

Dual myosin binding protein C3 and potassium voltage-gated channel subfamily H member 2 co-inherited pathogenic variants in a patient with hypertrophic cardiomyopathy and long QT 2 syndrome: A case report



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Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiomyopathy, with an autosomal dominant inheritance, incomplete penetrance, and variable expression. Ventricular tachyarrhythmias are the main cause of sudden cardiac death in young adults with HCM.¹ QT prolongation in HCM has been attributed mostly to dispersion of repolarization from myocardial hypertrophy.² We report a rare case of a 25-year-old man with familial HCM and prolonged QT interval, who presented with polymorphic ventricular tachycardia / ventricular fibrillation cardiac arrest. Genetic testing identified a pathogenic heterozygous variant in *MYBPC3* (myosin binding protein 3) responsible for HCM, as well as a heterozygous pathogenic variant in *KCNH2* (potassium voltage-gated channel subfamily H member 2), associated with long QT syndrome (LQTS) type 2. Management was tailored to both conditions. Our case demonstrates that genetic testing for genes associated with LQTS should be considered in HCM patients with prolonged QTc interval.

Case report

A 25-year-old African American man with a past medical history of familial HCM was transferred to our institution after initially presenting to an outside hospital after experiencing a witnessed out-of-hospital polymorphic ventricular tachycardia (PMVT) / ventricular fibrillation (VF) cardiac arrest while playing basketball. Return of spontaneous circu-

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KEY TEACHING POINTS

- A prolonged QT interval in patients with hypertrophic cardiomyopathy (HCM) should not just be attributed to myocardial hypertrophy alone, and genetic testing for congenital long QT syndrome (LQTS) should be strongly considered.
- Co-inherited pathogenic variants for genes responsible for LQT2 and HCM can be seen, which should prompt future studies to assess its prevalence.
- Monomorphic ventricular tachycardia is the predominant ventricular arrhythmia in patients with HCM who have implantable cardioverter-defibrillators. Polymorphic ventricular tachycardia in a patient with HCM should prompt further investigation.
- The diagnosis of concomitant HCM and LQT2 can alter the decision tree for patient care, including the most effective beta blocker (which in our case is nadolol), avoidance of QT-prolonging medications, and left cardiac sympathetic denervation.

lation was achieved after cardiopulmonary resuscitation, several defibrillations, 2 rounds of intravenous epinephrine administration, and intravenous amiodarone. The patient subsequently underwent targeted temperature management. After rewarming, he was extubated successfully, with good neurologic recovery. There was an episode of transient atrial fibrillation (AF) with rapid ventricular response during hypothermia, which spontaneously converted to sinus rhythm.

