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CASE REPORT
Arrhythmias/electrophysiology

Red herring pathogenic variants: a case report of premature ventricular contraction-triggered ventricular fibrillation with an incidental pathogenic *LMNA* variant

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Background Pathogenic variants in the lamin A/C gene (LMNA) can lead to a wide range of phenotypes from dilated and arrhythmogenic cardiomyopathies and conduction abnormalities to partial lipodystrophies. This case highlights a coincidental pathogenic LMNA variant identified in a patient with sudden cardiac arrest (SCA). We demonstrate the need for careful interpretation of pathogenic variants identified in cardiomyopathy genes by highlighting a case in which a coincidental pathogenic LMNA variant was found in a patient with premature ventricular complex (PVC)-induced ventricular fibrillation (VF).

Case summary We present the case of a 16-year-old male with SCA secondary to VF. Genetic testing identified a maternally inherited pathogenic variant in LMNA annotated c.1961dup; p.T655Nfs*49. The patient received an implantable cardiac defibrillator and was discharged on nadolol. The patient's two brothers were also variant-positive. However, the patient and both brothers had normal chamber dimensions on echocardiogram and no late gadolinium enhancement on cardiac magnetic resonance imaging. The family members with the variant were recommended to have prophylactic implantable cardiac defibrillators and thus sought a second opinion. The patient received an appropriate shock and device interrogation identified PVCs. Electrophysiology study identified PVC-induced VF which was ablated with no recurrent ventricular arrhythmias/implantable cardioverter defibrillator therapies over 8 months of follow-up. Although the variant in LMNA could lead to cardiac arrest, the clinical phenotype was consistent with a non-genetic aetiology. The family members were told to have periodic cardiac evaluation.

Discussion This case demonstrates the identification of a coincidental pathogenic variant in a cardiomyopathy gene in a patient with cardiac arrest. Although this variant could lead to cardiomyopathy, it appears the cardiac arrest was not due to the pathogenic variant. This highlights the need to consider the clinical phenotype when interpreting genetic test results for cardiomyopathies even in the presence of a positive genetic test result.

Keywords Cardiomyopathy • Cryogenic ablation • Genetic testing • Lamin A/C • *LMNA* • Case report

ESC Curriculum 6.5 Cardiomyopathy • 9.9 Cardiological consultations • 5.6 Ventricular arrhythmia • 5.10 Implantable cardioverter defibrillators

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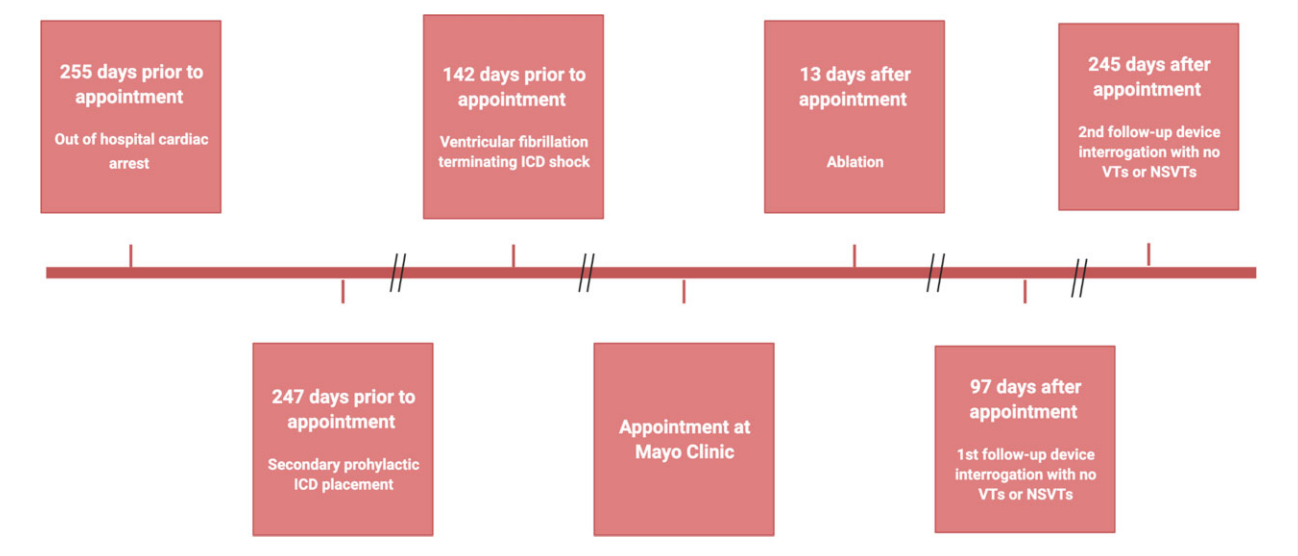
Learning points

