ORIGINAL ARTICLES

Familial cardiomyopathy caused by a novel heterozygous mutation in the gene \textit{LMNA} (c.1434dupG): a cardiac MRI-augmented segregation study

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In a five-generation family carrying a novel frameshift \textit{LMNA} variant (c.1434dupG, p.Leu479AlafsX72), imaging-augmented segregation analysis supports its association with lamin heart disease. Affected members exhibit conduction abnormalities, supraventricular and ventricular arrhythmias, dilated cardiomyopathy with non-infarct pattern midwall septal fibrosis, heart failure and thromboembolic complications.

Key words: familial dilated cardiomyopathy, lamin A/C, cardiomyopathies

Introduction

Lamin A/C are structural intermediate filaments encoded by the \textit{LMNA} gene. \textit{LMNA} gene mutations are responsible for various multi-system laminopathies including lamin heart disease (LHD) which is characterized by cardiac conduction system disease (CCD), dilated cardiomyopathy (DCM), heart failure, malignant ventricular arrhythmias (VA) and sudden cardiac death (1). Given the high arrhythmogenic risk, early recognition and intervention by implantable cardioverter defibrillator (ICD) can be life-saving.

Defining pathogenicity of novel \textit{LMNA} variants remains a challenge, but long-term surveillance of mutation-positive families permits segregation studies that are essential contributors to the validation of pathogenic mutations. Advanced tissue characterisation by cardiovascular magnetic resonance (CMR) may help clinicians better understand the potential pathogenicity of variants, especially when segregation studies include family members with borderline/subclinical phenotypes by other imaging modalities.

Here we describe the deep clinical phenotypes associated with a previously unreported \textit{LMNA} variant: c.1434dupG.

Case presentation

We report a family in which all affected members with cardiomyopathy (Fig. 1, left panel) carry the heterozygous \textit{LMNA} variant, c.1434dupG (Tab. 1). The variant is predicted to disrupt protein reading frame creating a premature termination codon confirmed by Alamut® software. As variant pathogenicity was unknown we performed an imaging-assisted segregation study, demonstrating a link between variant and LHD.

Within this five-generation family, four members are confirmed carriers of the variant by DNA testing, expressing a clinical phenotype that includes DCM, myocardial septal fibrosis [anecdotally found in 88% of \textit{LMNA} gene mutation carriers (2)], supraventricular and ventricular arrhythmias, CCD, heart failure and thromboembolic complications.
boembolic complications (Tab. 2). There was a history of sudden death in seven members, interestingly all males [male gender is an adverse prognostic marker in LHD (3)]; proband II-10 died suddenly in his 40s likely from paternal inheritance of the variant as his father (I-1) died abruptly in his 50s (no genetic data available for

Table 1. Novel LMNA genetic variant summary.

| Variant | c.1434dupG, p.Leu479AlafsX72 |
|---------|-------------------------------|
| Mutation status | Autosomal dominant, heterozygous |
| Variant type | Frameshift (truncation predicting mutation) |
| Molecular consequence | NM_170707: c.1434dupG: loss-of-function variant |
| Genomic location | Chr 1: 156,114,707-156,140,089 |
| Variant location | Exon 8: Single nucleotide duplication, premature termination codon; downstream of the nuclear localization signal (NLS, exon 7) but upstream of the C-terminal tail |

* Recent data suggests that there is an association between more adverse cardiac phenotype and LMNA mutations upstream of the NLS or upstream of the tail (Captur et al., 2018. Doi: 10.1136/openhrt-2018-000915).

| Phenotypic group | Dilated cardiomyopathy-conduction disease (DCM-CD) |
| GnomAD database | Absent |
| ClinVar clinical significance | Not reported |
| ACMG assertion of pathogenicity | Pathogenic (Ia) |
| Type of analysis | Direct fluorescent DNA sequencing for exon 8 |
Familial cardiomyopathy caused by a novel heterozygous mutation in the gene *LMNA*