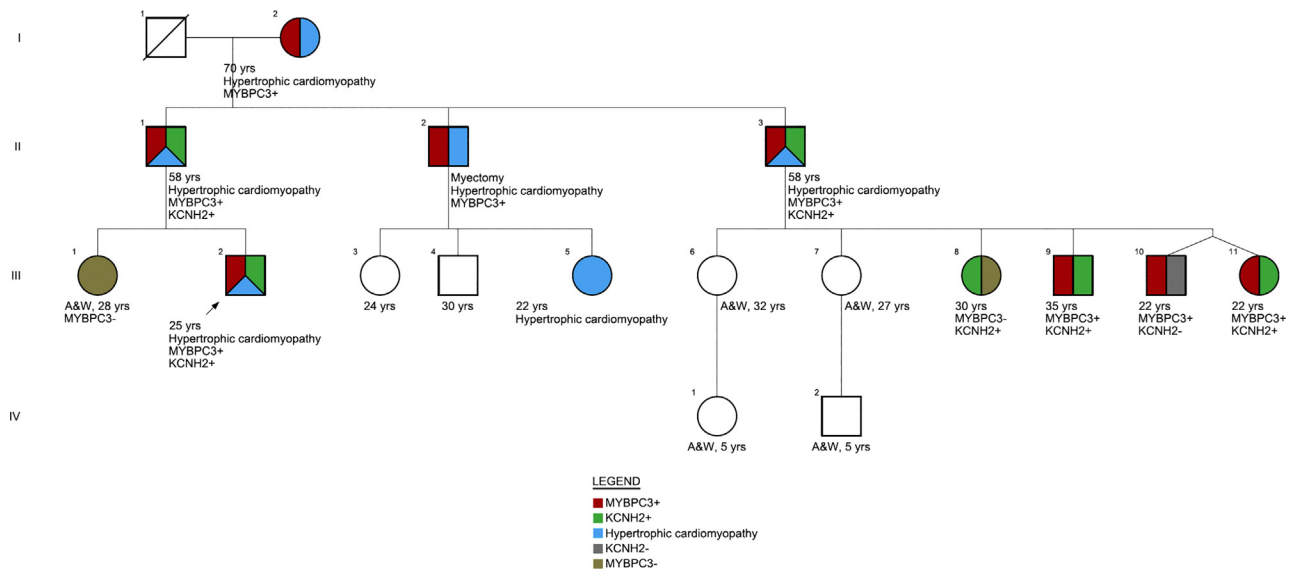


Figure 1 Genetic family pedigree.

The patient denied any prodromal symptoms preceding his cardiac arrest. There was no history of presyncope or syncope prior to the cardiac arrest. He was diagnosed with HCM 7 years prior, in the context of family screening. Family history included HCM in his father, 2 paternal uncles, and paternal grandmother (Figure 1 illustrates pedigree).

On physical exam, blood pressure on presentation was 110/70 mm Hg, pulse 76 beats/min and regular, respiration rate 18 breaths/min, weight 219 lb, and body mass index 31.42 kg/m². Cardiovascular exam revealed a left sternal border crescendo-decrescendo and systolic ejection murmur, grade 3/6 in intensity, which accentuated with Valsalva. Pertinent laboratory data revealed electrolytes within normal limits; normal thyroid function tests; peak cardiac troponin I of 18.08 ng/mL (reference <0.30 ng/mL), which trended down to normal; and elevated NT-proBNP of 6496 pg/mL (reference <125 pg/mL).

Electrocardiogram (ECG) demonstrated AF with rapid ventricular response at 133/min, left ventricular hypertrophy (LVH) with repolarization changes, and corrected QT interval (QTc) of 527 ms. QTc was measured in either lead II or lead V₅ using the tangent method and the Fridericia correction formula. If the end of the T wave was difficult to determine in lead II or V₅, another lead with clearly defined T waves was chosen. QTc during AF was calculated by averaging the QT of 5 consecutive beats.³

A transthoracic echocardiogram revealed normal biventricular size and function with left ventricular ejection fraction (LVEF) of 55%, asymmetric septal hypertrophy with a maximal septal wall thickness of 2.6 cm (Figure 2A), and peak left ventricular outflow tract (LVOT) gradient of 12 mm Hg. Valsalva maneuver was not performed, as the patient was intubated. Systolic anterior motion of the mitral valve was noted with mild-to-moderate eccentric posteriorly directed mitral regurgitation.

His hospital course was uneventful. Given his young age, the decision was to implant a subcutaneous implantable cardioverter-defibrillator (S-ICD) implantation rather than a transvenous ICD for secondary prevention. He was subsequently discharged on metoprolol succinate 100 mg daily. An outpatient exercise stress echocardiography revealed a peak stress LVOT velocity of 2.8 m/s with a peak gradient of 31.36 mm Hg. The test was terminated after 6 minutes of exercise owing to dyspnea. Five months later, while running up the stairs, he suffered a syncopal episode followed by shock from the S-ICD. ICD interrogation revealed PMVT/VF successfully terminated with a shock (Figure 3B). His QTc was prolonged at 533 ms on ECG (Figure 3A). Electrolytes were normal and he was not on any QT-prolonging medications. Owing to markedly prolonged QT, antiarrhythmic medications were avoided. Metoprolol succinate was increased to 75 mg twice daily, as he could not tolerate a higher dose owing to sinus bradycardia.

