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PD is the second most prevalent neurodegenerative disorder, affecting over one million individuals worldwide. The main pathological hallmark of PD is the loss of dopaminergic neurons within the substantia nigra, leading to insufficient formation and action of dopamine in the basal ganglia circuitry. The cardinal clinical signs are muscle rigidity, resting tremor, bradykinesia and, in more advanced cases, postural instability.

This complex disease is governed by many genetic and non-genetic factors. To identify novel susceptibility genes for idiopathic PD, we are using the "genomic convergence" approach with microRNA and proteomic profiling. This strategy converges data from genetic studies with expression profiling experiments.

We conducted microRNA expression profiles in peripheral blood mononuclear cells of 19 PD patients and 13 controls, using microarrays spotted with probes for 763 human microRNAs. 18 microRNAs were differentially expressed and pathway analysis of their predicted target genes revealed an over-represention of pathways recently linked to non-Mendelian forms of PD. We also carried out a proteomic analysis in pooled blood serum of 30 PD patients and 28 controls using a 2D-DIGE approach. 41 differentially expressed spots were obtained and 23 proteins have already been identified. Isoforms and post-translational modifications are being evaluated and their type and contribution to the disease mechanisms will be further analysed. The microRNAs and respective target genes, as well as proteins differentially expressed will be tested for association with PD. We believe that this approach will allow us to identify specific novel genes/transcripts playing a role in the etiopathogenesis of idiopathic PD.

P11.099 The Slc26a4 loop mouse mutant, a model for Pendred syndrome, has defects in biomineralization, with unique calcium oxalate stone formation in the inner ear

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Human mutations in *SLC26A4* lead to a non-syndromic and syndromic form of deafness, DFNB4 and Pendred syndrome, respectively. Here we show inner ear mineralization defects in a new mouse mutant identified in an N-ethyl-N-nitrosourea (ENU) screen, named loop, that carries a recessive missense mutation in a highly conserved region of *Slc26a4*, rendering this mouse a model for human deafness. Defects were identified in biomineralization, the formation of minerals, which is part of the process that produces skeletons, shells, and teeth. Impaired halide transport activity resulted in the formation of giant calcium oxalate mineral bodies not found in the body under normal circumstances and described here in the inner ear for the first time. Infrared and Raman spectroscopy, together with high resolution scanning electron microscopy and immunohistochemistry of otoconia components, demonstrated drastic changes in crystal morphology and composition. Detailed histological analysis revealed that the giant minerals are ectopically distributed within the vestibular apparatus, mimicking imbalance conditions in human as a result of displaced otoconia.

P11.100 Whole genome pharmacogenomic analysis of bipolar disease patients under lithium treatment

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Bipolar Disorder (BD) is a lifelong psychiatric disease characterized by manic and depressive episodes affecting 1-5% of the general population. Among the most effective mood-stabilizing treatments, lithium (Li) represents the mainstay in the therapeutic management of acute-mania and depression in BD and is still to date, the first choice prophylactic treatment. Besides the high rate of excellent Li responders (~30-40%), a significant fraction of patients present patterns of partial or non response to prophylactic treatment with Li. It has been shown that the variability in Li response is strongly influenced by genetic determinants. A large number of studies have investigated the role of genes in modulating the response to Li reporting contrasting findings. In our study, we have genotyped 50 individuals divided in two groups, according to their degree of Li response. The eleven-point treatment response scale we employed (full response cut-off ≥7) allowed us to classify 25 BD patients as non-responders (scored with 0) and 25 as full responders (scored with 8 or higher). These patients were genotyped using the Affymetrix Array 6.0 SNP microarrays (Santa Clara, CA, USA). Data were statistically evaluated using the *Genespring* software using a p-value cutoff of 0.01. We have identified 38 SNPs significantly associated with Li response, with p-values ranging from $1x10^{-5}$ to $4x10^{-6}$. The genomic loci hold genes encoding for elements of G-proteins coupled receptors, LIM-domain binding proteins, sodium channels and GABA receptors. This study enriches the battery of genetic biomarkers that would personalize Li treatment of BD patients.

P11.101 Epigenetics changes for the diagnosis of malignant pleural effusions

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DNA hypermethylation in promoter regions of a gene is recognized as an important epigenetic mechanism of transcriptional silencing of tumor regulatory genes during cancer development. This study could provide valuable information for diagnostic purposes.

We collected 60 patients with pleural effusion with diverse etiology: tuberculosis, para-pneumonia, or cancer.

DNA was extracted with a Qiagen Kit and after bisulfite treatment, a methylation-specific PCR (MSP) was performed. We analyzed the following genes: p16/INK4a, BRCA1 and RARβ.

The study population included 37 men (61.7%), with a mean age of 56.98±21 years. Thirty-three patients (55%) were former or current smokers. Malignant pleural effusion was diagnosed in 28 patients, while benign pleural effusion due to tuberculosis or para-pneumonia was present in 18 and 14 patients, respectively.

The promoter hypermethylation frequencies of benign and malignant pleural effusion, respectively were: p16/INK4a (9.4% vs 17.9%), BRCA1 (46.9% vs 35.7%) and RARβ (12.5% vs 17.9%), therefore no significant differences were detected. Promoter methylation of at least one gene was detected in 64.3% of the patients with malignant pleural effusion, while hypermethylation of at least two genes was observed in 14.3% of them.

Our preliminary results show that the methylation status of the promoter region of p16/INK4a, BRCA1 and RARβ has no diagnostic utility for malignant pleural effusion. The methylated condition of some of the benign pleural effusions could be related, as previously reported, with inflammation and infection, besides certain lifestyle factors such as smoking and high-fat diet, that are related with an increased likelihood of cancer risk.

P11.102 A study of angiotensin converting enzyme gene polymorphism in children with pulmonary hypertension

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Angiotensin converting enzyme (ACE) plays an important role in the pathogenesis of pulmonary hypertension. The ACE gene has been considered a candidate gene for contributing to the development of hypertension and cardiovascular diseases. The ACE gene contains a polymorphism based on the presence (insertion I) or absence (deletion D) within an intron of a 287-bp nonsense DNA domain, resulting in three genotypes (DD and II homozygotes, and DI heterozygotes).