JACC: CASE REPORTS VOL. 4, NO. 4, 2022

CASE REPORT

ADVANCED

CLINICAL CASE

Familial Hypertrophic Cardiomyopathy With Fasciculoventricular Accessory Pathway

Vikas Kalra, MD,[a] Krittapoom Akrawinthawong, MD, MS,[b] Maitri Kalra, MBBS,[a] Rahul Jain, MD, MPH[c]

ABSTRACT

Hypertrophic cardiomyopathy (HCM) is a common but an underdiagnosed condition. Fasciculoventricular bypass tract (FVBT) is rare. Concomitant presence of both conditions is well described in Danon disease. We report a case of familial HCM with FVBT linked to a heterozygous pathogenic variant, c.655G>C (p.Val219Leu), in the cardiac myosin binding protein C3 (MYBPC3) gene. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2022;4:198–204) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENT ILLNESS

A 53-year-old woman presented to the cardiology clinic with intermittent short-lasting palpitations. Physical examination was unremarkable, with no significant cardiovascular findings.

PAST MEDICAL HISTORY

The patient had no significant past medical history.

LEARNING OBJECTIVES

- To identify the association of HCM and accessory pathway in the patient with a unique genetic mutation that is not similar to Danon disease.
- To determine the risk of sudden cardiac death with appropriate management in this familial disease.

INVESTIGATIONS

Her 12-lead electrocardiogram (ECG) showed sinus rhythm with pre-excitation (**Figure 1A**). Her echocardiogram revealed features of hypertrophic cardiomyopathy (HCM) without significant outflow obstruction. Holter monitoring revealed several episodes of nonsustained ventricular tachycardia (NSVT).

She underwent an electrophysiology study that confirmed the presence of a fasciculoventricular bypass tract (FVBT) (**Figures 1C and 1D**) with inducible atrial fibrillation. No ablation was performed during the case. Given her history of NSVT detected on Holter monitoring, she underwent cardiac magnetic resonance (CMR) imaging. The CMR findings were consistent with HCM: maximal midventricular septal thickness of 22 mm in diastole with patchy myocardial enhancement throughout the ventricle encompassing 25% of the myocardial mass (**Figure 1B**).

From the [a]Department of Cardiology, Indiana University School of Medicine, Muncie, Indiana, USA; [b]Prairie Cardiovascular, Carbondale, Illinois, USA; and the [c]Department of Cardiology, Indiana University School of Medicine, Indianapolis, Indiana, USA.
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, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 20, 2021; revised manuscript received November 12, 2021, accepted December 9, 2021.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2021.12.011

MANAGEMENT AND CLINICAL COURSE

She subsequently underwent insertion of a dual-chamber implantable cardioverter-defibrillator (ICD), as well as genetic testing. Genetic testing (HCMNext, Ambry Genetics) revealed a heterozygous pathogenic variant, c.655G>C (p.Val219Leu) in the cardiac myosin binding protein C3 gene (MYBPC3).

Screening of her first-degree family members was therefore performed. Her mother already had an ICD in place for nonischemic cardiomyopathy. Her mother's ECG showed pre-excitation (**Figure 2A**), and her serial echocardiogram showed that she initially had HCM that progressed to dilated cardiomyopathy with worsening left ventricular systolic function (**Figure 2B**). Her mother had an ICD placed for severe nonischemic cardiomyopathy despite optimal heart failure therapy, but she never received an ICD shock. Her maternal aunt (mother's sister) died suddenly of cardiac arrest at the age of 42 years. Her maternal uncle also had a sudden cardiac arrest at the age of 40 years, with subsequent ICD insertion.