During his clinic visit following his discharge, he was found to be in AF with an average ventricular response of 100 beats/min. The patient reported shortness of breath on mild exertion. On physical exam a systolic ejection murmur grade 3/6 across the left sternal border, which increased with the Valsalva maneuver, was appreciated. Thus, repeat transthoracic echocardiogram was performed and showed an LVEF of 65%; peak LVOT gradient of 70 mm Hg, which increased with Valsalva maneuver to 89 mm Hg (Figure 2B); and systolic anterior motion of the anterior leaflet of the mitral valve with severe posteriorly directed mitral regurgitation and severe left atrial enlargement, with a volume index of 52 mL/m² (reference 16–34 mL/m²). He was started on apixaban 5 mg twice daily. An outpatient 14-day Holter monitoring revealed persistent AF. Cardiac magnetic resonance imaging revealed normal left ventricular size and function (LVEF 57%), severe asymmetric septal

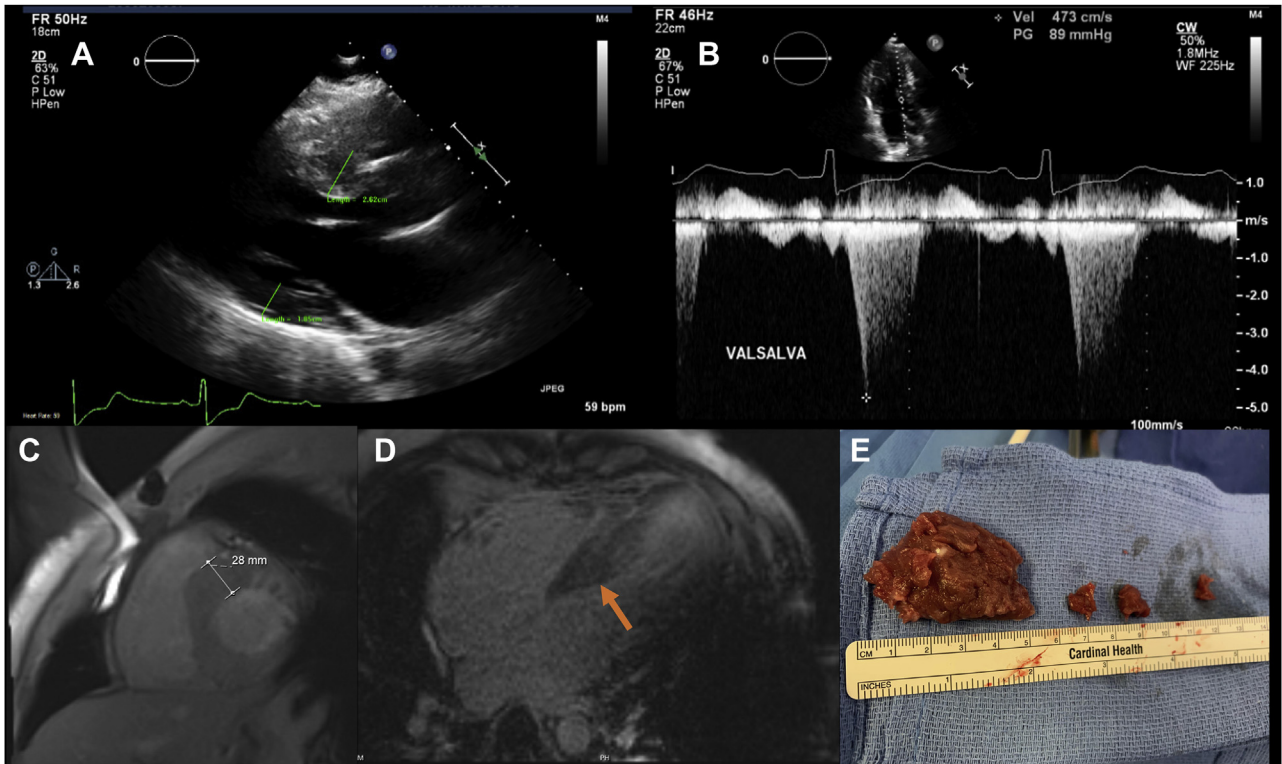


Figure 2 **A:** Transthoracic echocardiography (TTE) parasternal long-axis view demonstrating interventricular septal wall thickness of 2.62 cm and posterior wall thickness of 1.85 cm. **B:** TTE 3 chamber view with continuous wave Doppler at the left ventricular outflow tract (LVOT) during Valsalva maneuver revealing LVOT gradient of 89 mm Hg. **C:** Cardiac magnetic resonance imaging (MRI) short-axis view revealing maximal basal anteroseptal wall thickness of 2.8 cm. **D:** Cardiac MRI 4-chamber long-axis view demonstrating midmyocardial late gadolinium enhancement in the interventricular septum (orange arrow). **E:** Post-surgical myectomy specimen.

hypertrophy with a maximal wall thickness of 2.8 cm (Figure 2C) at the basal anteroseptum, midmyocardial delayed enhancement at the basal to mid septum (Figure 2D), severe left atrial enlargement (49 cm²), and mild right atrial enlargement (27 cm²).

