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Is Occult Genetic Substrate the Missing Link Between Arrhythmic Mitral Annular Disjunction Syndrome and Sudden Cardiac Death?

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Brief summary

We provide the first evidence of a truncating *LMNA* gene variant serving as a possible substrate for arrhythmogenic mitral annular disjunction syndrome, thus suggesting a possible interaction between concealed genetic variants (the arrhythmogenic substrate) and the presence of mitral annular disjunction (the trigger for ventricular arrhythmias). Could this be the missing link between mitral valve prolapse and sudden cardiac death?

Abstract

We present the case of a 28-year-old man with a history of unexplained syncope, frequent ventricular arrhythmias, familial LMNA-related dilated cardiomyopathy (DCM) and mitral annular disjunction (MAD). We provide the first association of a novel truncating *LMNA* variant serving as a potential vulnerable substrate for arrhythmogenic MAD syndrome. This could suggest a possible synergistic role between concealed genetic variants (resulting in fibrosis as a 'substrate' for arrhythmogenesis) and the presence of mitral annular disjunction (the 'trigger' with mechanical stretch initiating ventricular arrhythmias), which may provide a link between mitral valve prolapse and sudden cardiac death.

A 28-year-old male presented with frequent premature ventricular complexes (PVCs) at pre-participation screening 12-lead ECG (**Figure 1A)**. He described a previous syncopal episode during exertion. Physical examination revealed an apical mid-to-late systolic murmur but was otherwise unremarkable**.** Echocardiography revealed mild left ventricle (LV) dilatation with low-normal LV systolic function (LVEF 50%) and myxomatous mitral valve leaflets with bileaflet mitral valve prolapse (MVP) associated with moderate mid-to-late systolic mitral regurgitation (MR) (**Figure 1B**). Additionally, mitral annular disjunction (MAD) was present with a maximum height of 14mm (**Figure 1C**). ECG showed sinus rhythm with first-degree atrioventricular block (AVB) and PVCs of right bundle branch block morphology and superior axis, suggestive of a posteromedial papillary muscle origin (**Figure 1A**). Ambulatory ECG monitoring recorded frequent PVCs with runs of multifocal non-sustained ventricular tachycardia. Cardiovascular magnetic resonance (CMR) confirmed LV dilatation, bileaflet MVP, MAD (**Figure 1D**), and showed marked late gadolinium enhancement (LGE) of the posteromedial papillary muscle and mid-wall non-ischemic distribution of the basal- and mid-anteroseptum, inferoseptum and inferior segments (**Figure 1E-F**).

The patient's father was previously diagnosed with bileaflet MVP and MAD by echocardiography, required permanent pacing for advanced second-degree AVB, developed advanced heart failure (HF) with a non-ischemic dilated cardiomyopathy (DCM) phenotype, and eventually required cardiac transplantation. His paternal uncle and grandmother were also diagnosed with DCM, bileaflet MVP and MAD.

Familial DCM was assessed following genetic counselling. Target panel testing revealed the presence of a heterozygous frameshift and truncating variant of *LMNA* gene (1q22; NM_170707.3(LMNA): c.590_596del (p.Leu197Profs*2), encoding for the nuclear envelope protein lamin A/C, classified as pathogenic (**Figure 1G**). The patient was commenced on metoprolol, low-dose ramipril, and underwent ICD implantation for primary prevention of sudden cardiac death (SCD).

Pathogenic *LMNA* gene variants are a recognized cause of malignant DCM phenotype due to early conduction system disorders and life-threatening ventricular arrhythmias.[1] An individualized approach to SCD risk stratification is recommended, since the specific variant type may influence phenotype severity. MAD has recently been associated with high arrhythmic burden and SCD, particularly in younger female patients with LV systolic dysfunction, MAD, curling, and papillary muscle fibrosis[2]. However, no direct relationship between *LMNA* gene mutation and arrhythmic MAD syndrome has yet been described. Recently, a mutation of the *FLNC* gene, encoding for gamma-filamin and involved in the development of DCM, was reported as a potential genetically-determined substrate of arrhythmogenic bileaflet MVP syndrome[3].

The presence of inheritable proarrhythmic genetic substrate that may underlie some cases of MAD arrhythmic syndrome provided a possible explanation and may be the missing link between MVP and SCD. It is indeed plausible that MAD arrhythmic syndrome may constitute a manifestation of a concealed genetic substrate with propensity for arrhythmias (such as *LMNA* cardiomyopathy), where myocardial scarring is the signature of an underlying primary myocardial process and the structural substrate for arrhythmogenesis, and altered mechanics of the mitral annulus are the possible triggers of ventricular arrhythmias. Alternatively, DCM and mitral valve pathology may represent a trait of phenotypic heterogeneity of the same proarrhythmic genetic substrate, but this hypothesis would need larger-scale testing and segregation analyses of families to unequivocally link LMNA variants to MVP and MAD. The increasing availability of multimodality imaging and affordable genomic data should facilitate development of multicentre registries to help elucidate the complex interplay among genetic substrates, MAD and ventricular arrhythmias, providing possibilities of novel therapeutic strategies and targeted prevention of SCD.