Her sister (49 years old) had presyncopal symptoms, and her 12-lead ECG showed sinus rhythm with pre-excitation (**Figure 3A**). An echocardiogram revealed a normal ejection fraction with HCM features, and cardiac magnetic resonance revealed a maximal septal thickness of 20 mm in diastole and patchy late gadolinium enhancement at the mid-myocardium in the ventricular septum and anterior wall of the left ventricle (15% of myocardial mass) (**Figure 3B**). Her sister's event monitor showed NSVT correlating with palpitation and dizziness. Genetic testing revealed a similar heterozygous pathogenic variant in the *MYBPC3* gene. After shared decision making, she underwent ICD implantation without any complication and has not received any device therapy so far. Both her sons are healthy without abnormal ECGs, but they have not had genetic testing.

The patient has 2 daughters. Her elder daughter's ECG was normal, and no evidence of HCM was noted on the echocardiogram. Her younger daughter's (25 years old) ECG, however, showed sinus rhythm with subtle pre-excitation (**Figure 4A**), and no evidence of HCM was present on echocardiography (**Figure 4B**). She subsequently underwent genetic testing, and the result was positive for a similar heterozygous pathogenic variant, c.655G>C (p.Val219Leu) in the *MYBPC3* gene. She continues follow-up with our clinic uneventfully.

DISCUSSION

HCM is an autosomal dominant cardiac disorder with an estimated prevalence of 1 case per 500 population (0.2%).[1] It is characterized by unexplained left ventricular wall thickening that can lead to progressive heart failure, stroke, and sudden cardiac death.[2] Wolff-Parkinson-White (WPW) syndrome is a cardiac abnormality resulting from anomalous atrioventricular conduction pathways that can produce ventricular pre-excitation and paroxysmal re-entrant tachyarrhythmias. The prevalence of WPW syndrome varies between 0.68/1,000 and 1.7/1,000.[3] FVBTs are atypical accessory pathways that connect the His bundle to the distal Purkinje fibers or ventricular myocardium. These comprise the rarest variant of pre-excitation, with a reported incidence of 1.2% to 4% in pre-excitation cases.[4] We report a case in a patient with HCM and concomitant FVBT with a unique familial genetic linkage to a heterozygous pathogenic variant. Our patient's family pedigree chart is shown in **Figure 5**.

It is estimated that 5% of patients with HCM are reported to have ventricular pre-excitation. Both conditions are concomitantly detected in Danon disease, which is an X-linked dominant disease associated with loss-of-function mutations in the lysosome-associated membrane protein 2 (LAMP-2) gene.[5] The relationship between HCM and WPW syndrome remains unclear, but there is some clinical evidence to suggest that development of ventricular pre-excitation may reflect a genetic origin.[6] Shibata et al[7] described 2 patients with familial HCM associated with WPW syndrome who showed progression to left ventricular dilatation. There were no tachyarrhythmias seen during the clinical course, and these investigators concluded that the patients may not have had any accessory pathways. MacRae et al[8] reported familial HCM with WPW syndrome mapped to a locus on chromosome 7q3. Few cases were reported on unusual forms of HCM with accessory pathways.[9]

In contrast to Danon disease, our report describes a familial pathogenic variant of *MYBPC3* gene causing a unique combination of HCM and FVBT without other systemic organ involvement. Mutations of this gene were associated with attenuation of cardiomyocytes in a force-generating capacity and less myofibril density with hypertrophic myocytes.[10] A similar pathologic process could play a pivotal role in the evolving cardiomyopathy we observed during follow-up of the patient's mother.