Genetic testing confirmed the presence of the known familial pathogenic variant in *MYBPC3* (myosin binding

protein 3) (c.3624dup (p.Lys1209Glnfs*33)). Given his markedly prolonged QTc interval exceeding 500 ms without an identifiable reversible etiology, along with PMVT/VF, we also performed genetic testing for congenital LQTS. This identified a pathogenic heterozygous variant in the *KCNH2* (potassium voltage-gated channel subfamily H member 2) gene (c.1468G>A (p.Ala490Thr)). Metoprolol was

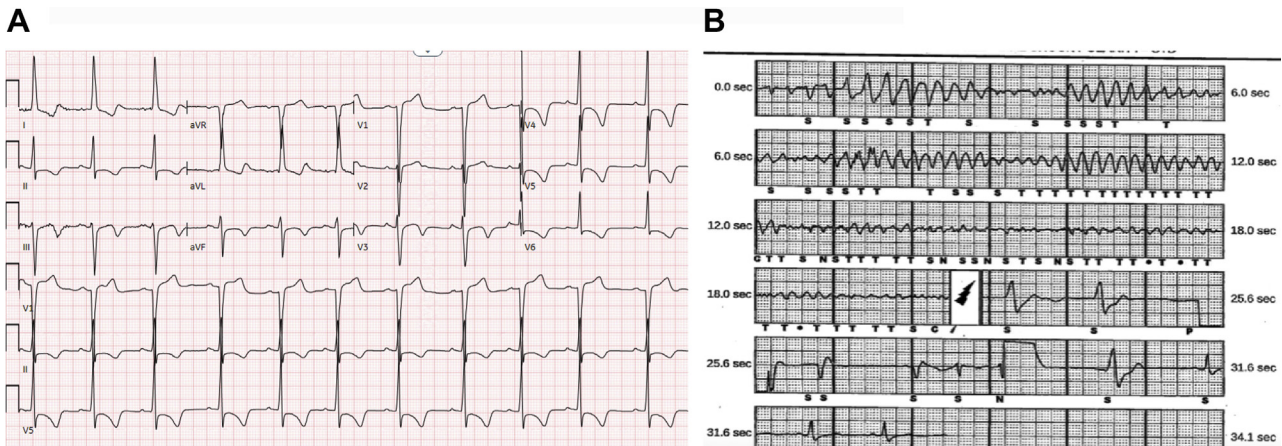


Figure 3 **A:** Initial electrocardiogram after second cardiac arrest demonstrating sinus rhythm 66/min, left ventricular hypertrophy with repolarization changes, and prolonged QT with corrected QT interval of 533 ms. **B:** Subcutaneous implantable cardioverter-defibrillator (ICD) interrogation demonstrating polymorphic ventricular tachycardia / ventricular fibrillation successfully terminated by ICD shock.

subsequently switched to nadolol 120 mg daily, which has been shown to be the most effective beta blocker among the more severely affected group of LQTS2 patients.⁴ On further review of his medical records from out-of-state institutes, he was noted to have a prolonged QT interval with a QTc of 520 ms, when initially seen 7 years earlier at another HCM center. Interestingly, this was appreciated but was attributed to LVH, and the patient was recommended to avoid QT-prolonging medications at the time.

With the identification of the *KCNH2* pathogenic variant, cascade screening was offered to family members for both genetic variants. Thus far, we have confirmed that the index case's father and 1 paternal uncle who have HCM and the *MYBPC3* variant also have the *KCNH2* variant. We also identified paternal first cousins, children of the uncle who had genetic testing, that are phenotypically negative, who carry either the *MYBPC3* variant alone, *KCNH2* variant alone, or both *MYBPC3* and *KCNH2* variants (Figure 1).

