Clinical genetic testing in arrhythmogenic mitral valve prolapse syndrome highlights a potential overlap with familial dilated cardiomyopathy

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Background/Introduction: Arrhythmogenic mitral valve prolapse syndrome (AMVPS) is a female-predominant sudden cardiac death (SCD)-predisposing disorder characterized clinically by myxomatous mitral valve prolapse (MVP), inferolateral T-wave inversions and complex ventricular ectopy. However, insights into the pathogenesis and potential genetic basis of AMVPS are currently lacking.

Purpose: Considering recent case reports that suggest a potential role for genetic cardiomyopathies in the pathogenesis of AMVPS, we sought to determine the yield of pathogenic/likely pathogenic (P/LP) genetic variants in strong evidence cardiomyopathy-susceptibility genes amongst AMVPS patients who underwent clinical genetic testing.

Methods: In this retrospective study, the medical records of 4,907 patients referred to our cardiovascular genetics clinic was used to identify those patients with a clinical phenotype consistent with AMVPS. After exclusion of individuals with severe mitral valve regurgitation, pertinent clinical, electrocardiographic, imaging and genetic testing data was extracted from the electronic record. For those AMVPS that underwent a form of genetic testing that encompassed 23 Clinical Genome Resource-defined strong/definitive evidence cardiomyopathy-susceptibility genes, ultra-rare (minor allele frequency ≤ 0.00005 in the Genome Aggregation Database [n=141,456 individuals]) non-synonymous variants identified within these genes were adjudicated independently as P, LP or variant of uncertain significance with the assistance of Varsome. The frequency of P/LP variants was then compared to a previously published cohort of 973 ostensibly healthy control exomes.

Results: Overall, 56 unrelated patients with suspected AMVPS were identified (82% female; average age at presentation of 31 ± 13 years; 32% with a family history of MVP and/or SCD). Of these, 24/56 (43%) underwent a form of clinical genetic testing that encompassed the pre-defined panel of cardiomyopathy-susceptibility genes. In comparison to control exomes (n=973), P/LP variants in strong/definitive evidence cardiomyopathy-susceptibility genes were over-represented in AMVPS patients [4/24 (16.7%) vs 20/973 (2.1%); p=0.002]. Interestingly, this enrichment was driven in large part by an excess number of A-band-localizing P/LP truncating variants in TTN-encoded titin in AMVPS cases [3/24 (12.5%) versus 4/973 (0.4%); p=0.0004].

Conclusion: This study provides further evidence that a subset of AMVPS may arise secondary to a "two-hit" model whereby an underlying cardiomyopathic genetic substrate is exacerbated by the mechanical force generated by genetically unrelated myxomatous MVP resulting in maladaptive and ventricular arrhythmia-predisposing fibrosis within the inferobasal left ventricle and posterior medial papillary muscles. Larger studies are needed to better understand the potential role of genetic testing in the diagnosis, risk-stratification and management of patients with suspected AMVPS.