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

ECG = electrocardiogram

FVBT = fasciculoventricular bypass tract

HCM = hypertrophic cardiomyopathy

ICD = implantable cardioverter-defibrillator

LAMP-2 = lysosome-associated membrane protein 2

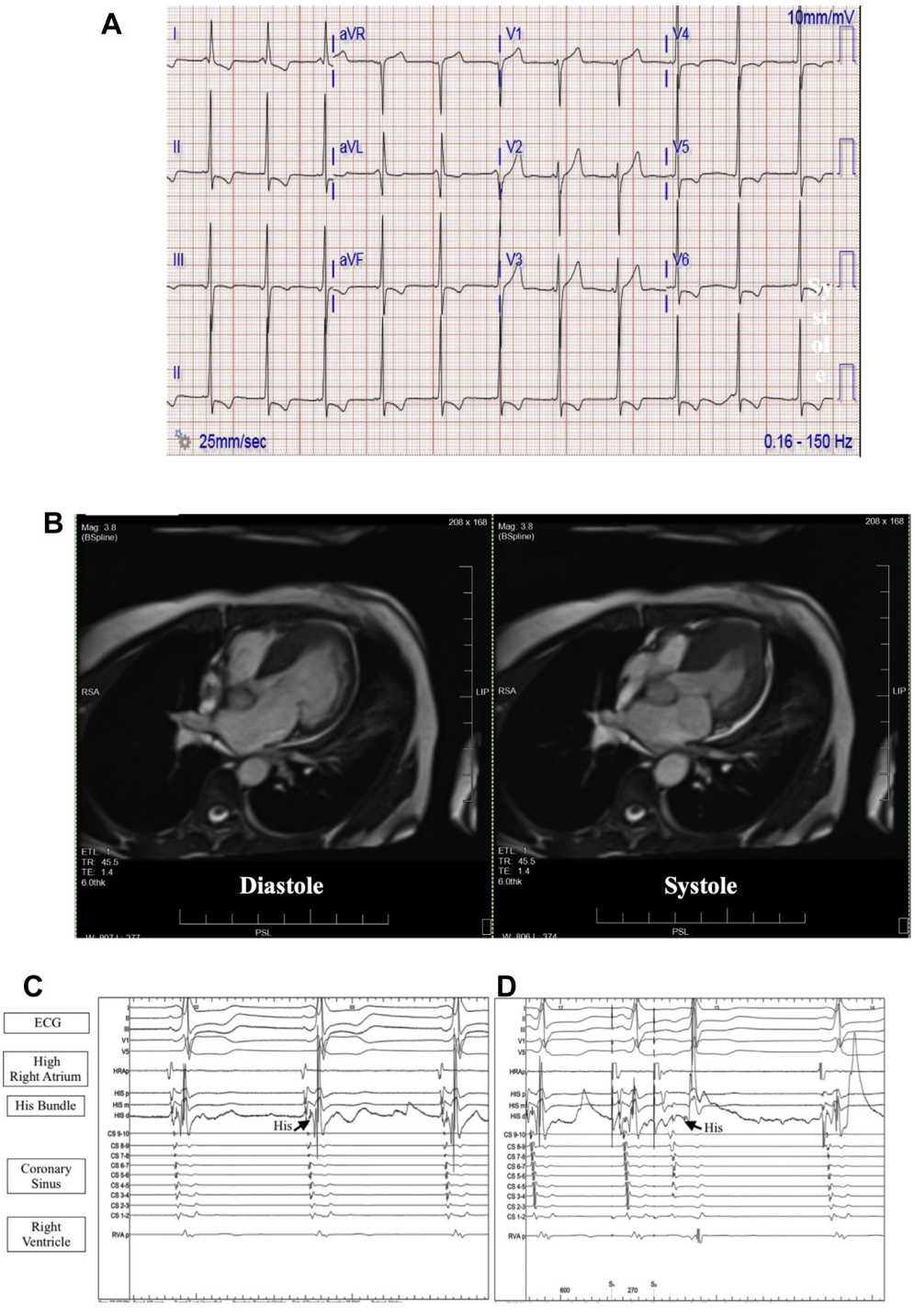
MYBPC3 = cardiac myosin binding protein C3