- The evaluation and management of patients with suspected genetic heart diseases such as cardiac laminopathy often requires the expertise of a multidisciplinary team (genetic counsellors, genetic cardiologists, electrophysiologists, and advanced heart failure specialists).
- When interpreting genetic test results in a patient/family with marked genotypic/phenotypic discordance, it is best to prioritize clinical phenotype.
- In a patient with a cardiac laminopathy-causative *LMNA* variant, LMNA-mediated sudden cardiac arrest in the setting of a pristine cardiac evaluation is unlikely.

Introduction

Pathogenic variants in the lamin A/C gene (*LMNA*) lead to laminopathies, which result in pleiotropic phenotypes such as dilated and arrhythmogenic cardiomyopathies, cardiac conduction abnormalities, muscular dystrophies, progerias, and partial lipodystrophies.[1] Herein, we present a case that highlights the importance of a nuanced and critical interpretation of clinical laboratory improvement amendments-approved, genetic testing laboratory-adjudicated likely pathogenic/pathogenic variants. The index case suffered a sudden cardiac arrest (SCA) concluded initially as stemming from *LMNA*-mediated ventricular fibrillation (VF). Instead, careful clinical assessment and genetic evaluation revealed this to be a case of premature ventricular complex (PVC)-induced VF with a coincidentally detected pathogenic *LMNA* variant that did not appear to be responsible for the SCA.

Timeline



Case presentation

A 16-year-old white male presented for a second opinion regarding out-of-hospital SCA secondary to VF. The index event occurred in the evening when the patient was found in their room making agonal breathing sounds with eyes rolled back and loss of urinary continence. Cardiopulmonary resuscitation was initiated, and emergency medical services applied four automated external defibrillator shocks for documented VF, two epinephrine shots, and midazolam for the seizure-like activity before the return of spontaneous circulation.

Transthoracic echocardiogram during initial hospitalization demonstrated decreased systolic function, but troponin levels were within normal limits. Cardiac magnetic resonance imaging (CMRI) revealed a structurally normal heart with no late gadolinium enhancement (*Figure 1*). The left ventricle dimension at end-diastole was 48 mm (within normal limits). Transient post-arrest QT prolongation and ventricular ectopy were observed on telemetry. The patient underwent Invitae™ genetic testing (150 gene Arrhythmia and Cardiomyopathy Comprehensive Panel®) which identified a heterozygous, maternally inherited frameshift variant annotated as c.1961dup; p.T655Nfs*49 in *LMNA*. This variant was classified as 'pathogenic' following the American College of Medical Genetics (ACMG) guideline criteria-based variant adjudication. In addition to the patient's 44-year-old mother, his 14-year-old and 10-year-old brothers were variant-positive. This variant had been published as causative for co-dominantly inherited laminopathy with phenotypes ranging from metabolic to cardiac conduction abnormalities.[2–4] Due to a perceived risk for recurrence, the patient received a single-

