

One family's clinical odyssey from evolving phenotypic and genotypic knowledge of catecholaminergic polymorphic ventricular tachycardia and long QT syndrome

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Introduction

Life-threatening arrhythmias in apparently healthy individuals can be due to diverse heritable cardiac channelopathies.¹ Ongoing advances revealing the underlying pathophysiology and genotype-phenotype associations are constantly evolving our approaches to diagnosis and management of these clinical entities.^{1–3} In some cases, initial diagnoses prove inaccurate over time, so routine reevaluation of each patient and family member remains an important element of care, with potentially life-altering ramifications.

We report a family whose proband originally presented with syncope, and was found to carry a *KCNE1* variant implicating long QT syndrome (LQTS), type 5 (LQT5). At that time, the rare variant was considered pathogenic, prompting family cascade screening (Figure 1). However, a recent large multicenter study demonstrated most *KCNE1* variants were weakly penetrant and over-represented in control populations.² Contemporary genetic testing of the proband identified a variant of uncertain significance (VUS) in *RyR2*, a more plausible explanation for her phenotype. Cascade screening for *RyR2*-related catecholaminergic polymorphic ventricular tachycardia (CPVT) ensued, and the longstanding familial diagnosis of LQT5 was reversed.

KEYWORDS Long QT syndrome; Catecholaminergic polymorphic ventricular tachycardia; *KCNE1*; *RyR2*; Variant readjudication (Heart Rhythm Case Reports 2022; ■:1–5)

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KEY TEACHING POINTS

- Knowledge of underlying genetic variants, molecular and cellular pathophysiology, and clinical manifestations of diverse cardiac channelopathies continues to evolve over time.
- Inherited arrhythmia specialists caring for families with known or suspected channelopathies must constantly reassess genotype-phenotype correlations, and maintain contemporary literature updates to provide up-to-date diagnosis and management.
- These principles facilitated promotion of a catecholaminergic polymorphic ventricular tachycardia variant of uncertain significance to likely pathogenic, and profoundly impacted diagnosis and management in family members.

Case report

Proband's case

In 2001, the 13-year-old proband presented with syncope triggered by exertion, anxiety, and startle. She was otherwise healthy, without contributory personal or family medical history. Her physical examination and echocardiogram were normal, and electrocardiogram (ECG) showed sinus rhythm with QTc (Bazett) of 413 ms. Treadmill testing revealed progressively frequent premature ventricular contractions (PVCs), bidirectional couplets, and polymorphic triplets (Figure 2), resolving with rest. The QTc was 430 ms and 437 ms in recovery at 1 and 4 minutes, respectively. She was clinically diagnosed with CPVT and treated with propranolol. Follow-up Holter monitoring recorded sinus

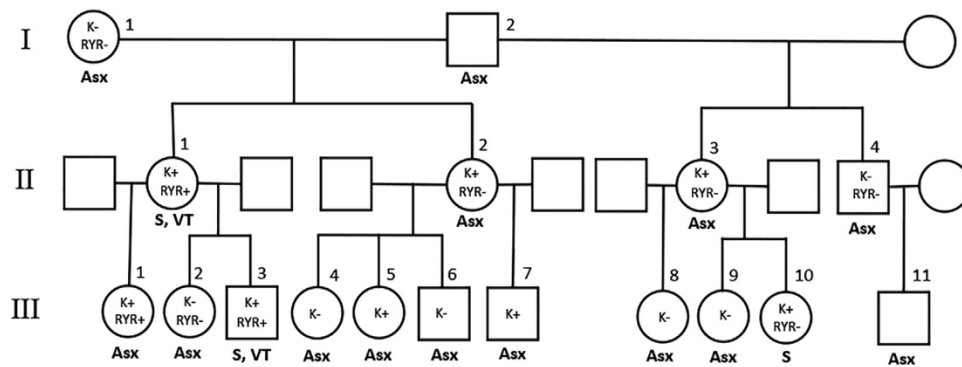


Figure 1 Pedigree of family whose proband (II-1) had both *KCNE1* and *RYR2* variants. Asx = asymptomatic; K+ = *KCNE1* positive; K- = *KCNE1* negative; RYR+ = *RYR2* VUS positive; R- = *RYR2* VUS negative; S = syncope; VT = ventricular tachycardia.

rhythm, rare premature atrial contractions, and no ventricular ectopy. The family requested an implantable cardioverter-defibrillator (ICD), as medications might not be protective.

In 2002, genetic testing via a research laboratory identified a rare heterozygous *KCNE1* variant (p.Asp76Asn). The full list of genes screened was unavailable; often only limited

RYR2 exons were tested by research laboratories at that time. Although her presentation was consistent with CPVT, clinical overlap seemed plausible given limited insight into the LQT5 phenotype; the diagnosis was then revised to LQT5. Management included propranolol, LQTS precautions, and regular clinic visits and device interrogations.

