PRINCIPE FELIPE
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Integrated omics to understand missing heritability in inherited retinal diseases causing blindness

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Place: Salón de Actos CIPF

Abstract: Integrated genomics and transcriptomics reveal an increasing number of non-coding mutations in Mendelian disorders including inherited retinal diseases (IRD), representing a major cause of early-onset blindness in 2 million people worldwide. Of these the majority are deep-intronic splicing mutations, typically leading to pseudo-exon inclusion and amenable to antisense oligonucleotide-mediated rescue, already implemented in the clinic. Non-coding mutations in *cis*-regulatory elements (CREs) are more scarce. Paradigms for regulatory variants are IRD subtypes with recognizable phenotypes and without or - in case of autosomal recessive disease - monoallelic coding variants in the presumed disease genes. Examples are Stargardt disease (*ABCA4*), choroideremia (*CHM*), Leber congenital amaurosis 9 (*NMNAT1*) and North Carolina Macular Dystrophy (*PRDM13* and *IRX1*). Particularly interesting CREs are ultraconserved non-coding elements (UCNEs) that are clustered in genomic regulatory blocks (GRBs) and that may act as distant enhancers. A search for IRD genes in GRBs revealed genes in 12 GRBs. In three of these genes (*CHM, PRDM13, USH2A*), non-coding mutations have already been reported. In a set of genes under control of the retinal transcription factor CRX, 138 genes were found in GRBs that harbor 3,424 UCNEs. Only four of these are known IRD genes. These GRBs strongly coincide with topologically associating domains or TADs, playing key roles in gene regulation and determined by chromosome conformation capture techniques such as 4C-seq and UMI-4C. Integration of UCNEs with epigenomic datasets generated in relevant cell types contribute to functional genome annotations in retina and accelerate diagnosis and therapy in IRD.

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