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ADVANCED

CASE REPORT: CLINICAL CASE

Novel *FHL1* Mutation Associated With Hypertrophic Cardiomyopathy, Sudden Cardiac Death, and Myopathy

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ABSTRACT

A 24-year-old man with muscle cramps and a family history of sudden death presented with palpitations. Electrocardiography showed signs of left ventricular hypertrophy and nonsustained ventricular tachycardia, and imaging studies confirmed hypertrophic cardiomyopathy. Genetic testing revealed a novel *FHL1* mutation associated with Emery-Dreifuss muscular dystrophy. An implantable cardioverter-defibrillator was placed. (**Level of Difficulty: Advanced.**)
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HISTORY OF PRESENTATION

We present the case of a 24-year-old man who experienced palpitations and left-sided chest discomfort after running. The night prior to admission, he had consumed multiple energy drinks combined with alcohol and cocaine. The next morning, he felt well and exercised on a treadmill. After running for 25 min, he experienced a racing heartbeat with associated chest tightness. He denied a history of prior chest discomfort, shortness of breath, paroxysmal nocturnal dyspnea, lower extremity edema, palpitations, dizziness, or syncope. He reported frequent cramps in his calves. On physical examination, he was tachycardic to 103 beats/min with blood pressure of 136/76 mm Hg. Results of cardiac examination were normal. He had difficulty raising his arms above his head and had mild bilateral contractures of his Achilles tendons. Upon further questioning, he reported walking on his tiptoes since 14 years of age.

His family history was notable for 2 male family members on the maternal side of the family who

LEARNING OBJECTIVES

- There are rare syndromic causes of HCM, and family screening is important.
- High-risk features may necessitate ICD implantation.
- There are benefits and limitations of subcutaneous ICD placement compared with transvenous pacemakers.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, or patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

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had died suddenly (at 44 and 65 years of age) (Figure 1).

MEDICAL HISTORY

The patient denied any significant medical history.

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DIFFERENTIAL DIAGNOSIS

Given his family history of sudden death, the differential diagnosis included inherited cardiomyopathies (hypertrophic cardiomyopathy [HCM], dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy/dysplasia), channelopathies (long-QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia), and acquired cardiac dysfunction, including cocaine-induced cardiomyopathy, substance-induced coronary vasospasm, and stimulant-induced supraventricular tachycardia.

INVESTIGATIONS

Electrocardiography showed left ventricular hypertrophy with secondary ST-T-wave changes and biatrial enlargement (Figure 2A). His cardiac troponin I and creatine kinase levels were mildly but persistently elevated at 0.366 ng/ml (reference range ≤0.302 ng/ml) and 632 IU/l (reference range 24 to 195 IU/l), respectively. His pro-brain natriuretic peptide level was elevated at 3,616 pg/ml (reference range <125 pg/ml). Transthoracic echocardiography showed left ventricular hypertrophy with a maximal septal thickness of 2.5 cm during diastole. During an exercise stress test, there was no evidence of exercise-induced ischemia or left ventricular outflow tract obstruction. Subsequent cardiac magnetic resonance imaging confirmed septal-predominant HCM without systolic anterior motion of the mitral valve