NSVT = nonsustained ventricular tachycardia

WPW = Wolff-Parkinson-White syndrome

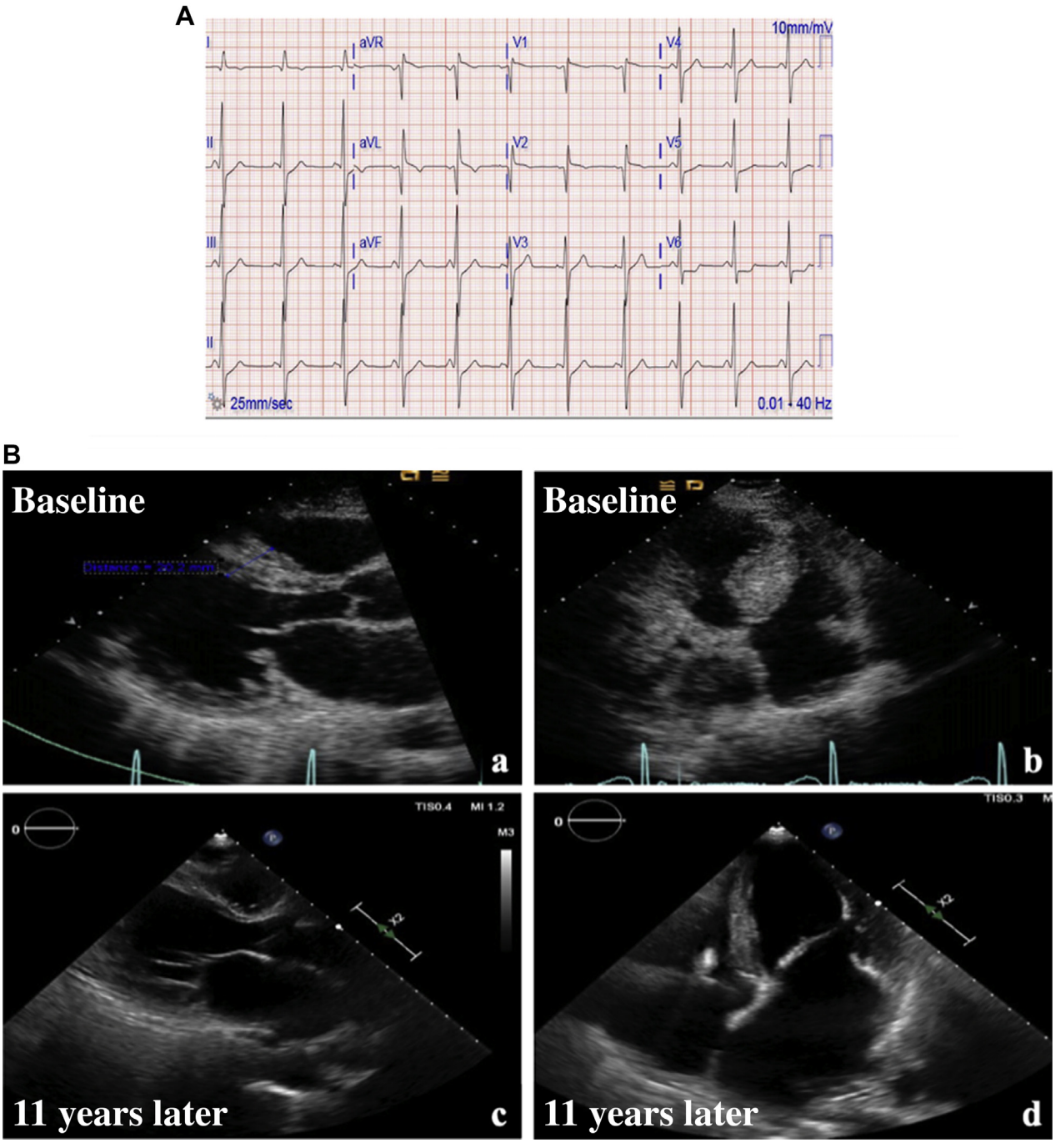
JACC: CASE REPORTS, VOL. 4, NO. 4, 2022
FEBRUARY 16, 2022:198–204