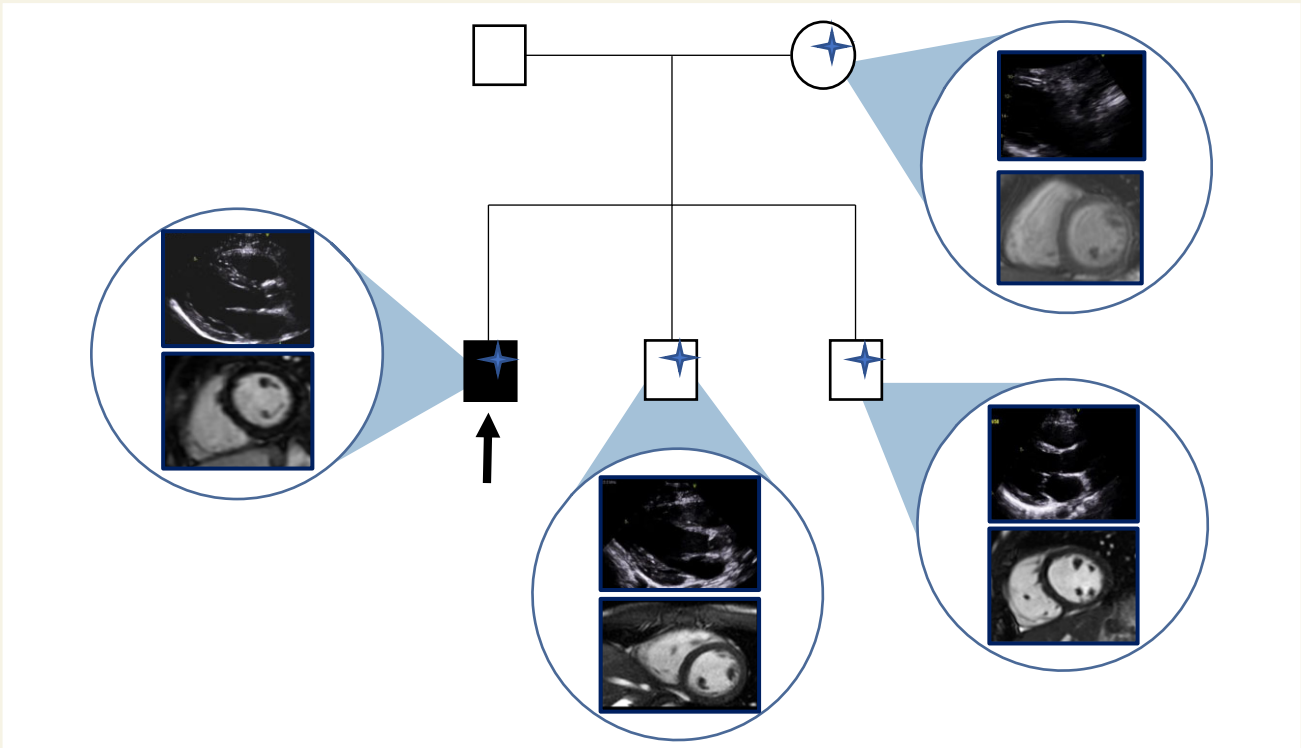


Figure 1 Family pedigree with structural imaging. The 16-year-old proband (black arrow) and all first-degree relatives with the p.T655NfsX49-LMNA variant (blue star) had structurally normal hearts with unremarkable echocardiogram with no late gadolinium enhancement on cardiac magnetic resonance imaging. Parasternal long-axis view at end-diastole and short-axis cardiac magnetic resonance imaging are displayed.

chamber implantable cardioverter defibrillator (ICD) and was discharged on nadolol 20 mg daily. It was suggested that the variant-positive family members consider a prophylactic ICD. Subsequently, the family sought out a second opinion.

The patient and all variant-positive family members had normal chamber dimensions on echocardiogram and no evidence of late gadolinium enhancement on CMRI (*Figure 1*). The patient had no signs of conduction disease on an electrocardiogram with a PR interval of 114 ms, QRS duration of 84 ms, and QTc of 380 ms (*Figure 2*). Additionally, the patient and the variant-positive family members showed no overt signs of lipodystrophy. However, a three-lead Holter monitor showed sinus arrhythmia and short-coupled PVCs ($\leq$350 ms)[5] with an overall PVC burden $<$1%. Induced ventricular arrhythmias were absent during exercise stress testing.

Device interrogation revealed that a few weeks prior, the patient missed a few doses of nadolol and had documented PVC-induced VF with two short-coupled PVCs (a 350 ms followed by a 250 ms PVC) deteriorating to VF with appropriate shock delivery restoring sinus rhythm (*Figure 3*). Subsequently, the patient underwent an electrophysiology (EP) study. At baseline, occasional PVCs (coupling interval of 350 ms) were observed with a left bundle branch block pattern, late precordial transition, and left superior axis, suspicious for a moderator band exit (*Figure 4A*). A morphology template of this PVC was formed. Endocardial mapping of the right ventricle (RV) was performed with a Saint Jude grid catheter and a NavX mapping system. Atrial extra stimulus while on isoproterenol was consistent with atrioventricular nodal reentry tachycardia (AVNRT) as it induced narrow complex tachycardia with a concentric sequence of retrograde atrial activation. Premature ventricular complexes occurred during withdrawal of atrial pacing. During tachycardia, there was a concentric sequence of retrograde atrial activation and the earliest atrial depolarization was a fast pathway. The septal V–A interval was 70 ms. The earliest PVCs were mapped to an area at the distal portion of the moderator band at the juncture between the moderator band and the RV papillary muscle (*Figure 4B*). A single, double, and triple ventricular extra stimulus protocol was performed with no inducible sustained ventricular arrhythmias with and without isoproterenol. Right ventricular voltage mapping demonstrated normal voltage and electrograms (*Figure 5*).

