortex and other species using intracellular injections of Lucifer Yellow in fixed material. During this period, I have published 17 articles about this issue.

### **BOADA ROVIRA, MERCÈ**

Dr. Mercè Boada Rovira is Doctor of Medicine, Neurologist. She is Neurologist at the Neurology Service in Hospital General Universitari Vall d'Hebron and Medical Director at Fundació ACE. Institut Català de Neurociències Aplicades, Barcelona (Spain). Her activity in the area of cognitive and behavioral disturbances and in the planning care resources and services for people with dementia in Catalonia started in 1986, as well as her collaboration as a consultant with Catalan Institutions.

### **BUENDIA TORRAS, MAR**

Psychologist

Coordinator of Clinical Assay in Fundació ACE. Institut Català de Neurociències Aplicades. Barcelona.

### **CASADO, ÀNGELA**

Ph Doctor and Pharmaceutical Degree (Complutense University of Madrid). Staff Scientist of the Centre for Biological Investigation (CSIC) since 1972. Group Leader of Oxidative Stress Biomarkers and Aging Processes in the Department of Physiopathology and Human Molecular Genetics in CIB. Author of more than 100 scientific articles and conferences. Professor of Doctoral Courses. Member of 5 Scientific Societies. Rewarded with 8 academical or scientific prizes.

### **COHEN, WILLIAM I.**

Serves as Director of the Down Syndrome Center of Western Pennsylvania at Children's Hospital of Pittsburgh (USA). He holds the rank of Professor of Pediatrics and Psychiatry at the University of Pittsburgh School of Medicine. Together with Bonnie Patterson MD, he is co-founder and co-chair of the Down Syndrome Medical Interest Group (DSMIG US). He has edited the "Health Care Guidelines for Individuals with DS" since 1996.

### **DELABAR, JEAN MAURICE**

PhD, Directeur de recherches au CNRS, Directeur de l'EA 3508 Univ Paris7  
Membre du Conseil Scientifique des Sciences de la Vie au CNRS  
Coordinator of the EU program T21 targets (2002-2005)

Main research interests: genotype phenotype correlations in Down syndrome studies; murine models of DS; variability assessment at molecular and phenotype levels; design and assessment of protective strategies.

### **DIERSSEN, MARA**

MD PhD. Group Leader at the Center for Genomic Regulation, Barcelona (Spain). The overall goal of our research is the understanding of the genetic substrates regulating the expression of complex behavioral traits. We investigate specific links between cognitive impairments memory disorders in Down syndrome (Functional Genomics of Down syndrome) and neuromorphological and genetic deficits in mouse models of this disease. Funded by different agencies through competitive applications.

Publications at different journals as Progress in Neurobiology, Neurobiology Disease, Behavioural Neuroscience, Cerebral Cortex, etc. Winner of the Fundación Dr. A. Esteve, Research Award 1986-87, Jaime Blanco Award to the research on Down syndrome 2002, Ramón Trias Fargas Award to the research on Down syndrome 2003 and Jérôme Lejeune Foundation Award 2004.

### **DOMENECH, JOAN**

Juan Domènech – Associate Professor. Dept. of Otolaryngology, School of Medicine, University of Barcelona.

ENT specialist, Fundació Catalana Síndrome de Down, Barcelona.

Senior specialist, Dept. of ENT, Hospital Clínic of Barcelona, Spain.

### **ESTIVILL, XAVIER**

1979 Graduated in Medicine and Surgery, Universitat Autònoma de Barcelona (Spain).

1987 PhD in Medicine, Universitat Autònoma de Barcelona, (Spain).

1995 PhD in Genetics, University of London (United Kingdom).

1991-1997 Head of the Genetics Service, Hospital Clínic, Barcelona (Spain).

1991-2001 Head of the Genetics Department, Institut de Recerca Oncològica, Barcelona (Spain).

2001- Director of the Genes & Disease Program, Centre de Regulació Genòmica, and Associate Professor of the Pompeu Fabra University, Barcelona, (Spain).

### **FERRER, QUERALT**

Dr. Queral Ferrer is Pediatric Cardiologist and specialist at the Department of the Pediatric Cardiology and Congenital Cardiopathies of Hospital Materno-infantil at Vall d'Hebrón Hospital, Barcelona. She collaborates with the adolescent and adult Congenital Cardiopathies Unit in the same Department. Her head of the Department is Dr. Jaume Casaldàliga, Cardiologist of Fundació Catalana Síndrome de Down.

### **FLÓREZ, JESÚS**

M.D.,Ph.D., Professor of Pharmacology at the University of Cantabria, Scientific Advisor of Fundació Síndrome de Down de Cantabria, Editor of *Revista Síndrome de Down*, a quarterly publication on information and research in Down syndrome, and Deputy-Director of the Spanish Web site [www.down21.org](http://www.down21.org). He has edited several books on Down syndrome, and is the author of over two hundred articles and scientific papers on developmental disabilities.

### **GARCÍA, MONTSERRAT**

Obtained her PhD degree characterizing human meiotic prophase at 1989. Since then, the study of the meiotic prophase in mammalian female, particularly human, has been one of her lab research topics. Last published papers related to this field have served as a guide to characterize the pairing process, using bouquet topology, and the initiation of recombination in euploid and aneuploid human oocytes.

### **HEAD, ELIZABETH**

Received a Masters degree in Psychology and a Ph.D. in Neuroscience from the University of Toronto, Canada. She is currently an Assistant Professor in Residence at the University of California –Irvine in the Department of Neurology and the Institute for Brain Aging & Dementia.

### **LEVERENZ, JAMES**

Is an Associate Professor of Neurology and Psychiatry and Behavioral Sciences at the University of Washington in Seattle. He is also an investigator in the UW Alzheimer's Disease Research Center and Center on Human Development and Disability, and in the VA Mental Illness and Parkinson's Disease Research Centers. His research interests include the neuropathology of dementia and the neurobiology of stress.

### **MOBLEY, WILLIAM**

M.D., Ph.D., Director, Neurosciences Institute at Stanford. Founding Board member of DSRTF and Director of the Centre for Research and Treatment of Down Syndrome at Stanford University. Since 1997 Dr. Mobley has been the Chair of the Department of Neurology and Neurological Sciences at Stanford University and holds the John E. Cahill Family Endowed Chair. He also serves as co-Director of the Stanford Brain Research Institute. His laboratory studies the signaling biology of neurotrophic factors in the normal brain and in animal models of neurodegenerative disorders, such as Alzheimer's disease and Down syndrome.

### **OLIVA, RAFAEL**

Medical Doctor (MD; 1984) PhD (1986), Postdoctoral 1986-1989, Department Medical Biochemistry, Faculty of Medicine, University of Calgary (Canada). Postdoctoral (Staff Scientist), Human Genome Center. Lawrence Berkeley Laboratories, California, USA. 1989-1990. Presently Geneticist, Hospital Clínic from Barcelona, and Professor, Faculty of Medicine, Universitat de Barcelona. [www.ub.edu/humangen](http://www.ub.edu/humangen).

### **PASTOR, XAVIER**

Professor of Paediatrics at the University of Barcelona. Chief of the Information Systems at Hospital Clínic of Barcelona. Attending physician at the Paediatric Intensive Care Unit of the Hospital Clínic since 1985 and 1995. Medical Coordinator of the Down's Medical Center of the "Fundació Catalana Síndrome de Down" between 1988 and 1990.

**PUIG GALY, Javier MD.**

Licenciado en Medicina y Cirugía (Universidad de Zaragoza). Especialista en Medicina Familiar y Comunitaria (Universidad Autónoma de Barcelona). Especialista en Oftalmología (Universidad Autónoma de Barcelona). Doctor en Medicina (Universidad Autónoma de Barcelona). Médico adjunto del Departamento de Oftalmología del Hospital Universitario Valle de Hebrón.

**REEVES, ROGER H.**

Ph.D., Professor, Johns Hopkins Univ. Schl. of Medicine, Department of Physiology and McKusick-Nathans Institute for Genetic Medicine. Scientific Advisory Board, National Down Syndrome Society. Director, JHU Post-baccalaureate Research Education Program and Transgenic Core Facility.

**ROSSELLÓ AUBACH, LLUÍS**

graduated in Medicine for the Autonomous University of Barcelona, unit Vall Hebron. Specialist in Rhumatologie, formation in Hospital of Rheumatic Diseases of Barcelona. Doctor in Medicine and Surgery with qualification Cum Laude for University Lleida. Qualified in Health for the Institute of Health Carlos III Madrid. Associate doctor in the Department of Internal Medicine, Division of Rheumatology, Hospital Santa María Lleida.

**SHOTT, SALLY R.**

M.D. is a Pediatric Otolaryngologist at Children's Hospital Medical Center, Cincinnati, Ohio, USA and is a Professor in the Department of Otolaryngology – Head and Neck Surgery at the University of Cincinnati. A specialist on the ear, nose, and throat (ENT) problems seen in children with Down syndrome, she is conducting a 5 year longitudinal study following the ENT manifestations of Down syndrome in a group of 65 children. She is also investigating alternative surgical options for children and young adults with Down syndrome with sleep apnea.

**SULTAN, MARC**

Native French, I studied biochemistry at the "Université Louis Pasteur" in Strasbourg, where I received the master degree in 1999. Until 2001 I completed my military service as a Technical Aid Volunteer at the Oceanologic Center of the Pacific IFREMER in Tahiti, where I worked on the pathologies of black pearl oyster *Pinctada margaritifera*. Since 2001, I am in the final phase of my PhD in department of Hans Lehrach, under the direction of Marie-Laure Yaspo. Since February I am in charge of a novel EU funded project [Eurexpress], aimed at generating and analyzing gene expression pattern for 15,000 mouse gene by ISH.

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(IX Ramon Trias Fargas Award)  
A. CASADO

13.00-15.30: Lunch - poster view

**OBSTRUCTIVE SLEEP APNEA SYNDROME: SHOULD ALL CHILDREN WITH DOWN SYNDROME BE TESTED? EVALUATION AND TREATMENT OPTIONS.**

**Sally R. Shott, MD, Professor, Cincinnati Children's Hospital Medical Center, Department of Otolaryngology – Head and Neck Surgery, University of Cincinnati, USA**

Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati Ohio 45229 USA. Sally.Shott@cchmc.org

Although most children with obstructive sleep apnea (OSA) are successfully treated with removal of the tonsils and adenoids (T&A), this is not always the case, especially in children with Down syndrome. This lecture will review the current data concerning the incidence of sleep apnea in Down syndrome, including results of a study investigating the incidence of OSA in a group of 3-4 year old children with DS. Current information on the effects of sleep disturbed breathing on school performance, growth rate, and behavior is presented. Evaluation of sleep apnea with a polysomnogram or sleep study is discussed with particular emphasis on how the pediatric sleep study differs from the adult sleep study. Appropriate timing of when to do a sleep study is discussed. Specific terms such as apnea, hypopnea, obstructive index, respiratory disturbance index, arousals and hypoventilation syndrome will be defined and discussed.

Our protocol for evaluating the causes of persistent OSA despite previous T&A will be reviewed. This includes the use of the cine MRI and a Sleep Team approach. Specific data on the various causes of persistent obstruction despite previous T&A will be presented. In addition to medical options, specific "site of obstruction" surgery will be presented including uvulopalatopharyngoplasty, lingual tonsillectomy, various techniques for tongue reduction, both radiofrequency reduction and surgical reduction, genioglossus advancement, palatal advancement as well as mandibular advancement surgery.

## **UPDATING THE HEALTH CARE GUIDELINES FOR DOWN SYNDROME**

### **William I Cohen MD**

Down Syndrome Center/Children's Hospital, 3705 Fifth Avenue, Pittsburgh PA 15213-2583 USA.

Many national organizations have developed guidelines for preventive healthcare for individuals with Down syndrome (DS). This presentation will discuss the history and evolution of the US guidelines through the most recent revision in 1999. These guidelines were coordinated with those published in 2001 by the Committee on Genetics of the American Academy of Pediatrics (AAP). The guidelines are currently under revision with expected publication late in 2005 and once again, members of the Down Syndrome Medical Interest Group (DSMIG) US will serve as consultants to the AAP. This presentation will discuss the anticipated changes and those areas of DS health care which need further refinement.

## THE DOWN SYNDROME CRITICAL REGION IS NOT CRITICAL FOR DOWN SYNDROME

L.E. Olson<sup>1,2</sup>, J. Leszl<sup>3</sup>, J.T. Richtsmeier<sup>3</sup>, and R.H. Reeves<sup>1</sup>,

<sup>1</sup>Johns Hopkins University School of Medicine, Baltimore, MD; <sup>2</sup>University of Redlands, CA; <sup>3</sup>Penn State University, State College, PA

Trisomy 21 is among the most complex genetic disorders compatible with human survival. Several major features of Down syndrome (DS) are posited to be caused by trisomy of a small subset of chromosome 21 genes located in a “Down syndrome critical region” (DSCR). The DSCR is defined as the smallest region of overlap between rare individuals who have segmental trisomy 21 and share a given feature of Down syndrome. Although the DSCR concept has dominated the field of DS research for four decades, to date there has been no method for definitive testing of this idea.

Among the features mapped to the DSCR are short stature, protruding tongue, facial dysmorphology related to the craniofacial skeleton, and mental retardation of the “DS type.” Ts65Dn mice have segmental trisomy for the region corresponding to the DSCR plus an additional ~70 genes. These mice have small stature. Quantitative morphological assessment demonstrates anomalies of the craniofacial skeleton, skull and mandible with direct parallels to DS. We used chromosome engineering to create a duplication and deletion of the mouse chromosome 16 segment orthologous to the DSCR. Mice with three copies of the DSCR do not display the craniofacial anomalies seen in Ts65Dn and in DS as predicted, and do have a mild but completely distinct dysmorphology. In contrast, mice trisomic for all of the Ts65Dn segment except the DSCR exhibit a craniofacial phenotype similar to Ts65Dn. These results are contrary to the simplistic predictions of both the DSCR hypothesis and the amplified genetic instability hypothesis, indicating that a new and more sophisticated basis is needed to understand the global effects of trisomy on development.