FIGURE 1 Imaging in the Index Patient



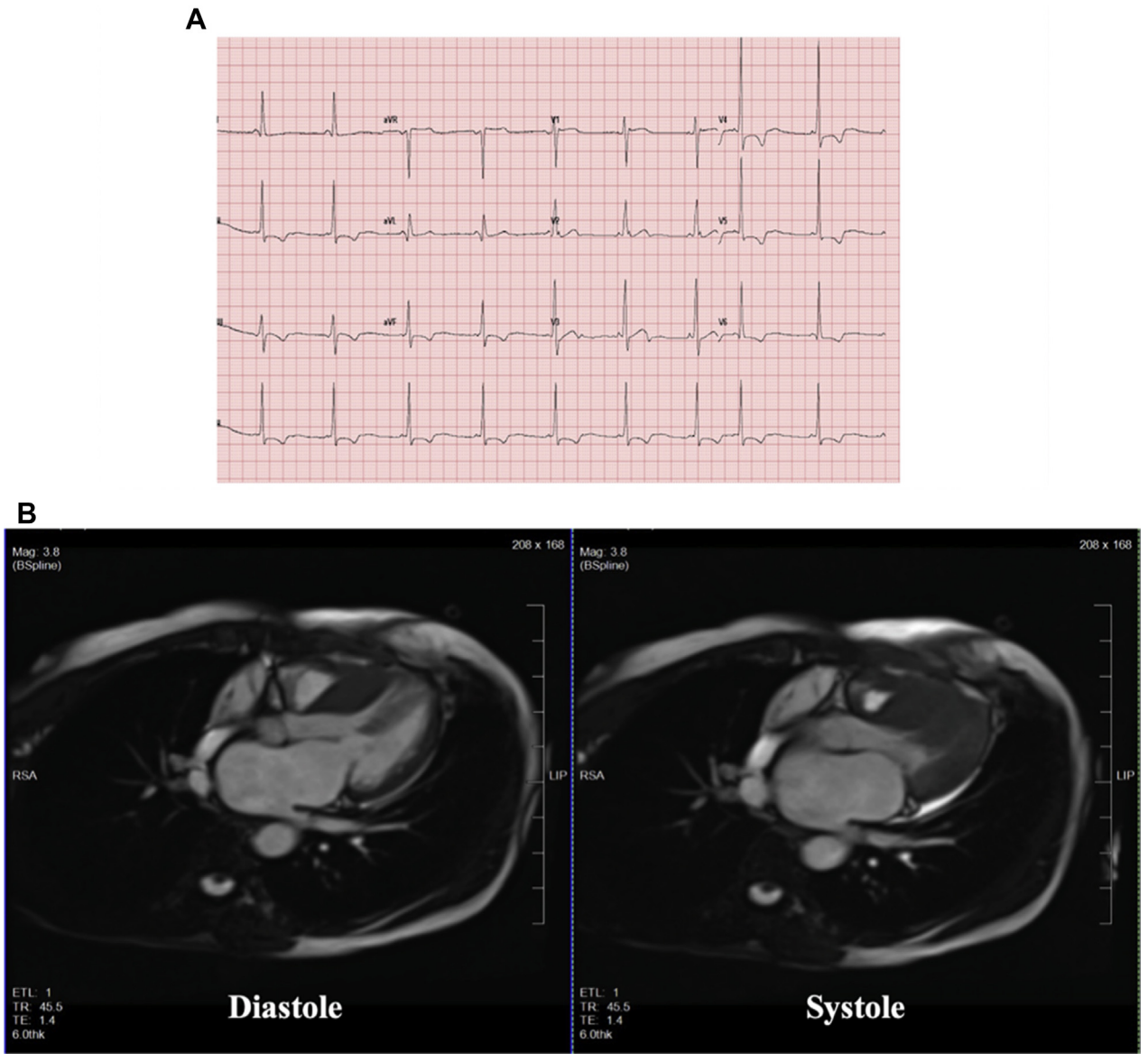
(A) The 12-lead electrocardiogram (ECG), **(B)** cardiac magnetic resonance images, and **(C and D)** electrograms from an electrophysiology study of the index patient. **(C)** Electrophysiology study with baseline electrocardiogram and electrograms showing sinus rhythm with a fixed PR interval and pre-excitation. **(D)** During the electrophysiology study, the atrial drive pacing's cycle length at 600 ms with a single atrial extrastimulation at 270 ms was given. It shows evidence of fasciculoventricular bypass tract with a fixed HV interval and a degree of pre-excitation during atrial extrastimuli. Differential atrial pacing from various atrial locations and decremental atrial pacing also confirmed similar findings.