Next, a cryoablation was performed since radiofrequency catheters have limited efficacy at the moderator band due to difficulty achieving constant contact. The use of a cryoablation catheter overcomes this limitation by forming an ice crystal that fuses to myocardial tissue which ensures consistent contact during the duration of the cryoapplication. Using an 8 mm Cryocatheter, a pace map along the moderator band revealed the best pace map was at the same location, the junction between the moderator band and the RV papillary muscle. Additionally, a small Purkinje potential was observed on the ablation catheter. As it appeared that this location was around the thick portion of the moderator band muscle, multiple cryo-lesions were placed. Also, slow atrioventricular node pathway ablation was performed. Atrial and ventricular extra stimulus protocols were performed following cryoablation, and there was no ectopy seen with or without isoproterenol. Additionally, both brothers underwent an EP study, AVNRT but neither had PVCs.

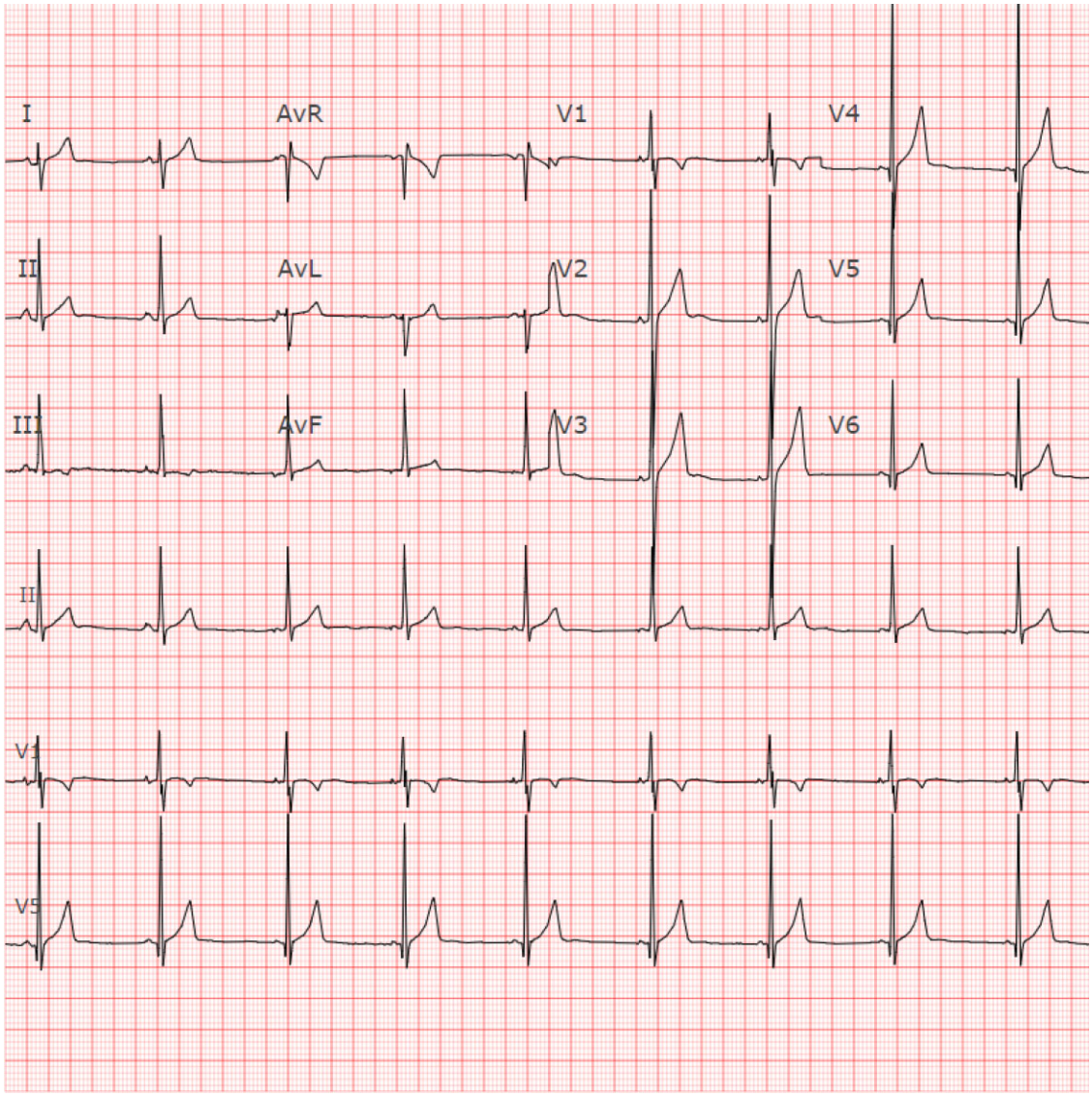


Figure 2 Electrocardiogram obtained on a patient showing sinus bradycardia with a PR interval of 114 ms, QRS duration of 84 ms, and QTc of 380 ms not showing any signs of conduction disease.

The patient returned for follow-up visits at both 3 and 8 months post-ablation without using any medication. During this early follow-up, there have been no ICD therapies and no recordings of any ventricular arrhythmias.

Discussion

Here, an LMNA variant (p.T655NfsX49) classified as pathogenic/likely pathogenic was detected in a 16-year-old individual with SCA secondary to VF, initially prompting suspicion for *LMNA*-mediated cardiomyopathy. This variant was classified as 'pathogenic' according to ACMG criteria. This is a null variant (PVS1) in a condition where null variants have been shown to cause disease, functional studies demonstrate a cellular effect consistent with laminopathy (PS3),[2,3] its absence in the genome aggregation database (gnomAD) ($n = 141\,456$ individuals) (PM2),[6] it results in the loss of a reside necessary for generating the mature form of the protein (PM1),[2,3] and it has been shown to cosegregate with laminopathy (PP1).