The latter). Members I-1, II-1, II-5, II-6 and II-8 died young and unexpectedly (no genetic data available). Patient III-8 carries the variant and expresses an overt DCM phenotype together with atrial fibrillation (AF). Two of his children were also found to be carriers: IV-4 expressed DCM with heart failure, advanced CCD and ventricular arrhythmias that required an ICD. A DCM-pattern of extensive myocardial midwall septal fibrosis was noted by cardiovascular magnetic resonance (CMR) imaging. His brother IV-6, exhibited isolated right ventricular enlargement and biatrial dilatation in the context of AF, supraventricular arrhythmias and progressive CCD. Following multidisciplinary team (MDT) meeting family member IV-6 received a primary prevention dual chamber ICD given his two risk factors for sudden cardiac death [male gender and non-missense *LMNA* mutation (4)]. His CMR similarly revealed midwall septal fibrosis matched by elevated native myocardial T1 times (Fig. 1, right panel). On follow-up, post-ICD, we detected a self-terminating ten-beat salvo of non-sustained ventricular tachycardia (VT).

DNA testing in their sister IV-8 with normal CMR, excluded the presence of an *LMNA* mutation but identified a variant of uncertain significance (VUS) in the *Obscurin* gene (*OBSCN*, c.21011C > G, p.Ser7004Cys). Although a few *OBSCN* mutations have been reported in the context of DCM and hypertrophic cardiomyopathy (5), their occurrence in heterozygous states in individuals from the general population argue against their pathogenicity.

### Discussion

Our report describes a family in which the proband and affected family member harbour a novel potentially pathogenic mutation in *LMNA* gene (c.1434dupG). The mutation was not previously described in the literature, however the clinical course and ominous outcomes resemble those reported in cardiolaminopathy. In this family there were seven premature sudden deaths (6). In a multicentre study of 269 *LMNA* mutation carriers male gender, non-missense mutation, left ventricular ejection fraction < 45% and presence of non-sustained VT were found to be independent predictors of malignant VA (4). In this regard, member IV-4 with ICD satisfies all four risk factors whilst member IV-6 with progressive CCD and ICD scored positive for two risk factors (male, non-missense mutation).

Pharmacological therapy in our *LMNA* gene mutation carriers with heart failure consisted of usual heart failure medications although in patients with bradyarrhythmias, beta blockers were reserved till after device implantation or else discussed in a dedicated cardiomyopathy MDT meeting. Arrhythmias were managed according to standard clinical practice, and all decisions related to device implantation were reached after considering SCD risk factors and broader MDT discussion.

This pedigree analysis highlights the added value of CMR in segregation studies of LHD. For example, CMR potentially enables clinicians to better: 1) differentiate *LMNA*-DCM from other phenotypic mimics such as dilated cardiomyopathy, hypertrophic cardiomyopathy, and cardiomyopathy caused by other mutations such as those in the *MBNL1*, *VAV3*, and *CHRNA1* genes.
as arrhythmogenic cardiomyopathy; 2) exclude ischemic DCM using quantitative perfusion mapping approaches; 3) monitor LHD progression over time; 4) detect subclinical phenotypes otherwise missed by other imaging modalities; 5) plan optimal timing of device implantation in patients with borderline phenotypes as part of a multidisciplinary team meeting discussion.

Previous CMR work reported that non-ischaemic (midwall) scar in patients with LHD and VA predominantly involved the basal septum, basal inferior wall, and sub-aortic mitral continuity (7), which tallies with our current data. Member IV-6 had non-infarct pattern mid-wall LGE in the basal-to-mid septum matched by high myocardial T1 but normal T2 times, suggesting true myocardial septal fibrosis. Indeed he had QRS fragmentation on ECG (Fig. 1, right panel).

Limitations include that other genomic changes in this family cannot be definitively excluded, CMR was not performed on all family members, and genetic data unavailable for the five family members in generations I/II with premature sudden deaths.

Conclusions

LMNA frameshift variant (c.1434dupG) seems to be causative of lamin heart disease on the basis of this CMR-augmented segregation analysis however further studies are necessary to confirm our hypothesis.

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Conflicts of interest

The Authors declare to have no conflict of interest.

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