ABBREVIATIONS AND ACRONYMS

EDMD = Emery-Dreifuss muscular dystrophy

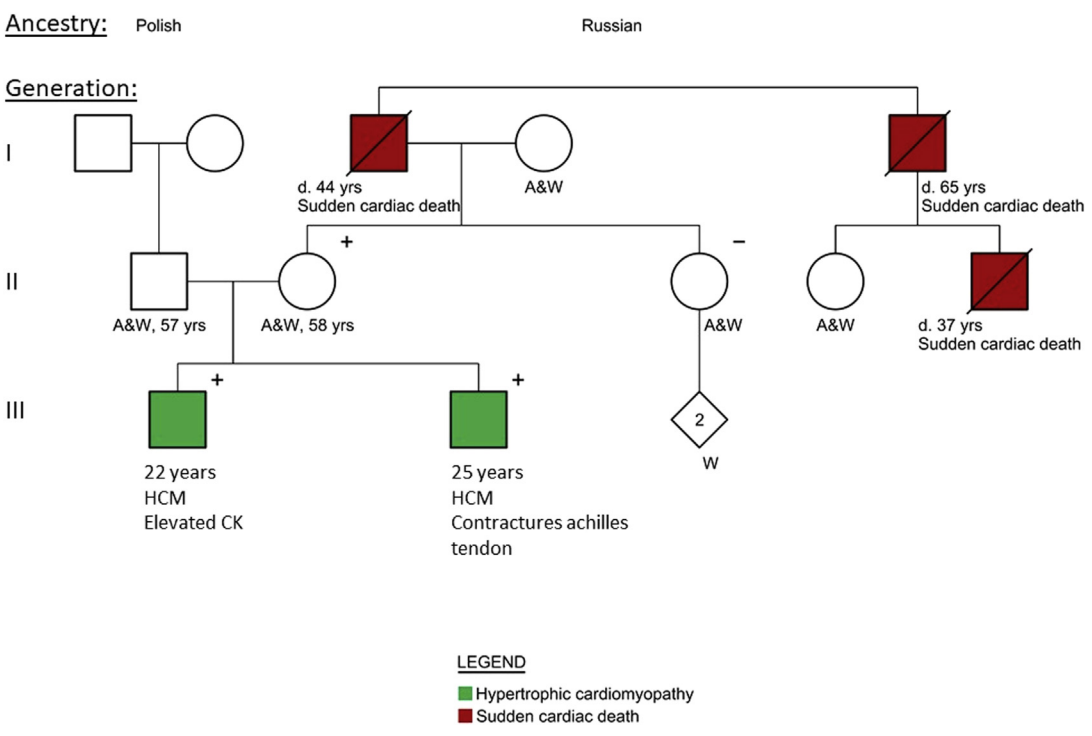
HCM = hypertrophic cardiomyopathy

ICD = implantable cardioverter-defibrillator

NSVT = nonsustained ventricular tachycardia

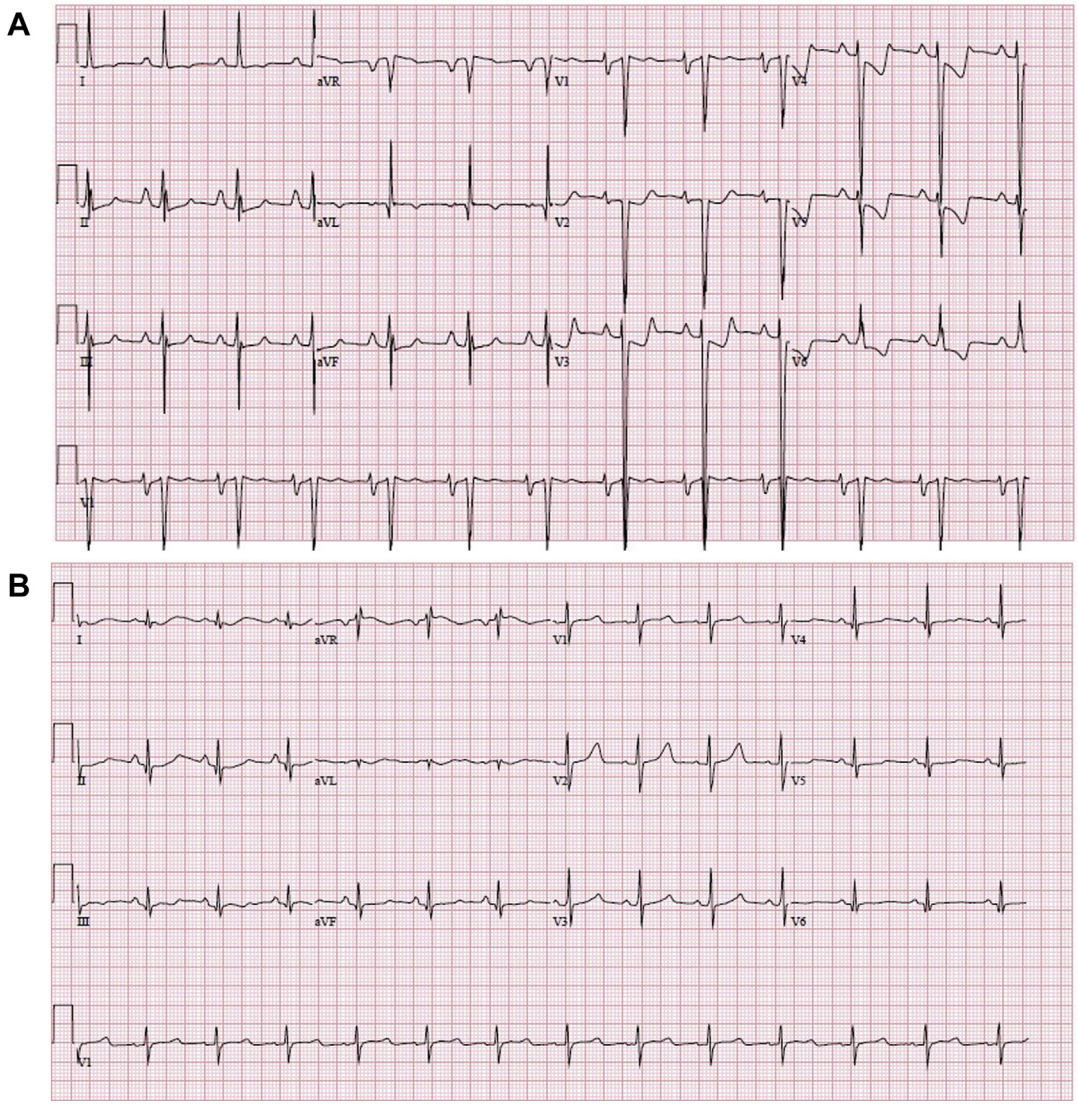
SCD = sudden cardiac death

FIGURE 1 Pedigree of Proband



The proband (III-2) had hypertrophic cardiomyopathy (HCM) with multiple muscle contractures, and his brother (III-1) has HCM with no muscular symptoms but an elevated creatine kinase (CK) level. The grandfather (I-3) experienced sudden cardiac death at 44 years of age. Two other maternal family members experienced sudden death. **Plus signs** indicate the presence of the FHL1 p.Cys255Arg mutation, and **minus signs** indicate the absence of the mutation. A&W = alive and well.