[3,4] The penetrance of this variant was not complete and 21% of heterozygotes displayed no features of lipodystrophy.[3,4] In addition, the effect on cardiac phenotype was particularly weak in heterozygotes with only 12% (4/33) having atrioventricular block and 3% (1/33) an atrial or ventricular arrhythmias. Consequently, this variant has a weak penetrance in heterozygotes unlike traditional cardiac laminopathies which tend to be highly penetrant.[7] Consequently, interpreting the pathogenicity of the variant requires caution.

In this patient, the clinical presentation is inconsistent with expected findings as the patient had normal structural and haemodynamic findings on echocardiogram and CMRI and a normal ECG. Although it is possible that a concealed cardiomyopathy may result in an electrical substrate

capable of generating SCA-predisposing ventricular arrhythmias,[8] this seems unlikely given the index case's completely negative family and personal history. Furthermore, the penetrance of *LMNA*-mediated cardiomyopathy is relatively high (85%) with a high percentage of initially asymptomatic *LMNA*-positive family members developing cardiac manifestations such as atrioventricular block, atrial arrhythmias, non-sustained or sustained ventricular tachycardia, or imaging evidence of dilated cardiomyopathy over time.[7] At the time there is not enough evidence to consider the pathogenic variant as being responsible for the SCA.

The patient and his two brothers all had AVNRT which can be seen in Brugada syndrome; however, the lack of a family history, negative genetic test for *SCN5A* variants, and normal ECG including a normal PR interval make Brugada syndrome unlikely. Consequently, a sodium blocker test was not performed as this has a false-positive risk, especially in the USA due to the inability to use ajmaline.[9] Additionally, AVNRT has been shown to cluster in families in an autosomal dominant pattern, suggesting a genetic aetiology independent of known cardiomyopathy or Brugada syndrome genes.[10]

