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Abstracts

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PLENARY LECTURES

PL1 Opening Plenary Session

PL1.1
RAS genes and Human Disease: From Rasopathies to Cancer

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RAS genes have attracted a significant deal of attention in biomedical research due to central their role in mediating mitogenic signaling and to their oncogenic activation in at least one third of all human cancers including some of the most frequent and malignant tumor types such as colorectal carcinoma, lung adenocarcinoma and pancreatic ductal adenocarcinoma. More recently, Ras genes have also been implicated in developmental disorders including Costello and Noonan syndromes. In spite of the wealth of information accumulated over the last 30+ years on these genes we still have rather scant information regarding how their misregulation affects human health. More importantly, as of today, there are no efficacious inhibitors to treat those diseases caused by mutations or alterations in *RAS* genes. Our laboratory has been interested in the development of genetically modified (GEM) animal models that faithfully reproduce the natural history of these diseases and in the identification and subsequent validation of targets with potential therapeutic value. I will describe our GEM models for Costello (H-Ras^{G12V}) and Noonan (K-Ras^{I14V}) syndromes along with our efforts to validate potential therapeutic strategies to correct their developmental defects. I will also describe our new generation of GEM models for K-*Ras* mutant lung and pancreatic tumors and review the genetic approaches that we are utilizing to validate the therapeutic value of each of the kinases involved in the MAPK signaling cascade, the key pathway involved in K-*Ras* oncogenic signaling. We hope that these studies will serve to guide the design of future clinical trails to treat people suffering from Rasopathy syndromes as well as cancer patients carrying K-*RAS* mutant tumors.

PL1.2
The Spanish Experience of Retinal Dystrophies

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The retinal dystrophies (RDs) are degenerative diseases involving RPE and/or photoreceptors of the retina and currently without treatment options for the patients. RD may be syndromic or non-syndromic and can affect peripheral, central retina or both. They affect about 1:4,000 individuals and there are more than 270 known causative genes-loci. Mendelian (autosomal recessive, autosomal dominant or X-linked inheritance) and non-mendelian inheritance have been described.

This great clinical and genetic heterogeneity and the need for a genetic diagnosis to help and refine clinical management and guide genetic counseling are a real challenge.

Two decades ago, we started the study of RD in Spain (EsREtNet: Antiñolo, Baiget, Carballo, Millan, Valverde & Ayuso). The modes of inheritance frequency were established (15% Syndromic; and 12% dominant, 39% recessive, 4% Xlinked and 41% sporadic cases and 4% unclassified *Clin Genet. 1995*) and the first mutated genes (*RHO*, *CRB1, USH2A, etc)* affecting Spanish population were identified, using gene mutation screening approaches (SSCP, dHPLC) or Sanger sequencing.

From 2007, we used array-based primer extension (APEX) technology, with a diagnostic yield from 14% (for autosomal dominant RD; *Blanco-Kelly et al; Mol Vis 2012)* to 54% (for Stargardt cases; *Riveiro et al IOVS 2012*) in RD patients.

In 2011 new genomic analysis technologies, including next generation sequencing (NGS) and chromosome microarrays were implemented. In total 36% of the ≈3000 RD families were characterized and we identified new mutations and genes, and clinical associations.

Molecular characterization allowed us to refine clinical diagnosis, to confirm or change the pattern of inheritance, improving clinical management of RD cases and families. Moreover, we have established very well characterized cohorts of *USH2A, NR2E3, RHO, XLRS, CHM or ABCA4* patients, useful for natural history of disease studies. Additionally, mutated cases for *RPE65, PDEA,* among others can be offered to be included in current clinical trials.

At present, a more accurate and efficient algorithms for molecular diagnosis are available for RD patients to improve their clinical care, however we need still to improve the diagnosis rate and fill the gap to obtain effective therapies.

International collaborative efforts for research on molecular, epidemiological and therapeutic aspects are needed to achieve these goals

PL2 What's New? Highlight Session

PL2.1
Genomic landscape of balanced cytogenetic abnormalities in subjects with multiple congenital anomalies

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Balanced chromosomal abnormalities (BCAs) represent a unique class of genomic variation that involves large rearrangement of the chromosomes. To date their detection has been limited to cytogenetic resolution as most first-tier genetic screening methods are blind to their presence. We defined the genomic landscape of de novo BCAs associated with human congenial anomalies in 235 subjects using whole-genome sequencing. We observed that 22% of all BCAs harbored additional cryptic complexity, ranging from three breakpoints to chromothripsis events involving up to 57 breakpoints. Compared to random expectations, BCAs were more likely to occur between loci in close physical proximity in the nucleus, and their breakpoints were significantly enriched for evolutionarily constrained and embryonically expressed genes. From our convergent genomic interpretation using orthogonal datasets, we predict that the congenital anomaly phenotype was likely attributable to the BCA in at least 30% of subjects. An additional 4% of BCAs disrupted long-range regulatory regions such as topologically associating domains (TADs) resulting in position effects on genes associated with specific clinical manifestations that were compatible with the proband sequenced here. Remarkably, we observed a cluster of six independent translocations that disrupted a TAD and consequently altered MEF2C expression, mimicking the 5q14.3 microdeletion syndrome. These results suggest that de novo BCAs represent a highly penetrant class of genomic variation associated with congenital anomalies, and that nucleotide resolution offers insights into phenotypic prediction from direct gene disruption and alteration of long-range regulatory domains that are likely to be a significant source of causal variation in human disease.

PL2.2
Formation and content of novel chromatin domains (neo-TADs) determine pathogenesis of genomic duplications

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Mammalian genomes are organized in distinctly folded chromatin modules, called topologically associated domains (TADs) that are separated from each other by boundary regions. TADs subdivide the genome into discrete chromatin domains that direct the contacts enhancers can establish with their target genes. How copy number variations interfere with TAD structure and how this might contribute to human disease, is not well understood.