FIGURE 2 Electrocardiographic Findings

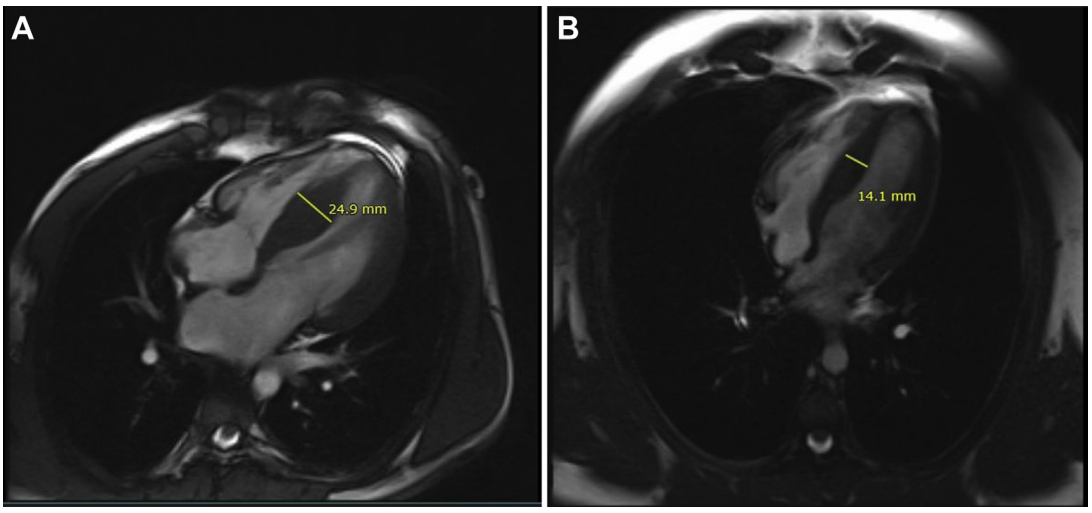


(A) Initial electrocardiogram of the proband, significant for biatrial enlargement and left ventricular hypertrophy with a strain pattern in the precordial leads. **(B)** Electrocardiogram of his younger brother, with a prolonged corrected QT interval of 477 ms.

(Figure 3A). Subendocardial delayed enhancement was not seen. During 30-day event monitoring, 1 episode of nonsustained ventricular tachycardia (NSVT) (10 beats, 133 beats/min) and 6 episodes of nonsustained supraventricular tachycardia, suggestive of an ectopic atrial focus, were recorded.