## **EXPLORING THE NEUROBIOLOGY OF DOWN SYNDROME: NEW INSIGHTS SUGGEST NEW TREATMENT STRATEGIES.**

**A. Salehi, J.D. Delcroix, P. Belichenko, A. Kleschevnikov, C.B. Wu, K. Zhan, J.S. Valletta, K. Sambamurti, W. Xia, R.A. Nixon, B.T. Lamb, C. J. Epstein, L.S.B. Goldstein, W.C. Mobley**

Stanford University School of Medicine, Department of Neurology and Neurological Sciences, 1201 Welch Road, Stanford, CA 94305

Cognitive deficits are present throughout the lifespan of individuals with Down syndrome (DS) and all show the neuropathology of Alzheimer's disease (AD) by age 40. Though few studies address brain structure and function in DS, existing data point to abnormal synapse structure and function. To explore the neurobiology of DS, we studied the Ts65Dn mouse, which is trisomic for the segment of mouse chromosome 16 (Ts65Dn) that contains genes homologous to those on human chromosome 21. Ts65Dn mice show both developmental and age-related changes in brain function; the latter includes age-related atrophy and apparent loss of basal forebrain cholinergic neurons (BFCNs) which is also found in elderly adults with DS and in AD patients. We are testing the hypothesis that specific genes, present in an extra copy, are responsible for cognitive changes in DS. Comparing Ts65Dn and 2N (i.e. control) mice, we found marked changes in both the structure and function of hippocampal synapses. There were widespread changes in size and shape of pre- and postsynaptic elements and in the pattern of innervation of GABAergic inputs. The changes were evident by the end of the development period and extended into old age. Complementing these findings, LTP was absent in the dentate gyrus and this change was due to excessive inhibition of dentate granule cells by GABAergic neurons. Finally, we explored further the cause of the degeneration of basal forebrain cholinergic neurons, showing that this is due to failed retrograde transport of the neurotrophic factor NGF. Ongoing studies point to a specific gene as both necessary and sufficient for interruption of NGF transport. We will discuss this work and suggest how through future studies it should be possible to better understand the neurobiology of DS and, eventually, to define effective treatments.

## OXIDATIVE STRESS MARKERS IN DOWN SYNDROME

**Ángela Casado, M<sup>a</sup> Encarnación López-Fernández and Rocío Ruíz**

Dra. Ángela Casado. Departamento de Fisiopatología y Genética Molecular Humana. Centro de Investigaciones Biológicas. Consejo Superior de Investigaciones Científicas (CSIC).

c/ Ramiro de Maeztu, 9 28040 MADRID (España)

**Background:** Down's syndrome (DS), a genetic abnormality associated with the presence of three copies of chromosome 21, is one of the most important human congenital diseases. There is evidence showing that individuals with DS are under unusual oxidative stress. Oxidative stress may result from excess of the enzyme Cu/Zn superoxide dismutase (Cu/ZnSOD) that is encoded by a gene located on chromosomal region 21q22.1. This overexpression of the Cu/ZnSOD gene may disturb the steady-state equilibrium of active oxygen species within the cells resulting in oxidative damage to biologically important molecules.

**Objective:** We analysed activities of Cu/ZnSOD, catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR), which form the main enzyme protection mechanism against harmful effects of reactive oxygen species, and the levels of malondialdehyde (MDA), an end product of lipid peroxidation, in order to develop a better knowledge of a new aspect in this syndrome's pathology.

**Material and Methods:** 100 individuals with DS, aged from newborns to 29 years (34 males and 66 females) were analysed: 90 individuals with regular trisomy 21, 4 with trisomy 21 by Robertsonian translocation and 6 with mosaic trisomy 21. A group of individuals without pathology was also included (40 males, 60 females) with similar ages to the DS individuals. In all cases we determined: 1) antioxidant enzymes activity: SOD, CAT, GPx and GR, 2) levels of MDA.

**Results:** We observed: a) an increase in the oxidative stress in DS individuals caused by an excess in Cu/Zn SOD, which they try to compensate mainly by increasing the activity of GPx and CAT; b) high levels of lipid peroxidation; c) no significant differences between male and female in DS individuals; d) lower oxidative stress in individuals with mosaic.

**Conclusions:** Trisomic cells are more sensitive to oxidative stress. This sensitivity could be caused by an imbalance in the hydrogen peroxide metabolism.

This Research Project was supported by grants of Fundación Inocente, Inocente

**friday, March 18, 2005**

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**AFTERNOON SESSION**

*auditorium 1*

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Chairperson: W. COHEN

- 15.30: Meiotic prophase features, pairing and recombination, in Down syndrome oocytes.  
M. GARCÍA
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Free oral presentations

**CHANGING LIVES: DOWN SYNDROME & THE HEALTH CARE PROFESSIONAL PROGRAM**

Lack Andrea

**CANADIAN REGISTRY ON DOWN SYNDROME: PARENT RESPONSES TO ADHERENCE OF THE HEALTH CARE GUIDELINES**

A. Eichmann, N. Virji-Babul, D. Kisly.

**IDENTIFICATION OF COUPLES AT RISK FOR DOWN SYNDROME OFFSPRING.**

Giuseppe Latini 1,2, Claudio De Felice 3, Stefano Parrini 4, Giovanna Chitano5,6, and Alberto Verrotti 7.

**LONG-TERM EFFECTS OF THE PALATAL PLATE THERAPY IN CHILDREN WITH DOWN SYNDROME WITH SPECIAL FOCUS ON PRIMARY AND SECONDARY PATHOLOGIES**

Korbmacher Heike

**HEALTHY EATING, AESTHETICS AND IMAGE IN DOWN SYNDROME PEOPLE**

Garvía Beatriz, Gutiérrez Alejandra

## **MEIOTIC PROPHASE FEATURES, PAIRING AND RECOMBINATION, IN DOWN SYNDROME OOCYTES.**

**P. Robles, I. Roig, R. Garcia, A. Ortega, J. Egozcue and M. Garcia**

Unitat de Biologia Cel·lular i Genètica Mèdica  
Facultat de Medicina, Universitat Autònoma de Barcelona  
08193-Bellaterra (Barcelona)-SPAIN

Trisomy 21 is the autosomal aneuploidy responsible for over 95% of Down syndrome. The origin of the extra chromosome 21 results from a maternal non-disjunction in meiosis I in 75.4% of cases. The most characteristic meiotic process such as sister chromatide cohesion, homologue pairing, recombination and cell cycle control, occur during prophase, so a failure in some of these may lead to a meiotic error or delay. Taking this fact into account, we have studied the pairing and recombinational process in trisomic 21 and euploid oocytes, applying immunofluorescence and fluorescent "in situ" hybridization techniques.

As bouquet topology promotes homologue encounters, bouquet proportion in trisomic 21 oocytes was analyzed. Similarly to trisomy 18, a statistically longer bouquet was found in trisomic 21 oocytes as compared to euploid data. This fact is supported by finding a pachytene bouquet topology frequency significantly different in trisomic 21 compared to euploid oocytes.

Analysis of the chromosome 21 pairing process is another goal of the present study. In this sense the obtained results indicate inter-sample variability in achieving trivalent conformation (ranging from 40% to 75% depending on the case studied).

According to preliminary results, these observed differences between euploid and aneuploid oocytes would fit with the existence of a distinct recombination process, as analyzed by  $\gamma$ -H2AX foci at pachytene.

## **CARDIAC PROBLEMS ON THE DOWN SYNDROME DURING ADULT LIFE**

**Ferrer Q, Casaldàliga J, Escobar MC, Sánchez C, Albert DC, Girona J.**

Unidad de Cardiología Pediátrica del Hospital Materno-Infantil del Vall d'Hebron.

Is well known the high incidence of congenital heart defects on Down Syndrome. Based upon our experience on dealing with Down syndrome patients affected by heart problems, we can say the main request for attention during adult life is the follow up of congenital cardiac disease.

Nowadays the majority of these patients underwent corrective cardiac surgery in their first months of life, with optimal outcome. In some cases residual defects can be found, being mitral regurgitation the most frequent sequel after the repair of an Atrioventricular defect, that need medical control and occasionally redo procedure.

Unfortunately we still see patients with a congenital heart defect that was not repaired or it was operated on too late, and pulmonary vascular disease secondary to unrepaired cardiac defect (Eissenmenger syndrome) is found. Although those cases are getting less frequent, they are the ones with worst quality of life.

We also have detected a progressive aortic and mitral insufficiency in individuals with Down syndrome without congenital cardiac disease. We have found a higher rate of aortic regurgitation than mitral insufficiency (36%,15% respectively), opposite of published data. Although most of these patients are asymptomatic, prophylaxis for bacterial endocarditis is mandatory.

## **TORTICOLLIS IN DOWN SYNDROME.**

**Puig Galy, Javier; Galán Terraza, Alicia; Wert Espinosa, Ana; Santos Blanco, Esther; Maciá Badía, Carmen.**

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**PURPOSE:** To ascertain the prevalence of torticollis in patients with Down syndrome.

**METHODS:** 760 patients with confirmed Down syndrome underwent complete ophthalmologic examination, which included refraction, ocular motility and head position.

**RESULTS:** Torticollis was present in 75 patients (9,86 %). 80 % of them were found to have an up or toward a shoulder head tilt. In 22 patients (29,33 %) no ocular reason for the abnormal head position could be identified. The most common ocular etiologies were unilateral fourth nerve palsy and nistagmus.

**CONCLUSIONS:** Abnormal head positions are more common in patients with Down syndrome than in general population. Some of them seem to have no ocular etiology. Superior oblique muscle paresis has been the most common ocular reason for torticollis in our group of patients.

## **SPOKEN PRESENTATIONS**

N° A-1Sp

### **CHANGING LIVES: DOWN SYNDROME & THE HEALTH CARE PROFESSIONAL PROGRAM**

**Lack Andrea**

National Down Syndrome Society 666 Broadway, 8th Floor New York, NY 10012.

Changing Lives: Down Syndrome & the Health Care Professional is a program designed by the National Down Syndrome Society to educate health care professionals on the medical and developmental needs of people with Down syndrome and best-care practices to address them; prepare professionals to deliver diagnoses and other sensitive information; provide information on local and national resources; supply materials and information for new and expectant parents; and foster on-going relationships between professionals and parents. Program materials include a training manual with step-by-step instructions to implement the program; two copies, health care professional videos with brochures; two copies, new parent videos with brochures; sample health care professional information portfolio; Down Syndrome Health Care Guidelines and access to customizable materials on-line. Accurate, up-to-date information about Down syndrome is a key factor that contributes to the health and well-being of people with Down syndrome and their families. The challenge is getting this information into the hands of those who need it most – new and expectant parents and the health care professionals who work with them. The NDSS Changing Lives program helps achieve this.

N° A-2 Sp

### **CANADIAN REGISTRY ON DOWN SYNDROME: PARENT RESPONSES TO ADHERENCE OF THE HEALTH CARE GUIDELINES**

A. Eichmann, N. Virji-Babul, D. Kisly.

Down Syndrome Research Foundation. British Columbia. Canada.

The Down Syndrome Research Foundation established the Canadian voluntary registry on Down syndrome in 2000 to document medical and health related conditions and concerns for individuals with DS and their families. In August 2004, we incorporated an additional survey to examine the adherence of the Health Care Guidelines established for Down syndrome. We observed that less than 30 % of children between the ages of 1-12 years are referred for behavioural auditory testing. Less than 20% of children between the ages of 1-4 years are screened for celiac disease. Thyroid function tests were conducted in approximately 70% of children and adolescents. However, less than 50% of adults were referred for this test. In general, parents reported that discussion of health issues such as diet, exercise, sexual education, behaviour and sleep difficulties were infrequently discussed with their physicians (less than 30%). In the adult age group, only 10% of women reportedly had a pap smear, pelvic exam or mammogram and only 14% of individuals over the age of 40 were referred to a neurologist. The implications of these results on the use and promotion of the Health Care Guidelines as well as the health of individuals with DS will be discussed.

N° A-3Sp

### **IDENTIFICATION OF COUPLES AT RISK FOR DOWN SYNDROME OFFSPRING.**

Giuseppe Latini 1,2, Claudio De Felice 3, Stefano Parrini 4, Giovanna Chitano<sup>5,6</sup>, and Alberto Verrotti 7.

**1** Division of Neonatology, Ospedale Perrino, Brindisi; **2** Clinical Physiology Institute, National Research Council of Italy, (IFC-CNR), Lecce Section, Italy; **3** Neonatal Intensive Care Unit, Azienda Ospedaliera Universitaria Senese, Siena; **4** Department of Odontostomatological Sciences, University of Siena, Siena; **5** University of Pisa; **6** Euro Mediterranean Scientific Biomedical Institute (ISBEM), Brindisi; **7** Department of Medicine, Division of Pediatrics, University of Chieti, Italy.

"The full acceptance of a baby with Down syndrome (DS) from the family is fundamental to attain his/her full potential. Therefore, a prenatal diagnosis is important not only for making a decision about interruption of the pregnancy, but also in helping those parents wishing to complete a DS pregnancy in receiving adequate support (1). In particular, a preconceptional identification of couples at risk for DS offspring would be highly advisable (2). Recently, we have examined the potential value of both oral mucosal microvascular network analysis (3) and spectrophotometry (4) in identifying parents at risk for DS offspring. Our preliminary results indicate 100% sensitivity and specificity. Although these data are going to be verified in larger and unselected population recruited in a prospective way, our preliminary findings suggests that vascular network and/or spectrophotometric analyses on the oral mucosa may represent new and non invasive complementary tools in the antenatal screening of DS offspring.

REFERENCES: 1.Latini G. Acta Paediatr. 2002;91:1291-3. 2.Latini G, et al, BMJ Published online 13 Oct 2004. 3.Latini G, et al, Pediatr Res 2003;54:562 4.Latini G, et al, Prenat Diagn. 2004;24:685-7.

N° A-4 Sp

### **LONG-TERM EFFECTS OF THE PALATAL PLATE THERAPY IN CHILDREN WITH DOWN SYNDROME WITH SPECIAL FOCUS ON PRIMARY AND SECONDARY PATHOLOGIES.**

H Korbmacher 1, J Limbrock 2, B Kahl-Nieke 1

1 Department of Orthodontics, University of Hamburg, College of Dentistry, Germany

2 Institute of Pediatric Medicine, University of Munich, Germany.

Introduction: Stimulating plate therapy aims at correcting the orofacial dysfunctions and at preventing the establishment of subsequent morphological characteristics. The purpose of the study was to investigate the effectiveness of this type of therapy in improving functional and skeletal traits in the long-term. Material and Methods: 27 juveniles with Down syndrome, whose orofacial dysfunctions had been successfully treated with a stimulating plate according to Castillo Morales in their infancy, were examined more than 12 years after initiation of treatment. In all patients the orofacial status has been evaluated. In 22 patients a lateral cephalogram was obtained. A parents-questionnaire completed the investigation. Results: The long-term orofacial development depends on the extend of orofacial symptoms in early childhood: Children with a pronounced orofacial dysfunction showed a greater stimulation-plate-induced improvement than those with initially moderate findings. The cephalometric results indicated a slight enhancement of the growth of the cranial base and maxilla but also a significant impact on the growth of the mandible. The anomaly-typical bialveolar protrusion of the anterior teeth could not be corrected. Conclusion: In children with severe orofacial dysfunctions stimulating plate therapy can significantly improve the long-term development. In children with a skeletal Class III pattern and minor orofacial findings this therapy approach may not always be indicated.