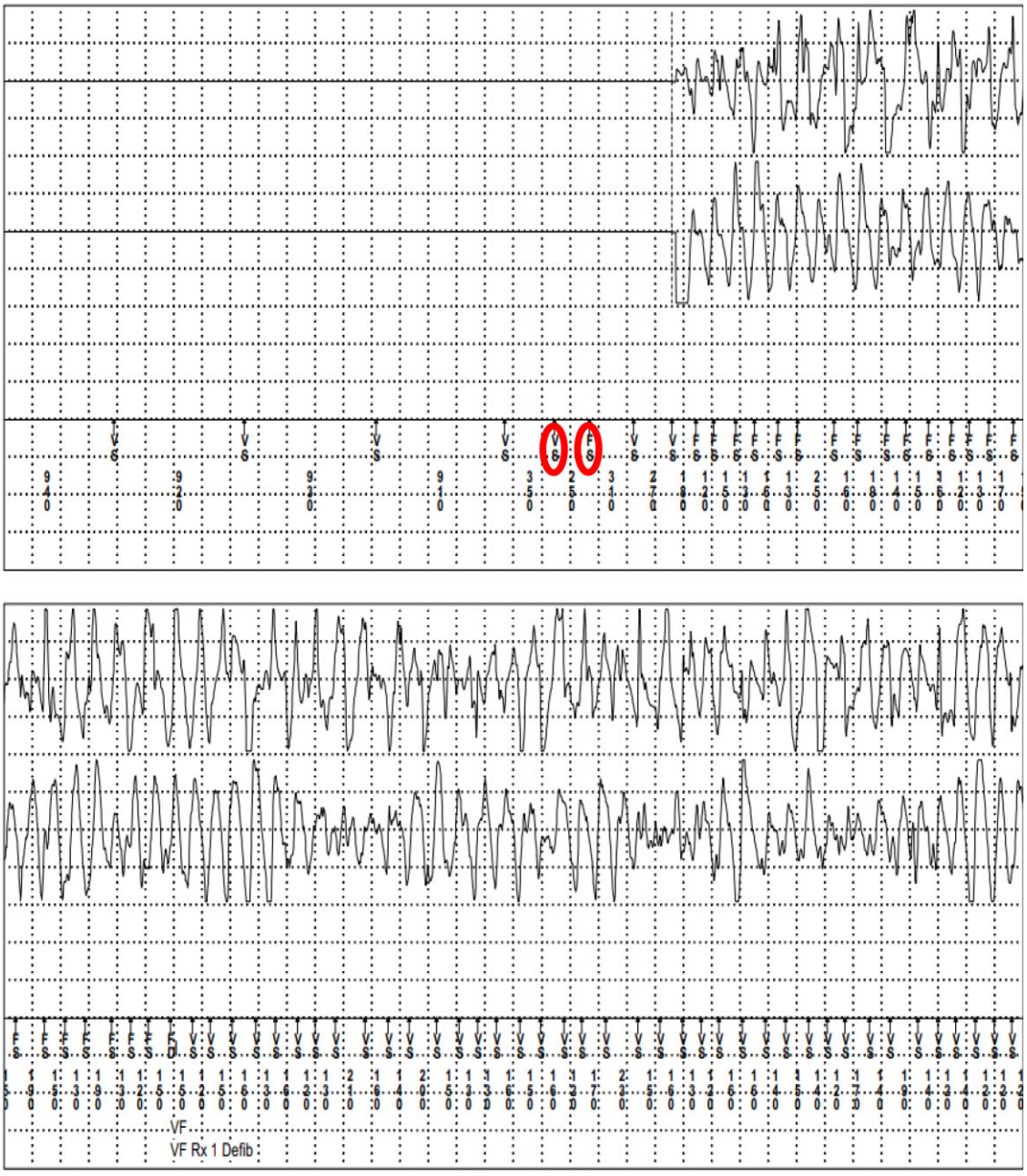


Figure 3 An implantable cardioverter defibrillator tracing demonstrating short-coupled premature ventricular complexes (≤350 ms) inducing polymorphic ventricular tachycardia that degenerates to ventricular fibrillation. Premature ventricular complexes are identified on the marker strip (red ovals) with coupling intervals of 250 and 350 ms.