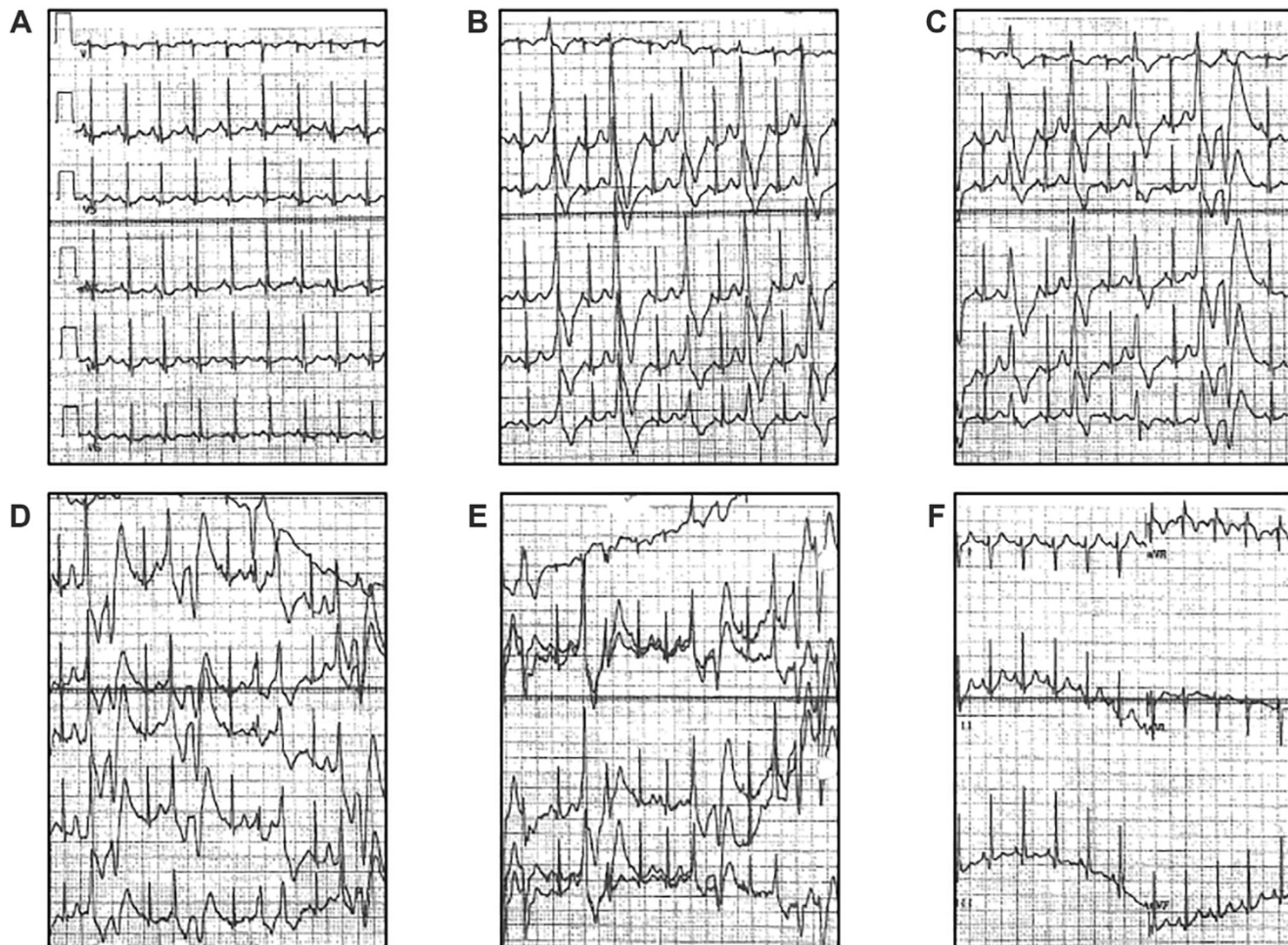


Figure 2 Electrocardiographic recordings during treadmill testing in the proband showing progressive ventricular ectopy with exercise (A–E), including bigeminal premature ventricular contractions (B, C), bidirectional couplets (C–E), and polymorphic triplets (E) prior to test cessation, with resolution during early recovery (F).