Nº A-5 Sp

## **HEALTHY EATING, AESTHETICS AND IMAGE IN DOWN SYNDROME PEOPLE**

Garvía Beatriz, Gutiérrez Alejandra

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We present an introduction about the physical aspect, health and image in DS people. Nowadays, the image plays a very important role in the everyday life. The attributes and physical conditions that people are born with, determine their aspect. Subsequently, everyone grows up creating its own style, its own image, referring/identifying himself with one or another social model. Nevertheless, this subject has not been properly treated with respect, DS people belong to our society, and their image and respect, many times/frequently don't go according/adapt to its situation/to the situation they find themselves in. Why this happens? In people with DS the predetermined image dominating it's the disability, and as Montobbio says, "in the DS there isn't a model of aesthetics given, there isn't an identification with the group given, the others expect from you, disability and more childlike, and the disability is anaesthetic." People with disability should agree to the same models as we have, up to us to make it possible. In order not to feel excluded of the society, they should be able to access aesthetics and fashion as well as the rest of the society. On the other hand, we should not forget the theme of the health. We overprotect excessively our son or daughter with disability because his/her vulnerability. Weakness favours capricious and frustration, and we treat him or her differently than other children just because we think he is vulnerable. Sometimes it's difficult to deny food, even though the child likes it very much indeed. We find ourselves giving them diets, which damages health and aesthetics.

Each individual is unique, genetic, psychological and physically, different, and has unaccountable differences with everybody else. His particular character demands/requires a personalized attention in whole levels, especially in diet, according to the physiologic and evolutive moment of time/ situation going trough.

A good training in diet, will favour enormously the acquisition of a healthy eating habits, which not only will keep the nutritional balance but also will help his physical aspect in aesthetics and personal level.

**friday, March 18, 2005**

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*auditorium 2*

**B - MOLECULAR STUDIES ON CHROMOSOME 21**

Chairperson: R. GONZÁLEZ

- 15.30: Characterization of the genes in the DSCR2 – SH3BGR region of chromosome 21.  
R. OLIVA
- 16.00: Phenotypic description and modeling of murine models overexpressing hsa21 genes.  
JM. DELABAR
- 16.30: DYRK1a and neuronal alterations in murine models of Down syndrome  
X. ESTIVILL
- 17.00-17.30: Break - poster view
- 17.30-19.00: Molecular studies on chromosome 21  
Free oral presentations

**TRISOMY 21 CAUSED DEREGULATION OF NON-HSA21 GENES PERSISTS FROM UNDIFFERENTIATED ES CELL TO ADULTHOOD, IN MOUSE MODELS OF DOWN SYNDROME**

Claire Mulligan<sup>1</sup>, Afua Mensah<sup>1</sup>, Ingo Burtcher<sup>1</sup>, Juergen Groet<sup>1</sup>, Felix Schnappauf<sup>1</sup>, Sandra Ruf<sup>2</sup>, Aideen O'Doherty<sup>3</sup>, Diana Hernandez<sup>3</sup>, Janet Shipley<sup>4</sup>, Gareth Denyer<sup>5</sup>, Charles J. Epstein<sup>6</sup>, Victor Tybulewicz<sup>2</sup>, Elizabeth M Fisher<sup>3</sup> and Dean Nizetic<sup>1</sup>

**STUDYING GENE DOSAGE EFFECTS FOR GENES LOCATED IN *HRMT1L1-CSTB* REGION USING DELETION IN THE MOUSE**

V. Besson<sup>1</sup>, A. Duchon<sup>1</sup>, V. Brault<sup>1</sup>, L. Magnol<sup>1</sup>, J.-C. Bizot<sup>2</sup>, L. Dauphinot<sup>3</sup>, M.-C. Potier<sup>3</sup> and Y. Héroult<sup>1,4</sup>

**PHENOTYPIC ANALYSIS OF THE MONOSOMIC MODEL FOR THE TELOMERIC REGION *HRMT1L1-COL6A1* ASSOCIATED TO HUMAN CHROMOSOME 21**

V. Besson, V. Brault, A. Duchon, D. Togbe, V. Quesniaux and Y. Héroult

**SEQUENCING THE SHORT ARM OF HUMAN CHROMOSOME 21**

R. Lyle<sup>1</sup>, K. Osoegawa<sup>2</sup>, B. ten Hallers<sup>2</sup>, B. Zhu<sup>2</sup>, E. Eyra<sup>3</sup>, R. Castelo<sup>3</sup>, C. Bird<sup>4</sup>, M. Cruts<sup>5</sup>, S. Dahoun<sup>1</sup>, X. She<sup>6</sup>, C. van Broeckhoven<sup>5</sup>, E. Eichler<sup>6</sup>, R. Guigo<sup>3</sup>, J. Rogers<sup>4</sup>, P. de Jong<sup>2</sup>, S. E. Antonarakis<sup>1</sup>

**OVEREXPRESSION OF *FABP7* IN FETAL DOWN SYNDROME BRAINS IS ASSOCIATED WITH THE INCREASED ALLELIC DOSAGE OF PKNOX1 (21Q22.3)**

M<sup>a</sup> Francisca Sánchez-Font, Anna Bosch-Comas, Roser González-Duarte & Gemma Marfany

**SUPPRESSION OF NEURAL FATE OF PLURIPOTENT MOUSE EMBRYONIC STEM CELLS IN VIVO BY TRISOMY 21, USING A NOVEL EXPERIMENTAL SYSTEM OF TRANSCROMOSOMIC TERATOMAS**

Afua Mensah<sup>1</sup>, Claire Mulligan<sup>1</sup>, Jackie Linehan<sup>2</sup>, Sandra Ruf<sup>3</sup>, Aideen O'Doherty<sup>2</sup>, Diana Hernandez<sup>2</sup>, Beata Grygalewicz<sup>4</sup>, Janet Shipley<sup>4</sup>, Juergen Groet<sup>1</sup>, Victor Tybulewicz<sup>3</sup>, Elizabeth M Fisher<sup>2</sup>, Sebastian Brandner<sup>2</sup> and Dean Nizetic<sup>1</sup>

## **CHARACTERIZATION OF THE GENES IN THE DSCR2 – SH3BGR REGION OF CHROMOSOME 21.**

**Rafael Oliva, José Manuel Vidal-Taboada, and Verónica Ramos.**

Genetics Unit, Faculty of Medicine and Hospital Clínic, IDIBAPS, Casanova 143, 08036 Barcelona, Spain. roliva@ub.edu.

Our group started in 1994 an effort to map and to identify novel genes potentially present in the ETS2-HMG14 region of chromosome 21. Towards this goal high resolution maps and ordered clone libraries were initially generated and transcribed sequences were identified (Vidal-Taboada et al, 1998, BBRC 243, 572). Subsequently, several genes were isolated and characterized in detail. From the centromere to the telomere a total of 6 genes have been identified and located at present: DSCR2 (Vidal-Taboada et al., 1998, BBRC 250:547), WDR9 (Ramos et al., 2002, BBA 1577:377), HMG1 (Pash et al., 1990, PNAS 87:3836), WRB (Egeo et al., 1998, Hum Genet 102, 289-293), C21orf13 (Hattori et al., 2000, Nature 405:311), and SH3BGR (Vidal-Taboada et al., 1997, BBRC 241:321). The DSCR2 – SH3BGR region of chromosome 21 spans 350 Kb. The gene density (6 genes / 350Kb) turns out to be the average for that present in the human genome but higher than the gene density previously expected for this region. The expression pattern throughout the foetal development together with the correlation observed with the cell cycle indicates a possible function for the DSCR2 gene related to cell proliferation. At present, functional data is available for several genes in the region: DSCR2 (Vidal-Taboada et al., 2000, BBRC 272:156; Possik et al., 2004, Eur J Histochem. 48:267), WDR9 (Huang et al., 2003, Dev Dyn. 227:608), HMG1 (Birger et al., 2003, EMBO J. 22:1665), WRB (Wang et al. Am J., 2004, Physiol Heart Circ Physiol. PMID:15591095), and SH3BGR (Vidal-Taboada et al. in preparation). Several of these genes could be related to the pathogenesis and to some of the features present in Down syndrome. Supported by FCSD, EU-BIOMED2, Ministerio de Ciencia y Tecnología BMC2003-03937, fondos FEDER, Ministerio de Sanidad y Consumo V-2003-REDC07A-O and by Generalitat de Catalunya 2001SGR00382 to RO.

## PHENOTYPIC DESCRIPTION AND MODELING OF MURINE MODELS OVEREXPRESSING HSA21 GENES.

Chabert C<sup>1</sup>, Sébrié C<sup>2</sup>, Verger E<sup>1</sup>, Costantine M<sup>1</sup>, Rachidi M<sup>1</sup>, Lopes L<sup>1</sup>, Ledru A<sup>1</sup>, Paly E<sup>1</sup>, Herault Y<sup>3</sup>, Gillet B<sup>2</sup>, Delabar JM<sup>1</sup>

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Study of human partial trisomies has indicated that gene(s) from the DCR-1 region (CBR1-ERG on HSA21) should be involved in facial and hand features and in mental retardation observed in Down syndrome. Smith et al have constructed low copy number transgenic mice containing four different human yeast artificial chromosomes that together covered approximately 2Mb (ie 80%) of DCR-1. We carried out a neuropathological study of these transgenic lines and found that integration of two of these YACs, 230-E8 and 152-F7 caused morphogenetic changes: YAC 230-E8 mice showed an abnormal cerebellar folial pattern, a decrease in transverse diameter of the cerebellum and an increase in cortical cell density; YAC 152-F7 mice showed an increase in brain weight and a clear learning and motor impairment; the brain weight increase was further explored by using magnetic resonance imaging along animal development.

The volumetric measurements, which were done on a 7T/20cm horizontal MRI scanner (Varian) using an image-processing software (AMIRA), showed that a total volume increase (17% in adult mice), already observable at P7, corresponded to region specific changes with the strongest increase for the thalamus-hypothalamus region (more than 25%). Moreover in brains of 152F7 mice, Dyrk1a, a serine threonine kinase, as well as other genes carried by the YAC, was found overexpressed both at RNA and protein levels. One of the dyrk1a targets, the transcription factor fchr, showed an increased phosphorylation associated with increased levels of cyclin B1. These results suggest i/that the DCR-1 contains important genes involved in brain morphogenesis and neurogenesis ii/that the study of their overexpression might unravel new signaling pathways modified in DS iii/ that the study of their interactions with other HSA21 genes necessitates the construction of single gene models which are currently obtained by using a BAC technology.

## DYRK1A AND NEURONAL ALTERATIONS IN MURINE MODELS OF DOWN SYNDROME

**X. Estivill, E. Martí, M. Álvarez, S. Porta, M. Martínez, G. Arqué, A. Amador, C. Fillat, S. de la Luna, M.L. Arbonés, J. de Felipe, M. Dierssen**

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Down syndrome (DS) is the most common genetic cause of mental handicap, affecting 1 in 1,000 newborn children in Europe. Among the different HSA21 genes that could play a role in DS, DYRK1A has shown to confer many features that involve the CNS and the skeletal muscle systems. DYRK1A is a protein kinase that likely participates in different cellular processes and signal transduction pathways. DYRK1A belongs to a family of protein kinases known as DYRK (dual-specificity tyrosine-regulated kinases or dual-specificity yak-related kinases). The human *DYRK1A* gene is ubiquitously expressed in fetal and adult tissues with high-levels of expression in the brain, and it is overexpressed in DS fetal brains. Gene inactivation of *Dyrk1A* results in embryonic lethality of *Dyrk1A*<sup>-/-</sup> mice. *Dyrk1A*<sup>+/-</sup> mice shows reduced neonatal viability and general developmental delay. *Dyrk1A*<sup>+/-</sup> brains were reduced in size in a region-specific manner, displaying normal cytoarchitectonics in most areas. Reduced number of neurons was observed in mesencephalic regions, which exhibited a remarkable size decrease. Moreover, we observed an altered pyramidal neuron phenotype, characterized by smaller size of the dendritic arbors with reduced number of spines. The neuroanatomical alterations of *Dyrk1A*<sup>+/-</sup> mice lead to abnormal behavioural patterns, indicating the involvement of DYRK1A in physiological aspects controlling motor activity and emotionality through an action on specific neurotransmitter systems. We have generated transgenic mice (TgDyrk1A) overexpressing the full-length cDNA of *Dyrk1A*. TgDyrk1A mice show altered motor skill acquisition and hyperactivity in the adulthood. TgDyrk1A mice show a significant impairment in spatial learning and cognitive flexibility, indicative of hippocampal and prefrontal cortex dysfunction, specifically related to reference memory. *Dyrk1A* haploinsufficiency results in a generalized increase of astroglial cells at some developmental stages. The identification of the pathways that regulate DYRK1A activity and expression should help to understand the participation of this protein in DS.

N° B-1 Sp

**TRISOMY 21 CAUSED DEREGLATION OF NON-HSA21 GENES PERSISTS FROM UNDIFFERENTIATED ES CELL TO ADULTHOOD, IN MOUSE MODELS OF DOWN SYNDROME.**

Claire Mulligan<sup>1</sup>, Afua Mensah<sup>1</sup>, Ingo Burtcher<sup>1</sup>, Juergen Groet<sup>1</sup>, Felix Schnappauf<sup>1</sup>, Sandra Ruf<sup>2</sup>, Aideen O'Doherty<sup>3</sup>, Diana Hernandez<sup>3</sup>, Janet Shipley<sup>4</sup>, Gareth Denyer<sup>5</sup>, Charles J. Epstein<sup>6</sup>, Victor Tybulewicz<sup>2</sup>, Elizabeth M Fisher<sup>3</sup> and Dean Nizetic<sup>1</sup>

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During development of foetuses with Down syndrome (DS), specific differentiation arrests have been described in neuronal and haematopoietic progenitor cell lineages. In order to study the molecular mechanisms underlying these phenotypes, a transchromosomal mouse embryonic stem (ES) cell line was previously generated which contained a freely segregating copy of human chromosome 21. We now report the use of Affymetrix MG-U74Av2 microarrays to elucidate the effect of supernumerary HSA21 on the remainder of the mouse transcriptome in this model. Four independent outgrowths each of the transchromosomal ES cell line (47-1) and its parental control (D3) were compared. Unsupervised clustering successfully segregated the two cell lines, implying a profound effect of HSA21 on the remainder of the transcriptome, even at the level of pluripotent, undifferentiated ES cells. A search for significantly altered transcripts yielded 107 increased and 8 decreased genes. A number of genes were verified in the original ES cells by quantitative RT-PCR. Among these, Retinoic Acid Inactivating 1 (CYP26A1, upregulated) and Neuron-Restrictive Silencing Factor (REST, downregulated) were further verified in adult tissues from two different mouse models of DS. Interestingly, the reduction of REST pathway transcription has been independently observed in DS human fetal tissues. Persistent dysregulation of these genes is predicted to disturb embryonic development and neuronal differentiation.

