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SEMINARIO

Targeting the mutational landscape of the human mitoribosome

12:30 h, Aula 1, Hospital Teresa Herrera - 10 de febrero de 2015

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Mutations of mitochondrial DNA are linked to many human diseases. Establishing the pathogenicity of these mutations is of major diagnostic importance. In the case of the mitochondrially-encoded rRNA (mt-rRNA) genes, a large number of potentially pathogenic variants has been identified. However, we lack direct methods to firmly establish their pathogenicity. We have devised an indirect approach named Heterologous Inferential Analysis or HIA that can be used to make predictions on the disruptive potential of a large subset of mt-rRNA variants (Elson *et al*. Methods in Molecular Biology *In press*). HIA is based on the high evolutionary conservation of the rRNA fold and combines conservational information with functional and structural data obtained from heterologous ribosomal sources. Recent developments in CryoEM technology have notably improved HIA's predictive power, by allowing the use of medium-resolution structures from mammalian mitoribosomal particles in the structural comparisons. In cases where sufficient information regarding the genetic and pathological manifestation of disruptive mt-rRNA mutations is available, HIA data alone can be used to predict their pathogenicity. In other cases, HIA will serve to prioritize variants for additional investigation. We have performed HIA on very rare mutations mapping to both human mitoribosomal subunits (Smith *et al.*, Hum Mol Genet. 2014 (4):949-67; Elson *et al. manuscript in preparation*). Such analysis provided an initial picture of the mutational landscape of the human mitoribosome. Notably, it has served to identify 11 expectedly and 15 likely disruptive mt-rRNA mutations. Eventually, HIA-inspired analysis, in the context of a scoring system specifically designed for mt-rRNA mutations, could lead to a powerful diagnostic tool.

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