Following identification of HCM, screening echocardiography was performed in the patient's first-degree relatives. Transthoracic echocardiography of his 22-year-old brother (Figure 1, III-1) revealed moderate left ventricular septal hypertrophy (1.6 cm) with an ejection fraction of 60% to 65%. Cardiac magnetic resonance imaging confirmed left ventricular septal thickening of 1.4 cm (Figure 3B) and no evidence of systolic anterior motion. Electrocardiography showed a prolonged corrected QT interval of 477 ms (Figure 2B). A 24-h Holter monitor showed a single 6-beat run of NSVT. The brother has been asymptomatic from a muscle perspective but also had an elevated creatine kinase level of 409 IU/l. His mother's echocardiogram showed mild focal septal hypertrophy with preserved left ventricular systolic

FIGURE 3 Cardiac Magnetic Resonance Imaging Findings



Septal measurements on cardiac magnetic resonance imaging of the proband **(A)** and his brother **(B)** in end-diastole.

function, and her electrocardiographic findings were normal. His father's echocardiographic and electrocardiographic findings were normal.

MANAGEMENT

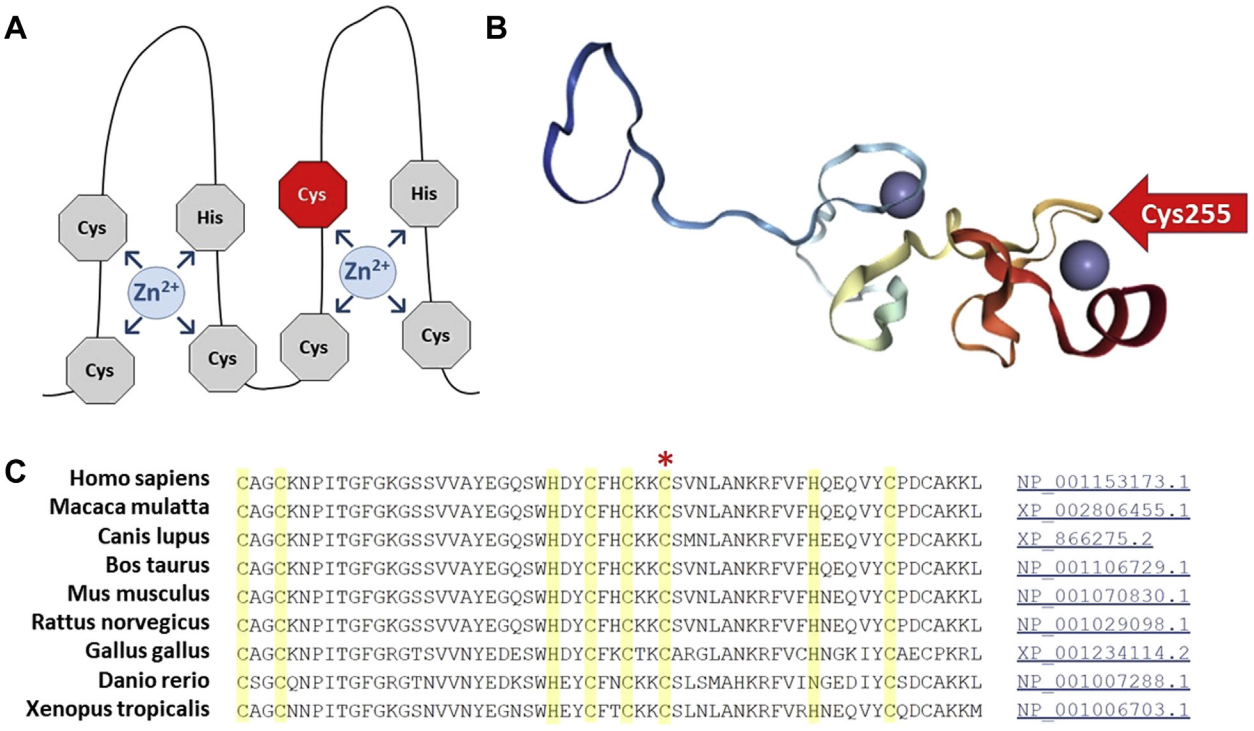
Given concerns for familial HCM, the proband proceeded with genetic testing using a HCM panel (26 genes; Invitae, San Francisco, California), which identified a genetic change in *FHL1* (c.763T>C, p.Cys255Arg), currently classified as a "variant of uncertain significance." Mutations in *FHL1* are associated with Emery-Dreifuss muscular dystrophy (EDMD) type 6. The same variant was subsequently identified in his brother, mother, and maternal aunt (**Figure 1**). A neurology consult was obtained for possible muscle involvement and revealed full muscle strength but decreased range of motion at his shoulders and mild bilateral contractures of his pronators, hamstrings, and Achilles tendons. Both brothers were started on metoprolol and underwent placement of subcutaneous implantable cardioverter-defibrillators (ICDs).