N° B-2 Sp

**STUDYING GENE DOSAGE EFFECTS FOR GENES LOCATED IN *HRMT111-CSTB* REGION USING DELETION IN THE MOUSE**

V. Besson<sup>1</sup>, A. Duchon<sup>1</sup>, V. Brault<sup>1</sup>, L. Magnol<sup>1</sup>, J.-C. Bizot<sup>2</sup>, L. Dauphinot<sup>3</sup>, M.-C. Potier<sup>3</sup> and Y. Héroult<sup>1,4</sup>

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Human chromosome 21 (HSA21) is associated with two syndromes that depend upon gene-dosage balance: the Trisomy 21 (or Down syndrome) and the Monosomy 21. Both syndromes lead to different set of features affecting various organs like the skeleton, the heart, the gastrointestinal tract and the nervous system. In the mice, the homologous regions to HSA21 are found on three distinct chromosomes: 10 (MMU10), 16 (MMU16) and 17 (MMU17). The most commonly used model, Ts65Dn, corresponds to a subpart of MMU16 and displays some features of the Down syndrome, but does not resume the complete panel of alterations. So we develop mouse models for the telomeric HSA21 regions in order to establish a genotype-phenotype relationship. The corresponding models display a deletion (or a tandem duplication) of the homologous regions to HSA21 leading to the corresponding Monosomy (or Trisomy) in the mouse. In this meeting, we will present the preliminary analysis of mouse mutants carrying deletions of the *Hrmt111-Cstb* interval trying to show how these genetic configurations are helpful to locate genes with dosage effects homologous to the human chromosome 21 genes.

N° B-3 Sp

### **PHENOTYPIC ANALYSIS OF THE MONOSOMIC MODEL FOR THE TELOMERIC REGION *HRMT111-COL6A1* ASSOCIATED TO HUMAN CHROMOSOME 21**

V. Besson, V. Brault, A. Duchon, D. Togbe, V. Quesniaux and Y. Hérault

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Dosage imbalance of human chromosome 21 (HSA21) genes leads to physiological and morphological abnormalities in numerous organs of affected patients. In humans, the monosomy of chromosome 21 (M21) is a rare pathology associated to a very complex variable phenotype. Because the genetic analysis of this pathology is restricted in humans due to a few partial M21 patients, the use of animal models and particularly the mouse is necessary to determine the relationship between phenotype and genotype for this pathology.

The HSA21 homologous regions are localized on three chromosomes 10, 16 and 17, in the mouse. The more telomeric segment of the HSA21, that contains a large number of genes, is homologous to the region encompassed between *Hrmt111* and *Cstb* on chromosome 10. As no model of monosomy for this region exists in mice, we have chosen to study the *Hrmt111-Col6a1* region that contains 14 genes and spans 0,7Mb.

We developed a new model corresponding to a deletion of the *Hrmt111-Col6a1* homologous region by using chromosomal engineering strategies. During this meeting, we will present the characterisation of the mutant mice using a panel of phenotypic assay that unravel the presence of key genes with dosage effect.

N° B-4 Sp

### **SEQUENCING THE SHORT ARM OF HUMAN CHROMOSOME 21**

R. Lyle<sup>1</sup>, K. Osoegawa<sup>2</sup>, B. ten Hallers<sup>2</sup>, B. Zhu<sup>2</sup>, E. Eyras<sup>3</sup>, R. Castelo<sup>3</sup>, C. Bird<sup>4</sup>, M. Cruts<sup>5</sup>, S. Dahoun<sup>1</sup>, X. She<sup>6</sup>, C. van Broeckhoven<sup>5</sup>, E. Eichler<sup>6</sup>, R. Guigo<sup>3</sup>, J. Rogers<sup>4</sup>, P. de Jong<sup>2</sup>, S. E. Antonarakis<sup>1</sup>

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The sequence of the euchromatic portion of the human genome is essentially complete. However, large regions of the genome, comprising ~5-7% of the total, remain to be sequenced. These regions include the short arms of the acrocentric chromosomes (13, 14, 15, 21 and 22). The acrocentric chromosomes are of great interest as they are involved in many translocations causing human genetic disease. Human chromosome 21 has special significance because of its involvement in Down syndrome. The sequence of the short arm of Hsa21 (21p) is thus important not only DS, but an important step in the characterisation of these unexplored regions of the genome and toward the completion of the human genome project. We have constructed a BAC library containing human sequence from only Hsa21 and have generated approximately 1.3 Mb of new sequence from 21p (estimated to be 10-15% of the total), which shows that 21p contains regions which have the characteristics of euchromatic sequence. Gene prediction by EST and in silico based methods, followed by confirmation of ~30% gene models by rtPCR in 24 human tissues, indicates the presence of many expressed sequence on 21p.

Nº B-5 Sp

**OVEREXPRESSION OF *FABP7* IN FETAL DOWN SYNDROME BRAINS IS ASSOCIATED WITH THE INCREASED ALLELIC DOSAGE OF *PKNOX1* (21Q22.3)**

M<sup>a</sup> Francisca Sánchez-Font, Anna Bosch-Comas, Roser González-Duarte & Gemma Marfany

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Suppression Subtractive Hybridization (SSH) performed on Down Syndrome (DS) fetal brains revealed a differentially expressed gene, *FABP7*, mapped to 6q22-23. *FABP7* overexpression in DS brains was verified by real-time PCR (1.63-fold). To elucidate the molecular basis of *FABP7* overexpression and establish the relationship with chromosome 21 trisomy, the *FABP7* promoter was cloned by genomic inverse-PCR. Comparison to the mouse orthologue revealed conservation of reported regulatory elements, among them a Pbx/POU binding site known to be the target of PBX heteromeric complexes. PBX partners include homeobox-containing proteins, such as *PKNOX1* (*PREP1*), a transcription factor mapping at 21q22.3. We showed: i) over-expression of *PKNOX1* in DS fetal brains, ii) *in vitro* specific binding of *PKNOX1* to the Pbx/POU site of the *FABP7* promoter, and iii) *in vivo* *FABP7* promoter transactivation in cultured neuroblastoma cells caused by *PKNOX1* over-expression. To our knowledge this is one of the first reports of a direct relation between dosage imbalance of a chromosome 21 gene and altered expression of a downstream gene mapping on another chromosome. Given the role of *FABP7* in the establishment, development and maintenance of the CNS, our data suggest that the overexpression of *FABP7* could contribute to DS-associated neurological disorders.

Nº B-6 Sp

**SUPPRESSION OF NEURAL FATE OF PLURIPOTENT MOUSE EMBRYONIC STEM CELLS IN VIVO BY TRISOMY 21, USING A NOVEL EXPERIMENTAL SYSTEM OF TRANSCHROMOSOMIC TERATOMAS.**

Afua Mensah<sup>1</sup>, Claire Mulligan<sup>1</sup>, Jackie Linehan<sup>2</sup>, Sandra Ruf<sup>3</sup>, Aideen O'Doherty<sup>2</sup>, Diana Hernandez<sup>2</sup>, Beata Grygalewicz<sup>4</sup>, Janet Shipley<sup>4</sup>, Juergen Groet<sup>1</sup>, Victor Tybulewicz<sup>3</sup>, Elizabeth M Fisher<sup>2</sup>, Sebastian Brandner<sup>2</sup> and Dean Nizetic<sup>1</sup>

**1** Centre for Haematology, Institute of Cell and Molecular Science, Barts & The London, Queen Mary's School of Medicine, University of London, Turner Street, London E1 2AD, UK. **2** Institute of Neurology, UCL, Queen Square, London WC1N 3BG, UK. **3** MRC-National Institute for Medical Research, Mill Hill, London NW7 1AA, UK. **4** The Institute of Cancer Research, Sutton, Surrey, SM2 5PT, UK.

During development of fetuses with Down syndrome (DS), specific differentiation arrests have been described in neuronal and haematopoietic progenitor cell lineages. In order to study the effects of trisomy 21 on the capacity of ES cells to proliferate, differentiate and form tumours *in vivo*, we have subcutaneously injected mouse pluripotent ES cells containing a single freely segregating supernumerary HSA21 into syngeneic mice, to generate transchromosomal teratomas. Transchromosomal cells and parental control cells were injected into opposite flanks of thirty mice in 3 independent experiments. When paired tumours from same animals were compared, transchromosomal tumours showed a three-fold lower percentage of neuroectodermal tissue, as well as significantly reduced mRNA levels for the neuron specific (*Tubb3*) and the glia specific (*Gfap*) genes. Three quarters of transchromosomal tumours also showed a lack of PCR amplification with multiple primers specific for HSA21, which were present in the ES cells at the point of injection, thus restricting a commonly retained segmental trisomy to <20% of HSA21 genes. In conclusion, we demonstrate for the first time in the study of trisomy 21 the use of an experimental system based on transchromosomal teratomas, capable of detecting reproducible differences on the cell and tissue level, relevant to some of the developmental phenotypes of DS. This system has the potential to easily dissect the gene dose contribution of small segments of HSA21 to the observed phenotypes.

**saturday, March 19, 2005**

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*auditorium 1*

C - CLINICAL ASPECTS

Chairperson: S.R. SHOTT

- 09.00: Updated growth charts for the spanish children with Down syndrome  
X. PASTOR
- 09.30: **Complementary and alternative treatments for Down syndrome**  
W. COHEN
- 10.00: External auditory canal size in DS. relationship with ear pathology in children and adolescents.  
J. DOMÈNECH
- 10.30: Compensatory responses in the brains of adults with Down syndrome.  
E. HEAD
- 11.00-11.30: Coffee break - poster view
- 11.30-13.00: Clinical aspects  
Free oral presentations

**INDEPENDENT GATA1 MUTATIONS IN TRANSIENT MYELOPROLIFERATIVE DISORDER (TMD) OF DOWN SYNDROME OCCUR IN CLONES AT DIFFERENT STAGES OF DIFFERENTIATION**

Jurgen Groet<sup>1</sup>, Monica Spinelli<sup>2</sup>, Anna Serra<sup>3</sup>, Claire Mulligan<sup>1</sup>, Suzanne McElwaine<sup>1</sup>, Finbarr E. Cotter<sup>1</sup>, Franca Dagna-Bricarelli<sup>4</sup>, Giuseppe Saglio<sup>3</sup>, Giuseppe Basso<sup>2</sup> and Dean Nizetic<sup>1</sup>

**PERCEPTUAL VISUAL PROCESSING IN CHILDREN WITH DOWN SYNDROME.**

N. Virji-Babul, E.Zhou, A. Kapur, K.Kerns, M. Shiffar

**COGNITIVE DECLINE IN DOWN SYNDROME; A 19 YEAR FOLLOW-UP OF 92 SUBJECTS**

Moore PB, Lana ML, Kay DWK, Perry RH, Morris C, Reid, BE, Berney TP & Tyrer SP.

**CRANIOFACIAL DEVELOPMENT IN CHILDREN WITH DOWN SYNDROME.**

Tobella Camps M.Luisa, Sanchez MA, Casal C, Sentis-Villalta J.

**SPEECH PERCEPTION IN DOWN SYNDROME CHILDREN IN THE FIRST YEAR OF LIFE.**

Rosana Maria Tristão and Maria Angela Feitosa.

## **UPDATED GROWTH CHARTS FOR THE SPANISH CHILDREN WITH DOWN SYNDROME**

**Xavier Pastor, Llorenç Quinto, M. Hernández, M. Corretger, R. Gassió and Agustí Serés**

Xavier Pastor, MD, PhD. Information Systems. Hospital Clínic. Villarroel, 170. 08036 Barcelona.

The Fundació Catalana Síndrome de Down, published in 1998 the first growth charts based on data collected from children with Down syndrome born in our country. The updated charts are made using a more specific statistical approach that makes these charts more accurate and precise. There are also more measurements included, taken since then. The sample has excluded patients with associated conditions that can interfere with growth like hypothyroidism, celiac disease or congenital heart disease. A total of 1.736 measurements have been used to build the charts from birth to 15 years old; 18 wrong measurements were rejected. From the remaining 1718 measurements, 763 (44,4%) were in females and 955 (55,6%) in males. The data management and analysis has been done with the STATA<sup>®</sup> statistical package. Several statistical models have been tested: linear regression, fractional polynomials with maximum likelihood and the Box-Tidwell model estimation. The Bayesian Information Criterion has been the statistic used to compare all the possible models and select the best one. The analysis showed that length and height follow a similar pattern in boys and girls with a maximum difference in the adolescence. There is a great variability with the weight, where the dispersion increases with age, specially since school age. Finally a graphical comparison is done with the current reference charts of the Spanish paediatric population.

## **COMPLEMENTARY AND ALTERNATIVE TREATMENTS FOR DOWN SYNDROME**

### **William I Cohen MD**

Down Syndrome Center/Children's Hospital, 3705 Fifth Avenue, Pittsburgh PA 15213-2583 USA.

This presentation will survey the popular complementary and alternative treatments suggested for Down syndrome. The discussion will examine the evidence to support the claim for effectiveness. Dr Cohen will discuss the differences of opinions that often arise between physicians and families when thinking about employing these treatments, and offer practical suggestions to both.

## **EXTERNAL AUDITORY CANAL SIZE IN DS. RELATIONSHIP WITH EAR PATHOLOGY IN CHILDREN AND ADOLESCENTS.**

**Juan Domènech MD, PhD, Miguel Caballero MD, PhD, and Marta Carulla MD.**

Hospital Clínic de Barcelona. Dept. of Otolaryngology. Villarroel 170, 08036 Barcelona, Spain.

The external ear (pinna and external auditory canal, EAC) are characteristic traits in Down's syndrome (DS), due to their small size. Although the size of the pinna has been measured in several age groups, the diameter of the EAC through growth and its relationship with several ear pathologic conditions is not completely documented. A prospective study was carried out to measure the size of the EAC in 624 children and adolescents with DS, with ages ranging from 8 months and 17 years. The diameter of the EAC was measured with calibrated ear specula and mean values were calculated for each age group. Furthermore, Eustachian tube function was assessed with tympanometry and the occurrence of several types of ear pathology (secretory otitis media, acute and chronic otitis media) and nasal discharge and/or obstruction was correlated with the size of the EAC. Results showed that there was a statistically significant relationship between the size of the EAC and the occurrence of Eustachian tube malfunction and secretory otitis media. This relationship was stronger in the younger age group (less than 5 years). A significant relationship was not found between EAC size and the occurrence of episodes of nasal discharge and/or nasal obstruction. We conclude that EAC size can be used in children and adolescents with DS to predict the probability of suffering Eustachian tube malfunction and secretory otitis media.

## **COMPENSATORY RESPONSES IN THE BRAINS OF ADULTS WITH DOWN SYNDROME.**

**Elizabeth Head, Richard J. Haier, Eric Doran, Ira T. Lott**

Department of Neurology, Institute for Brain Aging & Dementia, University of California, 1259 Gillespie NRF, Irvine, CA., 92697-4540

Aged individuals with Down syndrome (DS) develop senile plaques and neurofibrillary tangles (NFT) consistent with Alzheimer disease (AD) by the age of 40 years, prior to any recognizable clinical dementia. We hypothesized that prior to or in parallel with AD pathology, compensatory growth responses may occur in the brain. Archived brain tissues from 15 individuals ranging in age from 5 months to 67 years were studied using markers for growth responses. Experiments were conducted in sections from the hippocampus with the rationale that this region is vulnerable to AD pathology and also exhibits significant plasticity. The study used markers of normal and abnormal tau accumulation (phosphorylated tau (AT8, MC-1), tau-1 (N-terminal tau) that reflect both NFT pathology and also possible neuronal growth responses. Second, a series of markers for neuronal growth markers (BDNF, GAP-43, MAP-2) were used and compared with the extent and location of tau pathology. In middle-age (30-40 yrs), prior to entorhinal neuron loss, the earliest tau accumulation occurred in the dentate granule outer molecular layer (OML), which was consistent with both pathological and compensatory fetal tau expression. These events were followed at a later age, associated with entorhinal neuron loss, by an increase in GAP-43. Hilar neurons exhibiting a sprouting morphology were also noted. Age-dependent observations in the DS brain in this study parallel hippocampal compensatory responses described in entorhinal cortex lesion studies in rodents. Thus, compensatory growth responses may occur in DS prior to extensive AD pathology. These anatomical studies may also suggest a neurobiological substrate for observations in PET studies of hypermetabolism in the entorhinal cortex of middle-aged individuals with DS prior to the onset of dementia. Funding provided by ADRC P50 AG16573 (CWC), UCI MRDDRC 2P30HD28020-06 (ITL) and RO1 HD-37427 (RJH) from NICHD.