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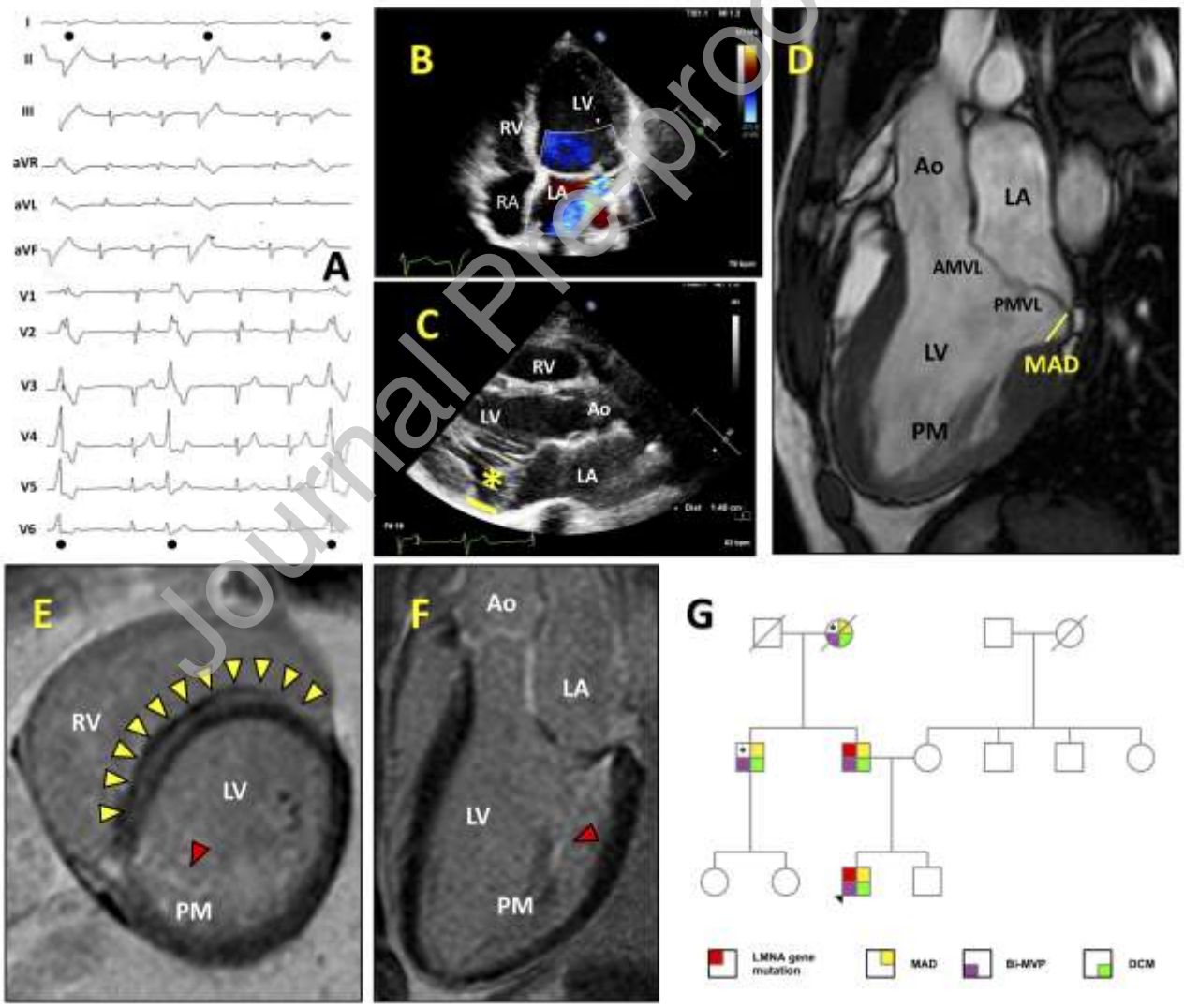

Figure 1: Summary of clinical findings. **Panel A**, ECG showing first-degree atrioventricular block (PQ interval 220ms) and multifocal ventricular ectopics (black dots) with RBBB morphology and

superior axis. **Panel B**, mildly dilated LV (end-diastolic diameter 63mm; end-diastolic volume 119ml/m2) and mild mitral regurgitation. **Panel C**, bileaflet mitral valve prolapse (MVP) and MAD (yellow asterisk). **Panel D**, MAD with maximum distance of 14 mm. **Panels E-F**, mid-wall LGE of the mid-basal septum (yellow arrowheads) and LGE of the posteromedial papillary muscle (red arrowheads). **Panel G**, multigenerational pedigree chart showing phenotypic expression of MVP (purple), MAD (yellow), dilated cardiomyopathy (*green*), and novel pathogenic mutation of *LMNA* gene (*red*). Paternal uncle and paternal grandmother (asterisk) did not undergo genetic testing.

Ao, aorta; AMVL, anterior mitral valve leaflet; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle; MAD, mitral annular disjunction; PM, papillary muscle; PMVL, posterior mitral valve leaflet; RA, right atrium; RBBB, right bundle branch block; RV, right ventricle.