Genetic variants as determinants of outcome in lamin A/C-related cardiac disease

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Background: Current guidelines for the diagnosis and management of familial dilated cardiomyopathy highlight the variables “male sex” and “non-missense type variants” as risk factors for malignant ventricular arrhythmias.

Objective: Quantitative evaluation of prognostic differences between different LMNA variants associated with cardio-laminopathy.

Method: Analysis of cardiac event-free survival (sudden death, major arrhythmic events, death from heart failure and transplantation) with Kaplan-Meier approach in relation to gender & variant LMNA type. The data come from a specific database containing information on more than 1200 carriers of disease-causing LMNA variants. In the first analysis, the groups of comparison were truncating-type variants (LMNAtv) VS the global of pathogenic missense variants in the gene associated with cardiolaminopathy (LMNAm), segregated by gender. In the second analysis, it was considered missense LMNA affecting different residues (p.Arg190, p.Arg377 and p.Arg541), located in different functional domains, with enough data for comparison and with statistically different clinical behavior from that of global pathogenic variants in the gene. They were compared with the group of LMNAtv variants, as reference. The variants included were p.Arg377Cys/His, p.Arg541Cys/Ser/Gly/Pro/His and p.Arg190Trp/Gln/Pro, all of them pathogenic and associated with cardio-laminopathy.

Results: No significant differences were observed in survival between LMNAtv versus LMNAm variants (log rank=0.56) with slightly worse outcomes in males (log rank 0.03). Median survival time was 56 years for men compared to 60 years for women with LMNAtv, and 55 years compared to 66 years, respectively, among carriers of LMNAm (analysis A). In analysis B, statistically significant differences were observed between the groups considered (Log Rank $p<0.001$). These differences were also clinically relevant (median survival time in groups p.Arg377, LMNAtv, p.Arg190 and p.Arg541 was 60, 58, 50 and 35 years, respectively). Importantly, more than 70% of the cardiac events observed were related to major ventricular arrhythmic episodes.

Conclusions: This quantitative analysis demonstrates that certain missense variants in LMNA may have a similar and even more adverse clinical course than the set of truncation-type variants. These findings highlight the relevance of the specific variant rather than the variant type in guiding actionable therapies to prevent adverse outcomes. Regarding the differences observed between genders, even though they are statistically significant, their magnitude could be clinically not relevant.