N° C-1 Sp

### **INDEPENDENT GATA1 MUTATIONS IN TRANSIENT MYELOPROLIFERATIVE DISORDER (TMD) OF DOWN SYNDROME OCCUR IN CLONES AT DIFFERENT STAGES OF DIFFERENTIATION**

Jurgen Groet<sup>1</sup>, Monica Spinelli<sup>2</sup>, Anna Serra<sup>3</sup>, Claire Mulligan<sup>1</sup>, Suzanne McElwaine<sup>1</sup>, Finbarr E. Cotter<sup>1</sup>, Franca Dagna-Bricarelli<sup>4</sup>, Giuseppe Saglio<sup>3</sup>, Giuseppe Basso<sup>2</sup> and Dean Nizetic<sup>1</sup>

**1** Centre for Haematology, Institute of Cell and Molecular Science, Barts and The London, Queen Mary's School of Medicine, University of London, Medical College Building, Turner Street, London E1 2AD, UK; **2** Italian National Association for Pediatric Haemato-Oncology (AIEOP), Department of Pediatrics, Faculty of Medicine, University of Padua, Italy; **3** San Luigi Hospital, Orbassano-Torino, Italy, **4** Laboratory of Human Genetics, Galliera Hospital, Genoa, Italy.

Recent reports show that multiple independent somatic GATA1 mutations can occur in the same Down Syndrome (DS) patient with Transient Myeloproliferative disorder (TMD). GATA1 mutations occur in fetal liver, but it is unclear in how narrow a time-window. If this window is very narrow, it would be expected that multiple, independent GATA1 mutation-containing clones in a same TMD patient would display a very similar stage of differentiation. We describe here a DS-TMD neonatal patient with blasts at different stages of differentiation, judged by the expression of the stem cell marker CD34. Interestingly, the blast populations differing in the presence of CD34, also differ in the GATA1 mutations. The CD34+, GATA1 expressing cells lacked a dup34bp mutation, whereas the CD34-, GATA1 expressing cells contained this mutation. Two other clonal expansions, containing an ins8bp and dup4bp mutations were detectable in both CD34+ and CD34- cells. In addition, the CD34+ cells differed from the CD34- cells in the complete elimination of any sequence of exon2 from their transcripts. The fact that we detect proliferating blasts at different stages of megakaryocyte differentiation bearing different GATA1 mutations, is most likely explained by the independent clones having a different differentiatonal stage at the time of acquisition of their respective GATA1 mutations.

N° C-2 Sp

### **PERCEPTUAL VISUAL PROCESSING IN CHILDREN WITH DOWN SYNDROME.**

N. Virji-Babul, E.Zhou, A. Kapur, K.Kerns, M. Shiffrar

Down Syndrome Research Foundation, University of Victoria, Rutgers University

Children with Down syndrome (DS) have specific perceptual deficits in tasks involving scanning of visual information, and attending and processing complex stimuli. The ability to process both motion and emotion cues is critical in developing an understanding of the physical and social world and is fundamental to cognitive development. We tested the ability of children with Down syndrome (mental age of 3-7 years) on a battery of tests using point light displays to 1) distinguish human motion from object motion, 2) discriminate four emotions (happiness, sadness, anger and fear) in dance forms of expressive body movements, and 3) differentiate between gaits of typical and atypical walkers. Performance was compared to a mental aged matched control group of children. Average accuracy scores for both groups were compared to chance performance. Our results show that children with DS performed significantly above chance in their ability to distinguish human from non-human motion as well as in recognizing expressive body movements. However, they showed significant impairments in their ability to distinguish typical from atypical walkers. The implications of these findings on visual-perceptual function will be discussed.

N° C-3 Sp

### **COGNITIVE DECLINE IN DOWN SYNDROME; A 19 YEAR FOLLOW-UP OF 92 SUBJECTS**

Moore PB, Lana ML, Kay DWK, Perry RH, Morris C, Reid BE, Berney TP & Tyrer SP.

Prudhoe Hospital. Northumberland & Dept. Psychiatry, University of Newcastle upon Tyne, UK

The Prudhoe Down Syndrome Cohort was examined originally in 1985 to study the natural history of Down Syndrome (DS). The cohort comprised all 92 subjects (M=63, F=29), resident in Prudhoe hospital, with an average age of 39 years who suffered severe learning disabilities. The first follow-up was completed in 2000. Members had either died (n=28) or had been resettled into the community (n=61), only two remained in hospital and one was lost to follow up. All subjects were tested using the Prudhoe Cognitive Function Test and the Adaptive Behaviour Scale part II. Mean performance improved slightly despite the passage of 15 years. Clinical investigation found that 23 out of 92 had suffered a dementia at or before follow up. The mean age of onset of dementia was 59.1+9.6 years and subjects on average survived 3.5+2.5 years. Neuropathological studies linked the dementia to the presence of neurofibrillary tangles. The apolipoprotein-#1108; profile of the cohort resembled that of a normal population. In 2004 a second follow-up was completed. 54 (m=37,f=17) of the cohort survived. Dementia had now developed in 35%. The mean age at death of demented patients was 58.3 years. Survival curves will be presented.

N° C-4 Sp

### **CRANIOFACIAL DEVELOPMENT IN CHILDREN WITH DOWN SYNDROME.**

Tobella Camps M.Luisa, Sanchez MA, Casal C , Sentis-Villalta J.

Departamento de ortodoncia y odontopediatria Hospital Sant Joan de Deu passeig Sant Joan de Deu,2 Esplugues de Llobregat Barcelona [ltobella@hsjdbcn.org](mailto:ltobella@hsjdbcn.org)

**Objective:** To analyze the morphology and development of the craniomaxillofacial area in patients with trisomy 21.

**Study design:** Retrospective study **Material and Methods:** The study is based on lateral cephalometric radiographs of 33 children with Down syndrome (average age: 12 years) and 43 controls (average age: 12 years) seen in the dentistry and orthodontia service of the Hospital Universitari Sant Joan de Déu, Barcelona, between 1987 and 2000. The following 8 angle measurements and four linear measurements were analyzed . The SPSS statistical package was used to analyze the data . The Student t test was used to compare the two groups (p<.05).

**Results:** In the study group the following 3 angular variables were found to be lower than in the control group, and the following 2 angular variables were found to be increased . In the study group all linear variables were found to be lower than in the control group.

**Conclusion:** In the study group, higher NSBa angle values account for the flattening and position of the base of the skull. A length deficit in the maxilla and mandible was observed. Brachycephalic development was indicated by higher values for the facial axis and mandibular arch, and lower values for face height and mandibular plane.

Nº C-5 Sp

**SPEECH PERCEPTION IN DOWN SYNDROME CHILDREN IN THE FIRST YEAR OF LIFE.**

Rosana Maria Tristão and Maria Angela Feitosa

UNIVERSIDADE DE BRASÍLIA - Brazil, Psychology Institute – Psychobiology Laboratory.

Infants with Down syndrome (DS) are at high-risk for retarded global development, in special for expressive language, related to early hearing disorders, and also to altered processes of perception and learning of speech. The speech perception ability in DS infants measured using psychophysical methods was investigated. The habituation paradigm for non sense disyllabic words was used to test the babies' ability to perceive changes in the speech stimulus. Methodological specific implementations were created using two methods, the visual habituation and the observer-based response procedures. A software, HAFA, was developed. The global and language development was evaluated by the Bayley Scales to investigate the relation between development and speech perception. The participants were 12 DS babies, three to twelve months old, matched by age to control non retarded babies. The DS group showed similar development at the first semester of age, but in the second semester the indexes were significantly lower than the control group. The groups showed tendencies to specific profiles of habituation and deshabituation. The two groups also showed discrimination ability between familiar and new stimuli, although they did not reach the criterion for categorical perception. Tendencies for specific profiles of responses and methodological improvements are discussed.

This paper has been possible thanks to a grant of "FINATEC".

**saturday, March 19, 2005**

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*auditorium 2*

**D - MOLECULAR STUDIES OF DOWN SYNDROME**

Chairperson: X. ESTIVILL

- 09.00:                   **The cerebral cortex in Down syndrome murine models**  
                                  **M. DIERSSEN**
- 09.30:                   **Foundations for therapy of neuronal deficits in Down**  
**syndrome**  
                                  **R.H. REEVES**
- 10.00:                   Protective effect of green tea on brain alterations in  
                                  murine models overexpressing dyrk1a.  
                                  **JM. DELABAR**
- 10.30:                   Gene expression profiles in Down syndrome and  
                                  in mouse models  
                                  **M. SULTAN**
- 11.00-11.30:           Coffee break - poster view
- 11.30-13.00:           Molecular studies of Down syndrome  
                                  Free oral presentations

**THE CEREBELLAR TRANSCRIPTOME DURING POSTNATAL DEVELOPMENT OF THE TS1CJE MOUSE, A SEGMENTAL TRISOMY MODEL FOR DOWN SYNDROME.**

M.-C. Potier(1), L. Dauphinot(1), R. Lyle(4), I. Rivals(3), M. Tran Dang(1), R.X. Moldrich(1), G. Golfier(1), L. Ettwiller(1), K. Toyama(2), J. Rossier(1), L. Personnaz(3), S.E. Antonarakis(4), C. J. Epstein(5), P.-M. Sinet(2).

**DYRK1A GENE DOSAGE IS CRITICAL FOR THE CORRECT MORPHOGENESIS OF MOUSE RETINA**

Laguna A, Ledru A, Delabar JM and Arbonés ML

**TGDYRK1A MICE SHOW Deregulation in the expression of the NMDA RECEPTOR SUBUNITS**

J. Ortiz Abalia1, X. Altafaj1, M.C. Poitier2, G. Golfier2, X. Estivill1, E. Martí1, C. Fillat1

**PERIPHERAL NERVE REGENERATION AFTER SCIATIC NERVE INJURY IS ALTERED IN HUMAN CUZN SOD1 TRANSGENIC MICE.**

1 J. London, 1M. Le Pécheur, 2W. Marcol, 2Lewin-kowalik J., 1E. Paly, 2K. Kotulska 1

**ANALYSIS OF NEURONAL DEVELOPMENT IN HUMAN DOWN SYNDROME NEURAL PRECURSOR CELLS.**

Anita Bhattacharyya and Clive Svendsen

## **THE CEREBRAL CORTEX IN DOWN SYNDROME MURINE MODELS**

**M. Dierssen, R. Benavides-Piccione, I. Ballesteros-Yáñez, M. Martínez de Lagrán, X. Estivill, J. DeFelipe and G. N. Elston**

Cajal Institute, 28002 Madrid, Spain

Program in Genes and Disease, Genomic Regulation Center, 08003 Barcelona, Spain

Down syndrome results in neuropathological alteration of cerebral cortex anatomy. However, the pathogenetic background of cortical irregularities is presently not known. The dual-specificity tyrosine-regulated kinase DYRK1A gene maps to the chromosomal segment HSA21q22.2 in the Down syndrome critical region (DSCR), and is believed to be involved in some neurological deficits of DS. It has been demonstrated previously that Dyrk1A has dosage-dependent effects on cognition and behaviour. In the present work we analysed the microstructure of cortical circuitry in Dyrk1A murine models and control littermates by intracellular injection of Lucifer Yellow in neurones in fixed cortical tissue. We found that pyramidal cells in Dyrk1A mice were considerably smaller, less branched and less spinous than those sampled from control littermates. These results suggest that Dyrk1A is involved in the determination of the size and complexity of pyramidal cells, and thus, in their capability to integrate information.

## FOUNDATIONS FOR THERAPY OF NEURONAL DEFICITS IN DOWN SYNDROME

**L.L. Baxter<sup>1,3</sup>, R.J. Roper<sup>1</sup>, N.G. Saran<sup>1</sup>, D.K. Klinedinst<sup>1</sup>, P. Beachy<sup>2</sup>, R.H. Reeves<sup>1,4</sup>**

<sup>1</sup>Department of Physiology and <sup>2</sup>HHMI and Department of Molecular Biology and Genetics, Johns Hopkins University School of Medicine, Baltimore, MD. <sup>3</sup>Current address National Human Genome Research Institute, NIH, Bethesda, MD.

Ts65Dn mice are trisomic for orthologs of about half of the genes on human chromosome 21 and display a number of developmental anomalies analogous to those in Down syndrome (DS). In particular, reduced size of the cerebellum of trisomic mice mimics the pathology seen in humans. We identified a granule cell deficit in the reduced cerebellum of Ts65Dn mice and showed that this reduction occurs in humans with trisomy 21. We then traced the first appearance of trisomy-induced morphological differences to a specific place, the external germinal layer of the cerebellum, and showed that although the number of granule cell precursors in this layer is normal at P0, the number of mitotic cells is significantly reduced. This results in significant reduction in the size and cellularity of the cerebellum by P6. Using in vivo and in vitro approaches, we demonstrated that a reduced response to the sonic hedgehog growth factor-induced mitogenic pathway underlies inadequate generation of granule cells. Although the response of trisomic granule cell precursors to sonic hedgehog is reduced, it is dose-dependent. These results identify a target for ameliorative interventions in a specific neuronal pathology of Down syndrome.

## **PROTECTIVE EFFECT OF GREEN TEA ON BRAIN ALTERATIONS IN MURINE MODELS OVEREXPRESSING DYRK1A.**

**Chabert C<sup>1</sup>, Sébrié C<sup>2</sup>, Arbones M<sup>3</sup>, Verger E<sup>1</sup>, Ledru A<sup>1</sup>, Paly E<sup>1</sup>, Gillet B<sup>2</sup>, Delabar JM<sup>1</sup>**

1 EA3508, UP7, IFR117, Paris, 75251, Paris, France

2 Laboratoire de RMN Biologique, ICSN-CNRS, Gif sur Yvette, 91198, France

3 Genetics and Disease Program, Genomic Regulation Center, Barcelona, Spain

A transgenic mouse containing a 500kb human YAC clone (152F7) (Smith et al.) was constructed to model the overexpression of genes from the Down syndrome chromosomal region-1 on HSA21. This model presents two interesting phenotypic modifications: a learning and motor impairment and a volumic increase of some parts of the brain with a more pronounced effect on the thalamic-hypothalamic region as evidenced through MRI experiments.

The transgenomic fragment contains five genes among which is *dyrk1a*, a serine threonine kinase, ortholog of *drosophila* minibrain. QPCR experiments have shown that the transgene is present in one copy and induces a 1.5 increase of the expression level of *dyrk1a* in the cerebrum.