FIGURE 2 **Imaging in the Index Patient's Mother**



(A) The 12-lead electrocardiogram and **(B)** echocardiographic images of the index patient's mother. **(B)** Significant progression of hypertrophic cardiomyopathy **(a and b)** to dilated cardiomyopathy **(c and d)** in 11 years.

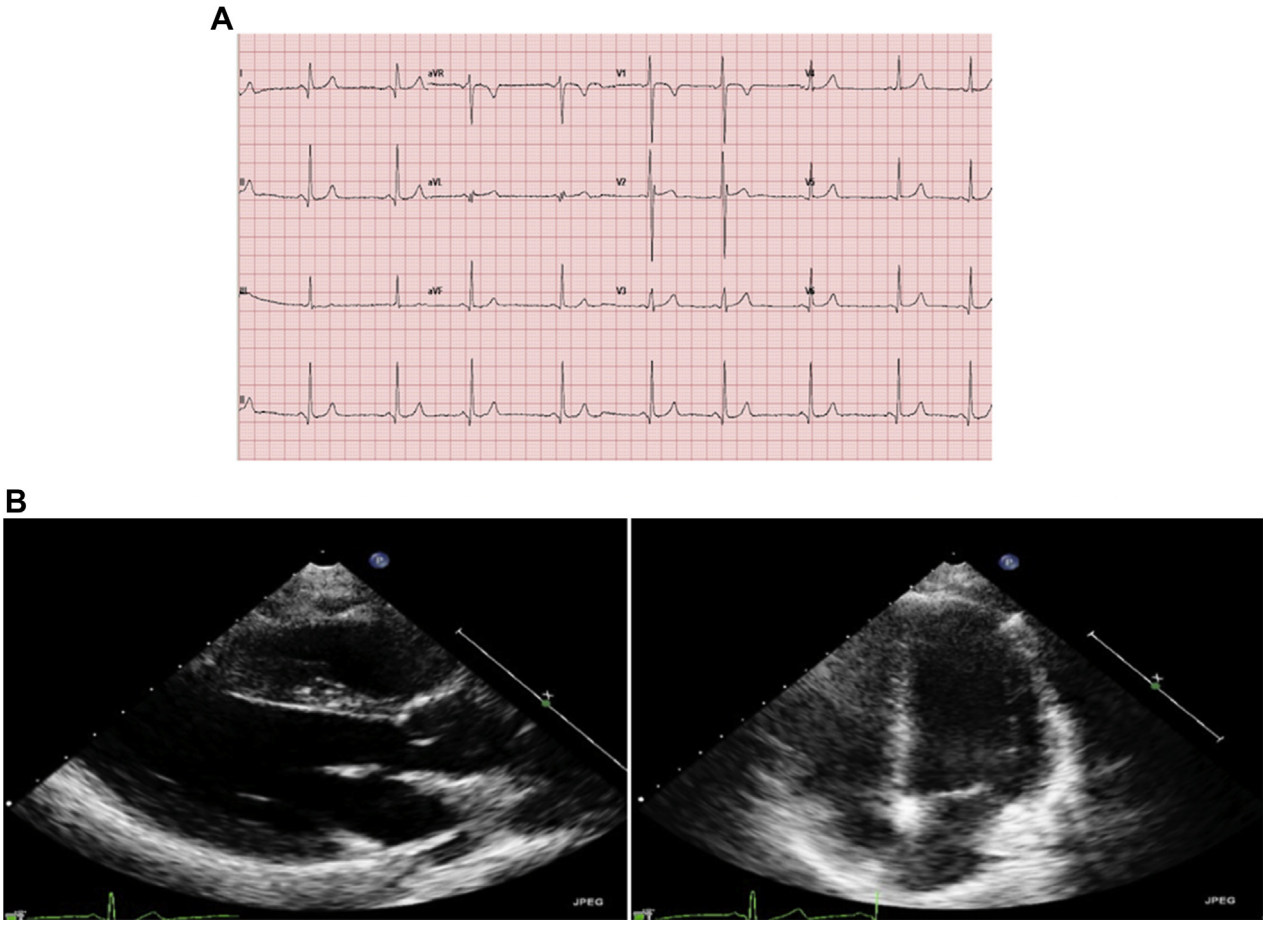
FIGURE 3 **Imaging in the Index Patient's Sister**