DISCUSSION

FHL1 is an X-chromosomal gene responsible for a variety of different X-linked myopathies with variable cardiac involvement (1). Zinc ion binding for *FHL1* is dependent on evolutionary conserved cysteine or histidine residues (**Figure 4**) (2). The variant observed (p.Cys255Arg) is predicted to disrupt the fourth LIM domain of *FHL1*, Cys255, one of the cysteine residues required for binding of the second zinc ion (**Figure 4C**) (2). However, bioinformatic tools to predict the possible impact of an amino acid substitution on the structure and function of *FHL1* gave conflicting results (SIFT: deleterious; PolyPhen-2: probably damaging; and Align-GVGD: class C0, indicating that a mutation is unlikely to be pathogenic). Given that the algorithms did not agree and the lack of prior reports of this variant in the literature, it was classified as a variant of uncertain significance. Importantly, 2 prior mutations at this site have been described, both being p.Cys255Ser mutations. These mutations also resulted in an arrhythmogenic cardiomyopathy, a prolonged QT interval, and elements of EDMD or myopathy (3,4). Given the segregation of the p.Cys255Arg variant in this family plus similar clinical phenotypes observed with other mutations at this highly conserved position, we propose the p.Cys255Arg variant to be pathogenic.

Following guidelines for primary prevention ICD placement in patients with nonischemic cardiomyopathies, there is a general consensus regarding the use of ICDs in patients with EDMD with reduced ejection fractions (5); however, the role of ICDs in preventing sudden cardiac death (SCD) in patients with EDMD with preserved systolic function is still poorly defined. In our patient with predominant HCM, current HCM guidelines recommend SCD risk stratification on the basis of a family history of SCD in a first-degree relative, personal history of unexplained syncope, left ventricular wall thickness ≥30 mm,

FIGURE 4 FHL-1 Protein Structure and Evolutionary Homology



Cartoon **(A)** and 3-dimensional model **(B)** of the fourth LIM domain of *FHL1*. The **blue dots** represent zinc ions, and the location of the mutated cysteine residue at position 255 is highlighted. **(C)** Sequence alignment of *FHL1* across 10 species. The cysteine and histidine residues of the fourth LIM domain are conserved across species and highlighted in **yellow**. The cysteine at position 255 is highlighted **(red asterisk)**.

presence of NSVT, and abnormal blood pressure response to exercise (6).

Given the syndromic HCM plus neuromuscular disease with documented episodes of NSVT and family history, primary prevention ICDs were recommended in both brothers. Given the patients' young age and lack conduction disease, subcutaneous ICD placement was discussed in a shared decision-making encounter and preferred by the patients to avoid long-term complications from transvenous ICD leads. Because EDMD can also present with sinus node dysfunction, atrial standstill, and heart block, continued monitoring is necessary to screen for conduction abnormalities that may necessitate pacing in the future.

FOLLOW-UP

Both brothers tolerated subcutaneous ICD implantation well and have required no ICD therapies after 1.5 years.

CONCLUSIONS

This case illustrates a novel *FHL1* mutation that leads to an EDMD phenotype, with associated HCM, Achilles tendon contractures, prolonged QT interval, and elevated risk for arrhythmias and SCD in genotype-positive male family members. Given the variable expressivity, particularly with respect to muscle symptoms, consideration for *FHL1* genetic testing should be considered in all cases of HCM. In young patients without pacing indication, subcutaneous ICDs may be an alternative to transvenous devices to reduce the long-term morbidity associated with transvenous ICD leads.

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KEY WORDS **cardiomyopathy, chest pain, congenital heart defect, electrophysiology, genetic disorders**