Crossing of tg152F7 with *dyrk1a* (+/-) heterozygote produces four genotypes (wt, tg, (+/-), tg (+/-)), analysis of which shows that the brain phenotypes are strongly correlated to *dyrk1a* gene copy number and to *dyrk1a* expression level. As a consequence any drug acting upon *dyrk1a* level or *dyrk1a* activity should also act upon the phenotype.

This kinase has been shown to be strongly inhibited in vitro by epigallocatechin gallate (EGCG) a major component of green tea (Bain et al).

We have studied the effect of a green tea diet on the brain volumic increase of YAC transgenic animals as compared to wild type: green tea administered orally during gestation and postnatally can reverse phenotypic changes induced by *dyrk1a* overexpression.

## GENE EXPRESSION PROFILES IN DOWN SYNDROME AND IN MOUSE MODELS

**M. Sultan<sup>1</sup>, P.Kahlem<sup>1</sup>, R. Herwig<sup>1</sup>, M. Steinfath<sup>1</sup>, D. Balzereit<sup>1</sup>, B. Eppens<sup>1</sup>, N.G. Saran<sup>2</sup>, M.T. Pletcher<sup>2,3</sup>, S.T. South<sup>2</sup>, G. Stetten<sup>2</sup>, H. Lehrach<sup>1</sup>, R. H. Reeves<sup>2</sup> and M.-L. Yaspo<sup>1</sup>**

<sup>1</sup>Max Planck Institute for Molecular Genetics, Dpt. of Vertebrate Genomics, Ihnestrasse 73, D-14195, Berlin, Germany

<sup>2</sup>Departments of Physiology, Obstetrics and Gynecology, Johns Hopkins Univ. School of Medicine, Baltimore, MD 21205

<sup>3</sup> Current address: Scripps Research Institute, La Jolla, CA 92037

Down Syndrome (DS) or trisomy 21 is associated with the presence of an additional chromosome 21. With a median incidence rate of 1:1000 live births, DS is the most frequent viable congenital chromosomal aberration syndrome and genetic cause of mental retardation in the human population. Chromosome 21 has been entirely sequenced and is estimated to encode 284 genes. So far the correlations between the complex phenotypes of DS and the gene dosage effects involving an extra chromosome 21 remain elusive. In order to establish relationships between gene dosage imbalance and phenotype, we are investigating the expression profiles of the genes encoded on chromosome 21 in trisomic samples versus control individuals. Using both cDNA arrays and real time quantitative PCR, we have investigated gene expression profiles in a number of DS cases (fetal cells) and in various tissues of a mouse model of DS (Ts65Dn). The Ts65Dn mouse carries ca.110 orthologs of the human chromosome 21 genes at dosage imbalance, and recapitulates some of the DS phenotypic features. Gene expression profiles indicated a general trend of 1.5 fold over expression of the trisomic animals versus euploid littermates. However we observed that some genes escaped this trend, showing apparently higher over-expression levels, compensation, or down-regulation. In order to investigate the effects of genetic variations between individual mice, we have now investigated the expression of 50 mouse orthologs of Chr21 in three brain regions in four individual Ts65Dn mice versus four control littermates. In accordance to our study using pools, we confirm that most of the trisomic genes had an increased level of expression of ~1,5 fold in Ts65Dn. Data suggest that only few genes are tightly regulated, and that many genes show a significant variation of their expression levels between the different individuals. This complicate the simple view of calculating ratios of gene expression between trisomic and control samples. It is likely that other gene regulation mechanisms including epigenetic factors are playing a role in the gene expression of Chr.21 genes, and that the simple model of 1.5 fold overexpression in trisomy may not be the most appropriate to understand the complex relationship between gene copy number and phenotypic effects.

N° D-1 Sp

**THE CEREBELLAR TRANSCRIPTOME DURING POSTNATAL DEVELOPMENT OF THE TS1CJE MOUSE, A SEGMENTAL TRISOMY MODEL FOR DOWN SYNDROME.**

M.-C. Potier(1), L. Dauphinot(1), R. Lyle(4), I. Rivals(3), M. Tran Dang(1), R.X. Moldrich(1), G. Golfier(1), L. Ettwiller(1), K. Toyama(2), J. Rossier(1), L. Personnaz(3), S.E. Antonarakis(4), C. J. Epstein(5), P.-M. Sinet(2)."

(1)Unité Mixte de Recherche 7637 Centre National de la Recherche Scientifique, Ecole Supérieure de Physique et de Chimie Industrielles, (2)Institut National de la Santé Et de la Recherche Médicale Unité 549, Institut Paul Broca, 2ter, rue d'Alésia 75014 Paris, France ; (3)Equipe de Statistique Appliquée, Ecole Supérieure de Physique et de Chimie Industrielles, 10, rue Vauquelin 75005 Paris France ; (4)Department of Genetic Medicine and Development, University of Geneva Medical School, 1 rue Michel Servet, 1211 Geneva, Switzerland ; (5)Department of Pediatrics, UCSF, San Francisco, CA 94143-0748, USA.

The central nervous system of persons with Down syndrome presents cytoarchitectural abnormalities that likely result from gene dosage effects that affect the expression of key developmental genes. To test this hypothesis, we have investigated the transcriptome of the cerebellum of the Ts1Cje mouse model of Down syndrome during postnatal development using microarrays and quantitative PCR. Genes present in three copies were consistently over expressed, with a mean ratio relative to euploid of 1.52 as determined by quantitative PCR. This gene dosage effect was associated with a dysregulation of the expression of some two-copy genes. Out of a total of 8258 genes examined, the Ts1Cje/euploid ratios differed significantly from 1.0 for 406 (80 and 154 with ratios >1.5 and <0.7, respectively), 333 (11>1.5 and 55<0.7) and 246 (59>1.5 and 69<0.7) at P0, P15 and P30 respectively. Overall, at P0, transcripts involved in cell differentiation and development were over represented among the dysregulated genes. Finally, global gene profiling revealed that transcription in Ts1Cje mice is more affected by developmental changes than by the trisomic state and that there is no apparent detectable delay in the postnatal development of the cerebellum of Ts1Cje mice.

N° D-2 Sp

**DYRK1A GENE DOSAGE IS CRITICAL FOR THE CORRECT MORPHOGENESIS OF MOUSE RETINA.**

Laguna A **a**, Ledru A **b**, Delabar JM **b** and Arbonés Ml **a**.

**a** Genes and Disease Program, Center for Genomic Regulation – CRG, Barcelona, Spain .

**b** Laboratoire EA3508. Université Denis Diderot, Paris, France.

"The phenotypes observed in transgenic mouse models of gain and loss of function of Dyrk1A gene have shown that dosage of this HSA21 gene is essential for the correct morphology and function of the brain. The retina is one of the nervous system structures expressing highest levels of DYRK1A at early developmental stages. We show here that DYRK1A is also expressed in specific neuronal populations of adult mouse retina. For these reasons, we have characterized the retinal phenotype of adult mice that are heterozygous for a Dyrk1A null mutation (Dyrk1A<sup>+/-</sup>) or that express a yeast artificial chromosome (YAC152f7) that contains three genes of HSA21 (DYRK1A, DCR3, TTC3). Dyrk1A<sup>+/-</sup> mice have smaller eyes and thinner retinæ than their control littermates. Although the general laminar structure is maintained, the number of cells in inner nuclear (INL) and ganglion cell (GCL) layers is severely reduced whereas, the number of photoreceptors is not altered. Immunohistochemical studies revealed decreased numbers of particular cell populations in the INL (rod bipolar cells and Müller glial cells) and in the GCL (ganglion cells) of Dyrk1A<sup>+/-</sup> mice. In addition, changes in the morphology of neuronal processes were observed in both, outer and inner plexiform layers. Interestingly, YAC152f7 mice presented thicker retinæ than their control littermates due to a specific increase in the number of cells in INL and GCL. All together, our findings show that changes in Dyrk1A gene dosage affect the establishment and maintenance of correct retinal morphology. Supported by: Fondation Jerome Lejeune and Fundació La Marató de TV3.

## N° D-3 Sp

### **TgDyrk1A MICE SHOW DEREGLATION IN THE EXPRESSION OF THE NMDA RECEPTOR SUBUNITS.**

J. Ortiz Abalia **1**, X. Altafaj **1**, M.C. Potier **2**, G. Golfier **2**, X. Estivill **1**, E. Martí **1**, C. Fillat **1**

**1** Programa Gens i Malaltia. Centre de Regulació Genòmica-CRG, Barcelona, Spain

**2** Neurobiologie et Diversité Cellulaire, CNRS UMR 7637, ESPCI, Paris, France"

DYRK1A encodes for a serine-threonine kinase thought to be involved in the neuropathology associated with Down Syndrome (DS). We have previously reported that TgDyrk1A, a partial DS murine model overexpressing Dyrk1A, presents motor and cognitive alterations. To gain new insights into the molecular mechanisms underlying TgDyrk1A phenotype, microarrays studies were performed on a chip of 96 genes involved in neurotransmission. Three genes showed a significant overexpression in two independent transgenic mice lines: the NR2A (NMDA receptor subunit), the 5HT1E/F (serotonin receptor subunit 1E/F) and GABA-\_3 (Gamma-amino-butyric receptor type A subunit \_3). In the present study, characterization of the deregulation in gene expression has been centered in the NMDA family of receptors because of their fundamental role in normal brain function. NR2A overexpression was confirmed by western blot in adult cerebella, however no changes were observed in NR2B subunits. Upregulation of NR2C and NR1 were also observed. Immunohistochemical analysis showed a similar distribution of the different subunits of NMDA glutamate receptors in control and TgDyrk1A adult cerebella. Current studies are in progress to characterize the expression of the NMDA receptor subunits at developmental stages P7 and P14. These results suggest that the upregulation of some of the NR subunits in the NMDA receptors could be involved in the motor discoordination as well as in the impairment in spatial learning observed in TgDyrk1A.

## N° D-4 Sp

### **PERIPHERAL NERVE REGENERATION AFTER SCIATIC NERVE INJURY IS ALTERED IN HUMAN CuZn SOD1 TRANSGENIC MICE.**

**1** J. London, **1** M. Le Pécheur, **2** W. Marcol, **2** Lewin-kowalik J., **1** E. Paly, **2** K. Kotulska.

**1:** University Paris 7 Denis-Diderot, EA3508, 2 Place Jussieu, 75251 Paris Cedex 05

**2:** Medical University of Silesia, Department of Neurology, Katowice, Poland

Down syndrome patients have some alterations in pain responsiveness. Transgenic mice for the human Cu/Zn Superoxide dismutase gene (hSOD1 Tg mice) have been the first murine model for studying trisomy 21. SOD1 is a key enzyme in the metabolism of free radicals in mammals and its overexpression in transgenic mice has been shown to be either protective or deleterious regarding neural cells or neuromuscular junctions and thymus respectively. Moreover regulation of SOD1 activity may have important role in inflammation. The aim of the present study was to examine the role of SOD1 overexpression in peripheral nerve regeneration after sciatic nerve transaction and neuropathic pain-related behaviour in hemizygous or homozygous hSOD1 transgenic mice versus control ones aged 5 months. It was shown that the functional regeneration was slower in hSOD1Tg mice than in control ones and less growth cones as well as Schwann cells were found in transgenic animals than in controls. Moreover they were more neuromas at the injury site in transgenic animals than in controls and the differences between transgenic animals and controls were more pronounced for homozygous hSOD1Tg mice. The poor regeneration in hSOD1 Tg mice associated with more frequent neuromas development can be at least partially ascribed to disturbed inflammatory reactions at the injury site.

**N° D-5 Sp**

**ANALYSIS OF NEURONAL DEVELOPMENT IN HUMAN DOWN SYNDROME  
NEURAL PRECURSOR CELLS.**

Anita Bhattacharyya and Clive Svendsen

Waisman Center, University of Wisconsin-Madison, Madison Wisconsin, USA

Development of the cerebral cortex is a complex process, and it is not surprising that mistakes in any step of development have lasting consequences on the organism. Down Syndrome (DS) is a human developmental disorder whose manifestations are due to defects that arise during early neural development. During the prenatal and early postnatal period, faulty development of the DS cerebral cortex includes accumulation of fewer neurons in specific cortical layers. To investigate the basis for the reduced accumulation of neurons in the DS cortex, neurospheres derived from human fetal DS cortical tissue are used to evaluate DS and normal cortical neurogenesis in vitro. Specific developmental processes in cortical development are studied with neurospheres, proliferation of precursors and progenitors, migration of progenitors, and differentiation of progenitors into neurons and glia. Cells within DS cortical neurospheres retain an extra copy of chromosome 21, even after expansion. DS neurospheres expanded in culture initially produce normal numbers of neurons, but produce far fewer neurons with time in culture. These observations suggest the failure of neurogenesis from DS neurospheres in vitro may correspond to the late phase of neurogenesis that occurs in the second half of gestation when DS prenatal brains have fewer cortical neurons.

**saturday, March 19, 2005**

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**afternoon session**

15.00-16.30: Concurrent symposia

*auditorium 1*

C - CLINICAL ASPECTS

Panel on Alzheimer disease and Down syndrome  
Chairperson: M. BOADA

Dementia and Down syndrome: neuropathological substrates of clinical variability.  
LEVERENZ, JAMES B.

Cognitive and behavioural effects of donepezil in adults with dementia associated with Down syndrome  
M. BOADA // M. BUENDÍA

*auditorium 2*

D - MOLECULAR STUDIES OF DOWN SYNDROME

Panel on toward understanding the molecular basis of Down syndrome  
Chairperson: M. DIERSSEN

Members: JM. DELABAR R. H. REEVES  
J. ESTIVILL M. SULTAN

16.30-17.00: Break - poster view

## **DEMENTIA AND DOWN SYNDROME: NEUROPATHOLOGICAL SUBSTRATES OF CLINICAL VARIABILITY.**

**Leverenz, James B.<sup>1-5</sup>, Peskind, Elaine R.<sup>2,4</sup>, Raskind, Murray A.<sup>2,4</sup>, Tsuang, Debby W.<sup>2,4</sup>**

Departments of Neurology<sup>1</sup> and Psychiatry<sup>2</sup>, and The Center on Human Development and Disability<sup>3</sup> Univ. of Washington. Mental Illness<sup>4</sup> and Parkinson's Disease<sup>5</sup> Research and Clinical Centers, VA-PSHCS (116MIRECC), 1660 S. Columbian Way, Seattle WA, 98108, USA.

The presence of Alzheimer's disease (AD) pathology in virtually all older adults with Down syndrome (DS) has been well documented. However, clinically there are substantial differences between DS patients with regard to age of onset and dementia-associated neuropsychiatric symptoms. This presentation will focus on the neuropathologic changes observed in the brains of DS cases from early childhood to adulthood and the possible implications for the clinical differences observed between DS patients.