(A) The 12-lead electrocardiogram and **(B)** cardiac magnetic resonance images of the index patient's sister.

FVBT is a well-known bystander of any arrhythmias because of its very short circuit, with little potential of re-entrant mechanism formation for arrhythmia. The risk of sudden cardiac death is therefore determined mainly by the ventricular arrhythmia substrates related to HCM, as evidenced here by CMR with gadolinium enhancement images. This is in contrast to patients who have HCM related to *PRKAG2* and *LAMP2* gene mutations, where preexcitation is secondary to an atrioventricular bypass tract and can increase the risk of sudden cardiac death from atrial fibrillation with a rapid ventricular response resulting in ventricular fibrillation. These patients can also experience supraventricular

FIGURE 4 Imaging in the Index Patient's Daughter

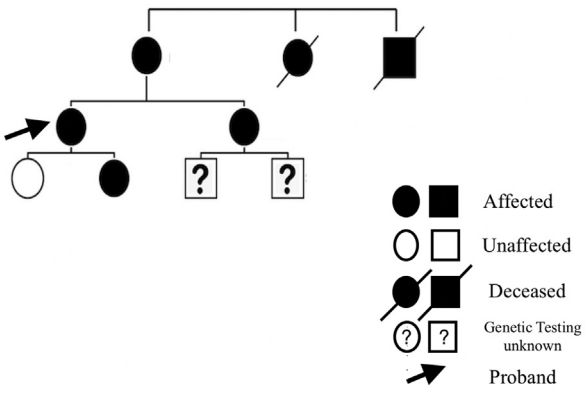


(A) The 12-lead electrocardiogram and **(B)** echocardiographic images of the index patient's daughter.

tachycardia resulting from an atrioventricular bypass tract, in addition to chronotropic incompetence and advanced heart blocks, which were not observed in our patient's family with a sarcomeric gene mutation (*MYBPC3* gene).

Shared decision making is a crucial process in ICD implantation for high-risk members of this family. For the patient's younger daughter with positive genotypes but silent phenotypes, close long-term follow-up is warranted because the risk of sudden cardiac death potentially evolves, as does her grandmother's. To our knowledge, this is the first report of a case of familial HCM with FVBT along with confirmed genetic analysis linked to a heterozygous pathogenic variant, c.655G>C (p.Val219Leu) in the *MYBPC3* gene.

FIGURE 5 Pedigree Chart of the Family



FOLLOW-UP AND CONCLUSIONS

The index patient has been following in our clinic for over four years. She has not received any shocks from her ICD device. Her mother developed paroxysmal atrial fibrillation. She has been treated with dofetilide and has also underwent catheter ablation procedure that revealed extensive scarring in the left atrium. Her daughters are doing well.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Vikas Kalra, Indiana University School of Medicine, 2525 West University Avenue, Suite 300, Muncie, Indiana 47303, USA. E-mail: vkalra@iu.edu.

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KEY WORDS accessory pathway, Danon disease, familial, hypertrophic cardiomyopathy