As the patient had dynamic LVOT obstruction with symptoms on mild exertion, we proceeded with septal myectomy (Figure 2E). Left atrial appendage closure and maze procedure were also performed. Following the surgery, the patient developed AF with rapid ventricular response. Rate control was pursued, and QT-prolonging antiarrhythmic drugs were avoided. The patient intermittently converted to sinus bradycardia. Subsequently, the patient underwent an uncomplicated removal of the S-ICD and implantation of a transvenous dual-chamber ICD to allow atrial pacing.

Discussion

Our case emphasizes that a markedly prolonged QT interval in HCM without an apparent cause should not be attributed solely to myocardial hypertrophy. Testing all HCM patients for LQTS would be very helpful to identify the true incidence of coexistent congenital LQTS. However, mild QT prolongation is commonly seen in HCM secondary to repolarization abnormalities resulting from LVH. Thus, QT dynamics during exercise and recovery should be assessed in all cases of HCM with QT prolongation. Genetic testing for LQTS should be done in cases of more pronounced QTc prolongation (ie, QTc >480 ms) or mild QT prolongation (ie, QTc >460 ms), but with abnormal QT response to peak exercise and/or during recovery.

Our patient was initially diagnosed with HCM in the context family screening. At that time, his ECG demonstrated marked QT prolongation with a corrected QT interval of 520 ms. It is noteworthy that other family members with HCM were also noted to have prolonged QT; however, this was attributed to myocardial hypertrophy and associated repolarization abnormalities. The patient's initial presentation with PMVT/VF, and later with PMVT/VF treated with appropriate ICD shock in the context of severe QTc of >520 ms, prompted genetic testing for congenital LQTS.

The most common cause of death in HCM is sudden cardiac death owing to ventricular tachyarrhythmia, with an

annual incidence rate of <1%.⁵⁻⁷ Monomorphic VT is the predominant sustained ventricular arrhythmia seen in HCM patients with ICDs. A study by O'Mahony and colleagues⁸ found monomorphic VT as the culprit arrhythmia in 86% of cases, whereas VF and PMVT were the culprit in only 9% and 5%, respectively.

The prevalence of prolonged QTc greater than 480 ms in HCM is reported to be around 12%, with ~5% of patients having QTc >500 ms.⁹ QT prolongation appears to mostly represent a phenotypic expression of myocardial hypertrophy. Furthermore, QTc prolongation in patients with HCM has also been associated with LVOT obstruction.¹⁰ In addition, QTc >440 ms has been shown to be a predictor of appropriate ICD therapy in patients with HCM.¹⁰ Our patient initially presented with PMVT/VF arrest and then received an appropriate ICD shock for PMVT. Indeed, he had severe hypertrophy and LVOT obstruction with high gradients. Thus, according to previous studies his QT prolongation would have been attributed to his obstructive HCM. However, it is noteworthy that HCM patients with prolonged QTc included in previous studies did not have genetic testing for genes associated with congenital LQTS. Hence, it is possible that some of these patients had concomitant congenital LQTS, similar to our patient.

Furthermore, it is plausible that some of the arrhythmic events these patients had experienced were caused by congenital LQTS rather than HCM or a combination of the 2 conditions. The finding of a pathogenic variant in *KCNH2* in our patient had affected his management (ie, switching metoprolol to nadolol, replacing the S-ICD with a transvenous dual-chamber ICD to allow atrial pacing, avoiding QT-prolonging antiarrhythmic medications for AF, consideration of mexiletine, and left cardiac sympathetic denervation if recurrent PMVT/VF).

The concomitant presence of (likely) pathogenic variants in genes known to be associated with congenital LQTS and HCM is rare and has only been reported in a few case reports and case series. Specifically, to our knowledge, only concomitant (likely) pathogenic variants of the *KCNQ1* gene (responsible for congenital LQT1) have been reported in the context of genotype-positive HCM.^{1,2} This is the first reported case of HCM and concomitant congenital LQT2.

Conclusion

Our case highlights that prolonged QTc in patients with HCM can be secondary to concomitant congenital LQTS and should not be attributed solely to myocardial hypertrophy. Genetic testing for genes known to be associated with congenital LQTS should be considered in patients with HCM and marked QT prolongation without a reversible cause, as this has clinical implications for the management of these patients and their family members. Further studies are needed to assess the true prevalence of co-inheritance of (likely) pathogenic variants associated with congenital LQTS and HCM, given the increased risk of

life-threatening arrhythmic events that this might carry and the need for tailored management.

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