Despite the consistent presence of AD pathology in DS brains after age 40, there is little data on the progression of this pathology prior to that age. We determined the distribution of AD neuropathologic changes across a broad age range of DS autopsy cases (42 cases, ages 4 days to 38 years). A $\beta$  deposition was evident as early as age 8 years, however some DS cases had no AD pathology as late as age 25 years. Within the medial temporal lobe we found a stereotypic pattern of progression of A $\beta$  deposition.

DS patients can also have variability in the neuropsychiatric characteristics of their dementing illness. We examined a group of DS cases referred to our center with psychotic symptoms (n=21). Most had a clinical history of dementia (62%), but some had onset in early adulthood without coexistent dementia. Seven of these psychotic DS cases have come to autopsy, all with clinical dementia and pathologic AD. While all seven cases had clinical parkinsonism and delusions, four had additional visual hallucinations (VH). The four cases with VH also had alpha-synuclein pathology (Lewy bodies) in the amygdala, while the non-VH cases did not.

The origin of the dementia age of onset and clinical dementia phenotypes in DS remains unclear. However, differences in age of onset for AD pathology and co-existent Lewy body pathology may account for some of the observed clinical differences.

## **COGNITIVE AND BEHAVIOURAL EFFECTS OF DONEPEZIL IN ADULTS WITH DEMENTIA ASSOCIATED WITH DOWN SYNDROME**

**M. Boada<sup>1,2</sup>, I. Hernández<sup>1</sup>, M. Buendía<sup>1</sup>, S. Badenas<sup>1</sup>, L. Tárraga<sup>1</sup>**

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<sup>2</sup> Hospital G.U. Vall d'Hebron. Servei de Neurologia. Pg de la Vall d'Hebron, 119-129. 08035 Barcelona.

The objective of this study was to evaluate the pharmacological treatment efficacy of Donepezil on the cognitive and behavioural disorders in persons with Down Syndrome (DS) older than 40 years with progressive cognitive decline (PCD) compared to DS control subjects. Moreover, this study was used for the validity analysis of Mini Mental Status Examination (MMSE) and Severe Impairment Battery (SIB) for this population; instruments developed to assess cognitive functions in patients with Alzheimer's Disease (AD).

A total of 45 DS subjects were evaluated: all had cognitive and behavioural disorders. 29 of these subjects were without dementia (DS) and were considered control subjects for this study; 16 subjects had PCD. The study was an open-label crossover design with patients receiving Usual Treatment (UT) when not taking Donepezil; thus, each patient received both Donepezil and UT. The outcome measures included: Early Signs of Dementia Checklist (ESDCH), Dementia Questionnaire for Mentally Retarded Persons (DMR), the Adaptive Behaviour Scale Residential Community ABS-RC2, MMSE and SIB Evaluations were made at baseline and after 3, 6, 9, and 12 months of study-cross-over occurred at 6 months.

The results of the study demonstrated that Donepezil slowed the progression of the cognitive dysfunction, especially during the first three months of treatment. This occurred for both cognitive and social-behavioural outcomes. We also demonstrated that SIB was a good tool to evaluate the cognitive impairment in subjects with DS. Although there were few adverse events, there was an unexpected hypersomnolentia in 3 subjects, aspect not reported in prior studies.

However, the sample sizes used in this study and all published studies are small and this emphasizes the need for a larger, multicenter trial to fully evaluate the nature and extend of the responses of DS patients to anticholinesterase therapy.

**saturday, March 19, 2005**

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*auditorium 1*

PLENARY SESSION

Chairperson: J. FLÓREZ

17.00-19.00:

17.00:

Behaviour and learning in the ts65dn mice, a model for Down syndrome: new contributions.

J. FLÓREZ

17.40:

The pyramidal neuron in cognition and mental retardation

R. BENAVIDES-PICCIONE

18.20:

Reducing oxidative damage and providing behavioural enrichment may promote successful aging in Down syndrome: evidence from a longitudinal study in a canine model of human aging.

E. HEAD

18.45:

Vitamin D supplements and exercise are related to the increase of mineral bone density in people with Down's syndrome.

(IX Ramon Trias Fargas Second Prize)

LL. ROSSELLÓ AUBACH

19.00:

CLOSURE

## **BEHAVIOUR AND LEARNING IN THE TS65DN MICE, A MODEL FOR DOWN SYNDROME: NEW CONTRIBUTIONS.**

**Jesús Flórez, Noemí Rueda, Carmen Martínez-Cué**

Laboratory of Developmental Neurobiology, Department of Physiology and Pharmacology, Faculty of Medicine, University of Cantabria, Avda. Card. Herrera Oria s/n. 39011 Santander, Spain. E-mail: florezj@unican.es

The Ts65Dn mouse is the most widely used animal model of Down syndrome. Previous work from this laboratory demonstrated that environmental enrichment had a positive effect on spatial learning in female Ts65Dn mice but deteriorated it in trisomic males. In order to determine the causes of this cognitive deterioration of Ts65Dn male mice after environmental enrichment, we evaluated these negative influences in control and Ts65Dn male mice allocated to one of the four following conditions: standard laboratory and social conditions, and enrichment in small or large groups. Learning, aggressiveness, anxiety and biochemical correlates of stress were evaluated. Corticosterone levels were increased in Ts65Dn mice housed or enriched in large groups. Living in large groups deteriorated learning in Ts65Dn mice, and environmental enrichment increased this deterioration. Ts65Dn mice showed less aggressiveness in all conditions, especially after environmental enrichment. In the elevated plus maze no differences were found between mice at any condition. All these results suggest that specific experimental social and physical stimuli may disturb socialization and learning in Ts65Dn males.

Since Down syndrome may be accompanied by anxiety-related psychopathology, the level of anxiety was assessed in Ts65Dn mice by using the Mouse Defense Test Battery, a paradigm that evaluates anxiety and panic responses of mice when confronted to a predator. Differences between males and females in the physiological and behavioural responses were found. Male Ts65Dn mice behaved similarly to controls when confronted to a predator and showed similar physiological activation; however, females showed higher corticosterone levels, and Ts65Dn females displayed increased defensive behaviours indicating a higher level of anxiety compared to controls.

The results emphasize the need to consider gender in the assessment of cognitive and behavioural patterns of the Ts65Dn mice.

## **THE PYRAMIDAL NEURON IN COGNITION AND MENTAL RETARDATION**

**Ruth Benavides-Piccione and Javier DeFelipe**

Instituto Cajal (CSIC), Ave. Dr. Arce, 37, 28002 Madrid  
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Information in the neocortex flows through synapses across a finely organized network of multiple, small vertical information processing units. The skeleton of these basic microcircuits is composed of pyramidal cells and their input-output connections. Pyramidal cells are the most abundant and the most characteristic neuronal type in the neocortex. They are cells with long axons through which the bulk of the processed information that leaves the cortex, and that is transmitted to other cortical or subcortical areas, is conveyed. Thus, our understanding of the synaptic organization of the neocortex and of how this information flow occurs largely depends on the knowledge available regarding synaptic inputs to pyramidal cells. Dendritic spines of pyramidal cells represent the main postsynaptic elements of cortical excitatory synapses. In turn, pyramidal cell axons constitute the main source of these synapses. Furthermore, since the discovery in the 1970s that dendritic abnormalities in cortical pyramidal neurons are the most consistent pathologic correlate of several brain diseases, including mental retardation, research has focused on how dendritic alterations are related to reduce intellectual ability. The recent identification of the genetic bases of some mental retardation associated alterations, coupled with the technology to create transgenic animal models and the introduction of powerful sophisticated tools in the field of microanatomy, has led to a growth in the studies of these disorders. Thus, the study of pyramidal cell microstructure will contribute significantly to our understanding of the mechanisms underlying cortical function in both health and brain disorders.

**REDUCING OXIDATIVE DAMAGE AND PROVIDING BEHAVIOURAL ENRICHMENT MAY PROMOTE SUCCESSFUL AGING IN DOWN SYNDROME: EVIDENCE FROM A LONGITUDINAL STUDY IN A CANINE MODEL OF HUMAN AGING.**

**Elizabeth Head, Norton W. Milgram, Bruce A. Muggenburg, Ira T. Lott, Carl W. Cotman**

Department of Neurology, Institute for Brain Aging & Dementia, University of California, 1259 Gillespie NRF, Irvine, CA., 92697-4540

By the age of 40 years, individuals with Down syndrome (DS) develop senile plaques (SP) and neurofibrillary tangles consistent with Alzheimer disease (AD). Further, an oxidative deficit may also be present in DS leading to increased brain oxidative damage. To test the hypothesis that providing a diet rich in a broad spectrum of antioxidants may reduce oxidative damage leading to improved cognition as a potential intervention to promote successful aging in adults with DS, we used a canine model of human brain aging. Aging canines naturally develop SP pathology, oxidative damage and impairments in learning and memory. We also hypothesized that behavioral enrichment may stimulate neuron growth and survival and may be synergistic with an antioxidant diet. Thus, 24 aged beagles (8-11 years) were placed into one of four treatment groups: (1) control/control, (2) behavioral enrichment/control diet, (3) control enrichment/antioxidant diet, and (4) behavioral enrichment/antioxidant diet. The antioxidant diet consisted of a senior dog diet enriched with  $\alpha$ -tocopherol (800IU), vitamin C (10 mg/kg), fruit and vegetable extracts (1%), dl-lipoic acid (2.7 mg/kg), and l-carnitine (6 mg/kg). The behavioral enrichment consisted of social and cognitive enrichment, and physical exercise. Animals were treated for 2.5 years and repeated measures of cognitive function were obtained. At the end of the study, SP pathology was quantified in 4 cortical regions. The antioxidant diet and the behavioral enrichment each led to significant improvements in learning ability. Spatial memory was improved with the combination treatment to a greater extent than either treatment alone. In the brain, the antioxidant diet slowed but did not reverse existing SP pathology. Given similarities between canine and human aging, the results of this study suggest that an antioxidant diet and behavioral enrichment may be promising interventions to promote healthy aging in DS. Funding provided by NIH/NIA AG12694 and ADRC P50 AG16573.

## VITAMIN D SUPPLEMENTS AND EXERCISE ARE RELATED TO THE INCREASE OF MINERAL BONE DENSITY IN PEOPLE WITH DOWN'S SYNDROME.

**Rosselló Aubach LI, Torres Palou R, Abella F, Torres Cortada G, Cabau Rubies J, Boronat Espasa T, Puerto Linares E, Llobet Fernández-Grandes R.**

Dr. Lluís Rosselló Aubach. Department of Rhumatology. Hospital Santa María Lleida. Rovira Roure, 44. 25198. Lleida. Spain. Irosello@gss.scs.es

**Objective:** In an initial transversal and observational study, it was observed that the prevalence of densitometric alterations in a group of 58 adults with Down's syndrome (DS) was very high (60.34%) and it was associated with hypovitaminosis D. The objective of the current study is to evaluate whether vitamin D supplements and a time increase in weekly physical exercise could have positive effects over bone mineral density and the prevention of fractures.

**Material and Methods:** It is a prospective, year-long study to evaluate the effectiveness of the two different measures of osteoporotic fracture prevention in the same group of patients, before and after therapeutic intervention. A total of 58 adults with DS, workers in two special workshops for intellectual disability, are studied, pre- and post treatment, for the prevalence of osteoporosis with a peripheral densitometer DEXA, levels of Vitamin D and parathormones (PTHi). The differences are analyzed, according to gender and work centre variables.

**Results:** Of the 58 workers with DS studied, 34 were male (58.62%) and 24 female (41.38%), with an average age of 41.56 +/- 9.61 years and with a corporal mass index (CMI) of 27.72 +/- 4.22Kg/m<sup>2</sup>. At the beginning of the study: 35 individuals (60.34%) were diagnosed by densitometry (DMO) as having osteopenia/osteoporosis, 22 (37.93%) had hypovitaminosis D and 9 (15.52%) high PTHi. A total of 10 subjects (17.24%) had suffered some type of fracture in the previous 5 years. The number of hours per week of physical exercise was increased for the whole group and those with hypovitaminosis D were treated monthly with Calcidiol. One year later there were changes in their DMO: 24 (41.38%) ( $p=0.0026$ ) without any fractures in the duration of the study. Significant differences were not found according to gender and work centre variables.

**Conclusion:** The study confirms that, during the year of treatment and in groups of people with DS, the increase of the number of hours per week of physical exercise and Vitamin D supplements are effective for the increase of bone mineral density and the prevention of fractures.

## **POSTERS**

### **1 P**

#### **VITAMIN D AND CALCIUM SUPPLEMENTATION IN INSTITUTIONALIZED ADULTS WITH DOWN'S SYNDROME.**

P Zubillaga PhD, A Garrido MD, I Mugica MD, J Ansa MD, R Zabalza MD, JI Emparanza PhD

Fundación Uliazpi, Diputación Foral de Guipúzcoa, San Sebastián, Spain

Objective: to assess the effects of calcium and vitamin D3 supplementation on the bone metabolism in a group of adults with Down syndrome.

Design: randomised, parallel, controlled and open clinical trial.

Setting: Institution for mentally handicapped: Fundación Uliazpi, Diputación Foral de Guipúzcoa, San Sebastián, Spain.

Subjects: A total of 23 persons with Down syndrome, residents at the Uliazpi Foundation were recruited and all completed the study.

Intervention: Twelve participants were randomly allocated to receive 1 gr of calcium and 800 iu of vitamin D once daily for one year while eleven were assigned to the control group, receiving no supplementation.

Results: We found no differences between groups regarding blood calcium and phosphorous levels. The remaining parameters showed differences between the two groups consistent with a beneficial effect of the intervention: serum levels of total alkaline phosphatase, intact parathormone, osteocalcin and crosslaps diminished while 25 OH vitamin D3 level increased.

Conclusions: Persons with Down syndrome are prone to a deficit of vitamin D, that can be corrected with vitamin D and calcium supplementation, and giving rise to an improvement of the biochemical markers related to the phospho-calcium metabolism and bone remodelling.

### **2 P**

#### **RISK FACTORS FOR HIGH FREQUENCY HOSPITALIZATION AMONG INFANTS WITH DOWN SYNDROME. 1998-2002.**

Hernandez, J and Barraza, X.

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The change in the pathology which requires hospitalization in the pediatric population makes possible to recognize groups of patients in mayor risk for frequent hospitalization. The patients with Down syndrome (DS) is a special vulnerable group, our goal is to recognize early in the evolution those patients with a greater risk for readmitted. We study our cohort of patients born in our hospital, with diagnosis of DS, following them for the first 24 month of life. Those patients with 3 hospitalizations or two with one longer than 12 days were considered in the high frequency group (HF). We compared different parameters evaluated in the newborn period and the first hospitalization between this group and other with those patients without hospitalization or at lesser frequency. In a first study we analyzed those parameters evaluated in the newborn period, the odds ratio (OR) was greater than 1.0 for the parameters of newborn weigh less than 2.500 gr (1,49), and for the diagnosis of cardiac malformation associated (2,44). In a second part of our study, we try to recognize the risk factors at the moment of the first hospitalization after the newborn period, all the parameters analyzed were no significant with an OR less than 1.0. Even though, our study was no conclusive we consider very important the evaluation of our patients early in the following for prevention of HF hospitalization and complications.