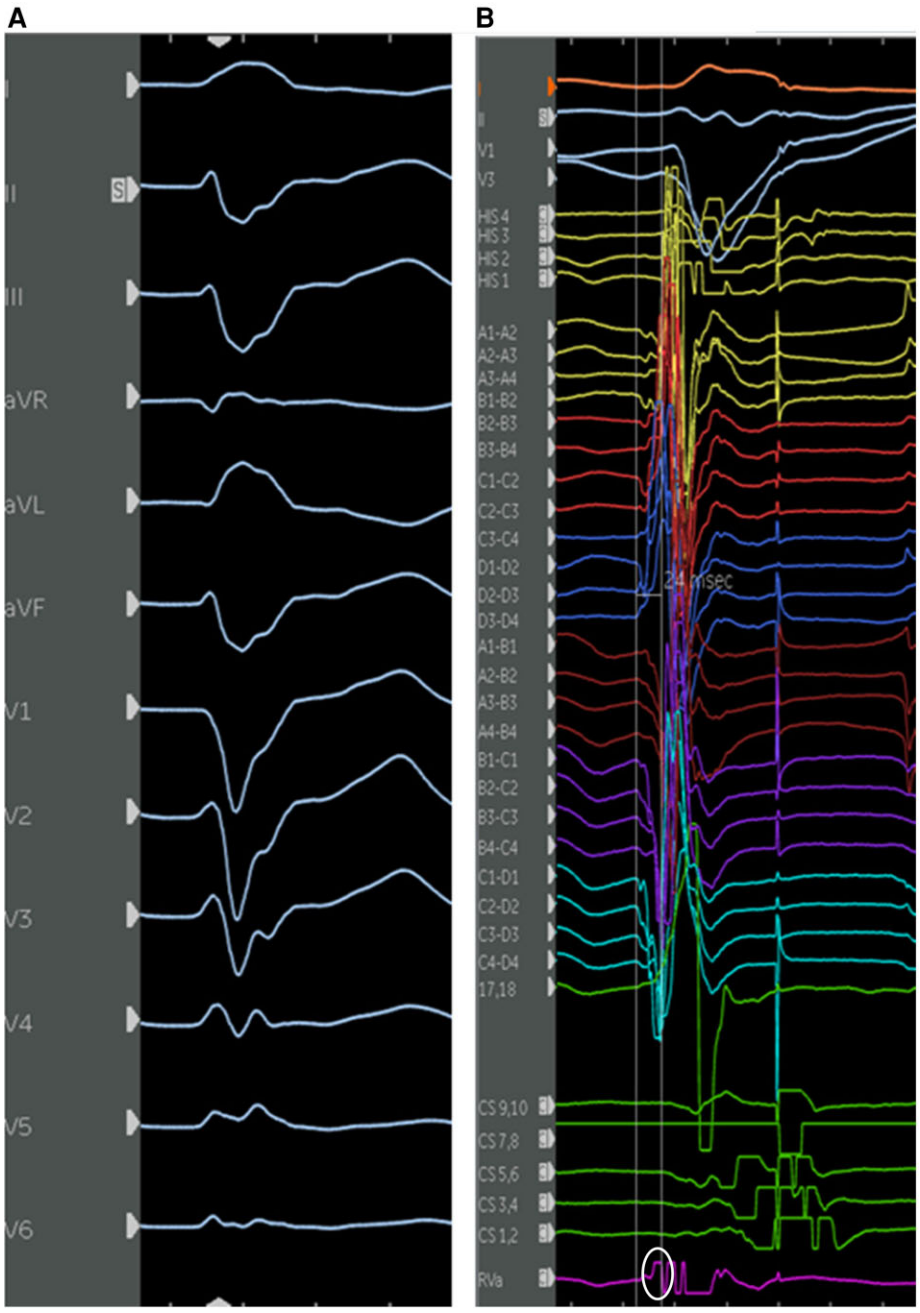


Figure 4 (*A*) The patient's clinical premature ventricular complex with a left bundle branch block pattern, late precordial transition, and a left superior axis originating from the moderator band. (*B*) During the premature ventricular complex, the Purkinje potential proceeds the QRS by 24 ms (white oval).

Short-coupled PVC-induced VF is more recently recognized as a discrete electrical disorder.[5] The mechanism(s) behind this phenomenon are still under investigation and it appears to be a Purkinje-mediated phenomenon due to triggered activity in the Purkinje tissues.[11] In concordance with this hypothesis, a Purkinje potential was identified during the EP study. In the case of PVCs, certain early stimulation may trigger Purkinje-mediated arrhythmias.

This variant was also present in three of the patient's asymptomatic relatives. Initially, the original clinical team recommended that the three relatives receive prophylactic ICD placement based on the possibility of a high-risk cardiac laminopathy.[12] The subsequent EP studies in the brothers were not able to induce ventricular arrhythmias.

