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CIPF Lecture Series

Modelling the pathological long-range regulatory effects of structural variation with patient-specific hiPSC

Speaker: **Dr. Álvaro Rada Iglesias**
CMMC Center for Molecular Medicine, Cologne, Germany
Date: **23/11/18- 12:30h**
Place: Salón de Actos CIPF

Abstract: Structural variants can cause congenital abnormalities by disrupting the 3D organization of gene regulatory landscapes. However, elucidating the pathomechanism of human structural variation in vivo is complicated by the limited access to appropriate patient material and/or the differences in gene dosage sensitivity between mice and humans. These limitations are well illustrated by Branchio-Oculo-Facial Syndrome (BOFS), a rare congenital disorder caused by heterozygous mutations within TFAP2A, a neural crest (NC) master regulator for which humans, but not mice, are haploinsufficient. Here we describe a unique BOFS patient carrying a de novo heterozygous inversion in which one of the breakpoints is located downstream of TFAP2A, within a large Topologically Associating Domain (TAD) which we show contains distal enhancers essential for the expression of this gene in human NC cells (hNCC). Importantly, using patient-specific hiPSC and various genomic approaches, we systematically evaluate the molecular consequences of the inversion. Although the inversion shuffles the TFAP2A hNCC enhancers with potentially novel gene targets within the same TAD, this leads to neither productive enhancer-gene interactions (i.e. enhancer adoption) nor ectopic gains in gene expression, illustrating how placing enhancers and genes within the same TAD might not be always sufficient to drive gene expression. In contrast, we conclusively demonstrate that the inversion disconnects one of the TFAP2A alleles from its cognate enhancers, leading to TFAP2A monoallelic expression in hNCC. In turn, this results in TFAP2A haploinsufficiency due to reduced TFAP2A binding to enhancers controlling the expression of genes involved in craniofacial morphogenesis and NCC migration. Overall, our work illustrates the power of combining patient-specific hiPSC differentiation with different genomic and genetic engineering tools to unveil the long-range pathological consequences of human structural variation.

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