3 P

### **INFLUENCE OF POLYMORPHISMS OF THE AMYLOID PRECURSOR PROTEIN LOCUS ON THE AGE OF ONSET OF DEMENTIA IN DOWN'S SYNDROME.**

Margallo-Lana ML, Morris CM, Gibson AM, Jones E, Tan AL, Tyrer SP, Moore BP, Ballard CG

Northgate Hospital, Morpeth, Northumberland, NE 61 3BP

Down's syndrome is caused by the triplication of chromosome 21. The amyloid precursor protein (APP) locus on chromosome 21 influences the development of Alzheimer disease. The authors investigated the relationship between a tetranucleotide repeat on intron 7 of the APP gene and the age at onset of dementia in a group of 105 adults with Down syndrome (DS). There was a 13-year difference in the age at onset of dementia in DS associated with the number of tetranucleotide repeat alleles in APP. We are now sequencing the region next to the intron 7 of the APP in Chromosome 21 in the original sample. Any single nucleotide polymorphisms (SNPs) found will be looked for in further samples. Following this the results will be examined alongside clinical data to determine if any of the polymorphisms may affect the age of onset of dementia in the study group. We will be using real-time PCR with the 'Taqman' system as our method for genotyping. Results will be checked against a copy of Mutation Surveyor, a sequence analysis program which is able to detect heterozygous mutations on triplicated chromosomes. We will be presenting the results in the forthcoming meeting.

4 P

### **DNA DAMAGE AND ANTIOXIDANT LEVELS IN DOWN SYNDROME**

Aishah Adam<sup>1</sup>, M Mahmood<sup>1</sup>, MH Hasan<sup>1</sup>, C Sunggip<sup>2</sup>, M Ali Mukhti<sup>2</sup>, NA Hamid<sup>2</sup>, A Marzuki<sup>3</sup>, WZ Wan Ngah<sup>2</sup>

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The presence of triplicate copies of chromosome 21 in Down Syndrome (DS) persons is believed to lead to a condition of oxidative stress which may contribute to the weaknesses seen in them. Oxidative stress is the mechanism that underlies many pathological conditions and results from an imbalance in the prooxidant-antioxidant status in favour of the former. In Down Syndrome, oxidative stress may arise as a result of overexpression of a gene present on chromosome 21, which codes for superoxide dismutase (SOD). This enzyme plays a double role, it is an antioxidant which removes superoxide anion radicals by converting them to hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), a reactive oxygen specie. H<sub>2</sub>O<sub>2</sub> may undergo the Fenton reaction to produce the highly reactive hydroxyl radicals. If produced in excess of the body's antioxidant capacity, reactive oxygen species may attack cellular macromolecules leading to damage.

The aim of this study was to determining the antioxidant-oxidative stress status in DS persons. Antioxidant status was determined by assaying for plasma SOD, Se-glutathione peroxidase, catalase and vitamin E. Oxidative stress was indicated by the FORT test while DNA damage was assessed by the Comet assay. Blood was obtained from DS persons or controls with informed consent. Results showed no difference in the antioxidant enzyme activities of DS persons from controls. There was also no difference in the oxidative stress status as measured by the FORT test. DNA damage was greater in DS persons than controls especially in the older age groups (more than 21 years). Whether this is a consequence of oxidative stress is not evident from measurements of antioxidant enzymes.

## CLINICAL OVERVIEW ON A DOWN'S SYNDROME POPULATION ATTENDING THE FUNDACIÓN JOHN LANGDON DOWN, IN MEXICO CITY.

Alessandra Carnevale<sup>1,2</sup>, Sandra Plascencia<sup>1</sup>, Nora Urraca<sup>1</sup>, Marco A. Urbina<sup>1</sup>.

<sup>1</sup>Fundación John Langdon Down, <sup>2</sup>Instituto Nacional de Pediatría, Mexico City, Mexico.

In Mexico City is an institution that offers a complete educational program to children and adults with Down Syndrome. During 2003, the Clinic was created as part of the Fundación, with the purpose of providing specialized medical care with a preventive approach to the students and to people with Down Syndrome from outside the Fundación. The clinical services are provided by two pediatricians, two geneticists and consultants in cardiology, audiology and dermatology. Patients are referred to other specialists and hospitals when needed. The purpose of this study is to describe the clinical findings of Down Syndrome patients attending the Clinic. We have seen 264 individuals, 120 female and 144 male. Mean age was 5 years ranging from 2 months to 36 years. The most frequent karyotype in 211 patients was regular trisomy 21 (93.4%), but we found 5.2% mosaicisms and 1.4% translocations. Congenital heart disease was present in 141 (53.4%), the most frequent being patent ductus arteriosus, followed by septal defects. Ocular abnormalities were seen in 31.1%, and hypothyroidism was found in 5%. Seventy eight (30%) patients underwent surgery for correction of congenital defects, most frequently cardiac and gastrointestinal. These are preliminary data from our population of students where it is possible to learn about the development and clinical problems of people with Down Syndrome in our country.

## OCULAR DISORDERS IN DOWN'S SYNDROME OVER 40 YEARS OLD.

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**Objective.** To determine the refractive status and ocular health in Down's Syndrome patients older than 40, with possible involvement of Alzheimer's disease (AD).

**Methods.** 49 patients, between 40 and 62 years old, had their eyes examined. Measurements of visual acuity (VA), binocularity status, ocular motility, retinoscopy and ocular health were evaluated. **Results.** We found 24.5% diagnosed as suffering AD and were treated accordingly. 68.7% of the patients presented VA below 0.5 at distance and 48% had values below 0.4 at near. Results showed 61.4% myopia, 45.8% astigmatism and 23% hyperopia. 31.2% of the patients showed signs of presbyopia. 66.7% showed strabismus and altered ocular motility. Pathologies found were: 59.4% of crystalline opacities, 25% nystagmus, 13.5% previous cataracts surgery, 6.2% keratoconus, among others **Conclusions.** Findings confirm the high incidence among this population of ametropies and pathologies, especially cataracts, and also the low VA values, far and near, outside functional limits. No significant differences were found among patients who had been diagnosed and those who had not been diagnosed as suffering from AD

## 7 P

### **A COMPARISON OF TWO FORMS OF THE PRUDHOE COGNITIVE FUNCTION TEST WITH THE KAUFMAN BRIEF INTELLIGENCE TEST (K-BIT)**

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The Prudhoe Cognitive Function Test (PCFT) is a schedule designed to assess the cognitive abilities of people with learning disability. It has been employed to measure the cognitive status of individuals with Down Syndrome. The advantage of the test is that it is administered directly to the individual concerned and does not rely on the assessment of others. The PCFT examines orientation, recall, language, praxis and calculation and takes between 30-45 minutes to administer. To shorten the administration of this test two short forms of the PCFT were developed. These forms were administered alternately with the long form to a stratified sample of 168 individuals with learning disability and controlled for order of presentation. The K-BIT, an instrument that is a valid measure of intelligence of people with reduced intellectual ability, was administered to the same individuals. The correlation coefficient between the short forms of the PCFT was extremely high at 0.97. There was also an excellent correlation with the K-BIT ( $r=0.88$ ). The short forms of the PCFT can be administered as effectively as the long form with very little reduction of reliability. There is a close correlation between performance on this test and intellectual function generally.

## 8 P

### **MNB/DYRK1A, A PROTEIN KINASE WITH MULTIPLE BRAIN FUNCTIONS AND PROBABLY INVOLVED IN DOWN SYNDROME NEUROPATHOLOGIES.**

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The Mnb/Dyrk1A gene encodes a new family of protein-kinases. The human MNB/DYRK1A gene maps in chromosome 21 and there are compelling data pointing to MNB/DYRK1A as a DS candidate gene. Mnb/Dyrk1A kinases are conserved both at the molecular and genomic level. This suggests a conservation of the gene regulatory mechanisms and supports the use of MNB/DYRK1A animal models in DS oriented studies. Our lab has focused on the role that MNB/DYRK1A plays in the brain, particularly during development. By using several experimental systems (*Drosophila*, chicken and mouse), our results indicate that MNB/DYRK1A is involved in diverse brain functions. In early brain development, MNB/DYRK1A appears to regulate proliferation as a determinant of the transition from proliferative to neurogenic cell divisions of neural progenitor cells. In intermediate developmental stages, it is involved in neurogenesis. Later in development, MNB/DYRK1A seems to be involved in neuronal differentiation probably by regulating dendritogenesis. In the adult brain, a clear role in learning/memory has been found. Molecular data point to MNB/DYRK1A kinases as transducers of several signalling pathways and provide a diverse repertoire of functional levels, such as transcriptional regulation and membrane dynamics. The possible involvement of MNB/DYRK1A in DS neuronal deficit and dendritic atrophy will be discussed.

## 9 P

### **MODULATION OF GENE EXPRESSION BY CALCIPRESSIN 1 IN DEVELOPING MOUSE CEREBELLUM.**

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Calcipressin 1 is encoded by DSCR1 (Down Syndrome Candidate Region 1), a HSA21 gene overexpressed in the brain of Down Syndrome individuals. Calcipressin 1 is a modulator of calcineurin activity, the most abundant serine-threonine phosphatase in the brain where it regulates synaptic transmission, neuronal proliferation, axonal guidance and outgrowth, among others biological responses. Some of these calcineurin-dependent functions require the activation of NFAT transcription factors. Dscr1 is highly expressed in the brain during mouse development, suggesting a possible function of this gene in neurogenesis. We report here the effect of calcipressin 1 lost of function on cerebellar transcriptome at mouse post-natal day 5, where proliferation and differentiation of neuronal cells are taking place. A whole genome microarray analysis was performed by comparing the gene expression profiles of cerebella from Dscr1 knock-out mice and control littermates. Three biological replicates were performed using a 22K mouse oligo-chip (Agilent). Analysis steps involved image quantitation (Gene Pix 6.0, Axon) and normalization of gene expression by Lowess using the R Limma package. Taking the upper 3 percentile of genes, ranked by B-statistics computed in the 3 replicates, we identified 11 genes up-regulated and 35 down-regulated in the knockout mice with an absolute fold-change greater than 1,4. No particular cellular function seems to be preferentially affected by the lost of calcipressin 1. This result indicates that changes in Dscr1 gene dosage may disturb the cerebellar transcriptome thus contributing to some of the functional alterations observed in the mouse model for Down syndrome, Ts65Dn.

## 10 P

### **ANALYSIS OF CARDIAC RHYTHM MODIFICATIONS IN TRANSGENIC MICE OVEREXPRESSING THE HUMAN CuZn SUPEROXIDE DISMUTASE (HSOD1) GENE.**

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Trisomy 21 is often associated with cardiac anatomic abnormalities in the interventricular communication and cardiac arrhythmias: auriculo-ventricular bloc or auricular fibrillation. Several murine models are now available to study trisomy 21 and transgenic mice for the hSOD1 gene was the first model to study this condition. We explored the cardiac control by neurovegetative system, in transgenic mice overexpressing the hSOD1 gene (TghSOD1) and controls on the same FVB/N genetic background. A telemetric device (TA11 ETA F20, DSI) was subcutaneously implanted under isoflurane anaesthesia in 12-18 months mice. Two weeks later, telemetric recordings of ECG, cardiac frequency, body temperature and spontaneous activity (SA) were performed during 24 hours. Heart rate variability (HRV) and cardiac arrhythmias were also explored in the presence or absence of agonists and antagonists. Heart rate and SA were lower in transgenic mice than in controls, during 24 hours ( $583 \pm 16$  bpm versus  $610 \pm 8$  bpm,  $p < 0.01$ ) but the nycthemeral cycle was present in both. Atrioventricular blocks of second and third degrees were frequently observed in TghSOD1 mice but rarely in control ones. HRV was increased in parasympathetic parameters (PNN6) but not changed in sympathetic parameters (SDNN). These results were confirmed by a specific sensitivity to parasympathetic stimulating and blocking drugs. These results show that SOD transgenic mice displayed severe atrioventricular blocks which could be favoured by an increase in parasympathic tone.

## 11 P

### **CALCIPRESSIN 1 IS INVOLVED IN NEURONAL SUSCEPTIBILITY TO OXIDATIVE STRESS**

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DSCR1 is a resident gene of the “Down syndrome candidate region” on human chromosome 21q21.1-21q22.2 that is induced during oxidative stress (OS) and calcium overload. It is highly expressed in brain, and its product, calcipressin 1 (CALP1), modulates the activity of the calcium/calmodulin-dependent phosphatase calcineurin (CaN). In the central nervous system, CaN participates either in physiological, excitotoxic and apoptotic processes thus suggesting important roles of CaN/CALP1 in neuropathology. In this context, the possible implication of CALP1 in neuronal death induced by calcium overload and OS was investigated in cerebellar granule neurones (CGNs) from Dscr1 knockout mice. Our results showed that CGNs lacking Dscr1 displayed increased resistance to H<sub>2</sub>O<sub>2</sub>-induced OS. Rises in intracellular calcium concentration [Ca<sup>2+</sup>]<sub>i</sub> induced by H<sub>2</sub>O<sub>2</sub> were investigated next as one of the possible mechanisms underlying the differential susceptibility of Dscr1 <sup>-/-</sup> CGNs to neuronal damage. Interestingly, Dscr1 <sup>-/-</sup> CGNs presented a delayed and reduced calcium influx in response to H<sub>2</sub>O<sub>2</sub>. Taken together, our data suggest a participation of CALP1 in OS-mediated neuronal death through the regulation of [Ca<sup>2+</sup>]<sub>i</sub> in response to OS. Whether lower calcium signals are the direct and sufficient mechanism to explain the increased resistance of Dscr1 <sup>-/-</sup> CGNs to OS remains to be elucidated.

## 12 P

### **MODIFICATIONS OF PROTEASOME ACTIVITIES IN THYMUS OF MICE OVEREXPRESSING HUMAN Cu/Zn SUPEROXIDE DISMUTASE (hSOD1) AND AMYLOID PRECURSOR PROTEIN (hAPP), A MODEL OF DOWN SYNDROME.**

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Premature aging is one of the Down syndrome (DS) characteristics and it has been proposed that enhanced oxidative stress present in DS might be the cause of some aspects of this condition. The proteasome is a complex enzymatic system, known to remove altered proteins during aging and which is very sensitive to stress conditions. Two genes of chromosome 21, SOD1 (Cu/Zn SuperOxide Dismutase) and APP (Amyloid Precursor Protein) might be important to study aging and indeed, we have previously shown that SOD1 overexpression induces an early thymic involution, which is an aging characteristic present in trisomy 21 patients. We thus evaluated the proteasome activities in the thymus of transgenic mice for SOD1, APP and both transgenes and compared them to control thymus. We showed that these proteasome activities are decreased in SOD1 transgenic mice in comparison to control at different ages (15, 30 and 80 days) but are similar in hAPP transgenic mice. In double transgenic mice APP/SOD1, the proteasome activities are also decreased in comparison to controls but much less than in the transgenic mice for human SOD1 transgene only. These results show for the first time at the biochemical level an interplay between the two genes APP and SOD1, further experiments will be performed to understand the respective roles of APP and SOD1 on proteasome activities.

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