The index case received appropriately an ICD for secondary prevention. In the absence of a conventional ICD Class I indication(s) [e.g. ventricular tachycardiac (VT)/VF arrest, sustained VT, and/or a left ventricular ejection fraction $\leq$35%], an ICD may be considered in individuals with suspected *LMNA*-mediated disease who satisfy $\geq$2 *LMNA*-specific ventricular arrhythmia/SCD risk factors (left ventricular

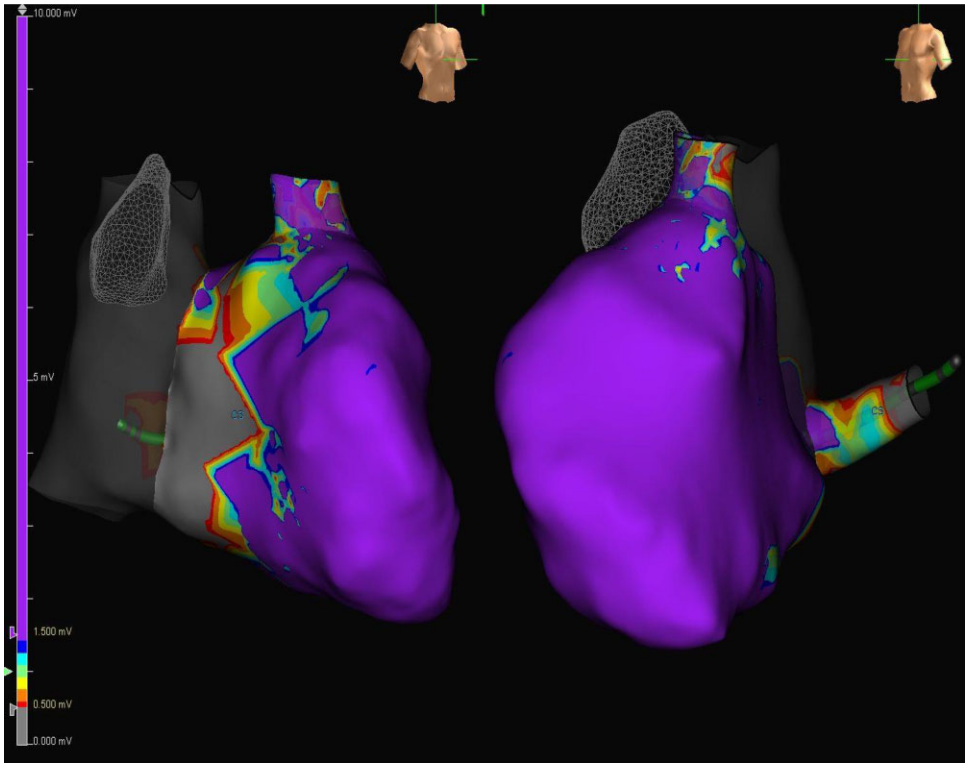


Figure 5 A voltage map of the right ventricle demonstrating normal voltage. The areas outlined in purple indicate the high-voltage zone (>1.5 mV), indicating that there is no area of fibrosis/mild disease in the right ventricle. The grey area in this voltage map was not assessed.

ejection fraction <45%, non-sustained ventricular tachycardia, and male sex) or have a pacing indication as outlined in the 2019 HRS ACM expert consensus guidelines.[13] Therefore, even if p.T655NfsX49-LMNA is pathogenic, neither the index case's variant-positive brothers (male sex) nor mother (no *LMNA*-specific risk factors) fulfil existing criteria for consideration of a primary prevention ICD.

Instead of classifying this family as having a high-risk form of genetic heart disease requiring an ICD in all variant-positive individuals, the patient was treated for potentially curable, non-genetic, PVC-triggered VF with cryoablation. The *LMNA* variant-positive relatives were advised to have a primary evaluation for subclinical lipodystrophy and periodic cardiac surveillance evaluations as an initial precautionary measure.

Lead author biography

Michael J. Ackerman, MD, PhD, is a paediatric cardiologist and serves as the director of the Windland Smith Rice Sudden Death Genomics Laboratory at the Mayo Clinic in Rochester, MN, USA. Additionally, he serves as the president of the Sudden Arrhythmia Death Syndromes (SADS) Foundation Board of Trustees. He specializes in diagnosing and treating patients with sudden death predisposing genetic heart diseases and has published extensively on this subject.

Supplementary material

Supplementary material is available at *European Heart Journal—Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for publication of this case report including images and text has been obtained from the patient in line with COPE guidance.

Conflicts of interest: M.J.A. is a consultant for Abbott, ARMGO Pharma, Boston Scientific, Daiichi Sankyo, Invitae, LQT Therapeutics, Medtronic, and UpToDate. M.J.A. and Mayo Clinic have a royalty/equity relationship with AliveCor and Anumana. However, none of these entities have contributed to this study in any manner. The remaining authors have no conflicts to declare.

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