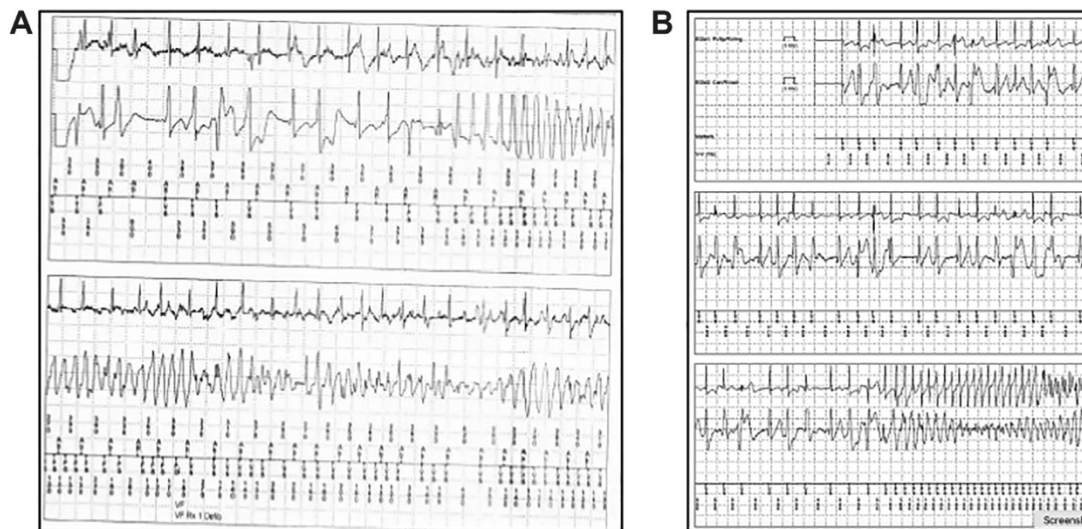


Figure 3 A: Proband's dual-chamber implantable cardioverter-defibrillator (ICD) recording showing sinus tachycardia, progressively frequent ventricular ectopy, and onset of rapid polymorphic ventricular tachycardia. B: Recording from the single-chamber ICD in proband's son showing similarly progressive ventricular ectopy. See text for details.

Follow-up QTc values ranged from 393 to 452 ms. She did well for 4 years until her first ICD shock for polymorphic ventricular tachycardia (PMVT) (Figure 3A) during moderate physical activity and uncertain medical compliance. Over the next 7 years, she experienced few appropriate shocks, especially during periods of medication noncompliance. Fortunately, she has since done well, with no recurrences, bringing 3 pregnancies to term uneventfully.

After initial identification of the *KCNE1* variant in the proband, cascade family screening included testing for this variant, symptom-event histories, and ECGs (Figure 1). At that time, all *KCNE1*-positive relatives had been asymptomatic, and were managed empirically per routine LQTS protocols. In 2017, the proband underwent comprehensive commercial genetic testing, confirming the *KCNE1* variant but also revealing she was heterozygous for a VUS in the *RYR2* gene (p.Lys3997Glu). This finding was compelling given her initial presentation; we suspected the *RYR2* variant may indeed be the culprit for her arrhythmias. Subsequent cascade screening for the *RYR2* variant was positive in 2 family members. Of note, the *KCNE1*-positive family members were considered for enrollment in the multicenter LQT5 study,² but those also positive for the *RYR2* variant were excluded owing to the suspicion of concomitant CPVT.

Relatives positive for both *KCNE1*-p.Asp76Asn and *RYR2*-p.Lys3997Glu

Most family members agreed to be tested for the *RYR2* variant, and this was positive only in 2 of the proband's children (III-1 and III-3, Figure 3); both have the *KCNE1* variant. III-3 had been treated with beta blockers since initial identification of the *KCNE1* variant. He remained asymptomatic for years; maximum QTc was 451 ms and Holters only showed rare nonsustained atrial tachycardia. He experienced effort syncope at 9 years old (38 kg) despite nadolol 40 mg

daily with good compliance. Treadmill testing on nadolol showed a blunted peak heart rate (140 beats/min) and exertional ventricular bigeminy that resolved with rest. QT intervals shortened during exercise. The family's concern by his mother's course prompted implantation of an ICD. He did well until 14 years old, when he experienced abrupt syncope while horseback riding; an ICD shock terminated PMVT (Figure 3B). Noncompliance of daily nadolol 80 mg was suspected. ICD interrogation confirmed acceptable performance, inpatient telemetry showed no arrhythmias, and nadolol was increased to 80 mg twice daily. He has since had no additional arrhythmias or syncope. Commercial testing identified both *KCNE1* and *RYR2* variants.

III-1 is now 8 years old and also has both *KCNE1* and *RYR2* variants. She has had a benign course on beta blockers with a maximum QTc of 448 ms and no significant arrhythmias on Holters. Recent treadmill testing off nadolol for 1 day showed PVCs including bigeminy appearing at peak exercise; peak HR of 158 beats/min suggested residual beta blocker effect.

Relatives positive for *KCNE1*-p.Asp76Asn and negative for *RYR2*-p.Lys3997Glu

The proband's sisters (II-2, III-3) have the *KCNE1* variant but tested negative for the *RYR2* variant. Two of II-2's children (III-5, III-7) have the *KCNE1* variant. Except for II-3 having occasional PVCs at rest by Holter monitoring, other Holters and stress testing have been negative. Maximum QTc values of these individuals were 443–455 ms, and all have been asymptomatic and chronically treated with beta blockers.

A *KCNE1*-positive niece of the proband (III-10) experienced syncope when almost 4 years old while compliant with propranolol. Follow-up exam and ECGs were unremarkable. An ICD was implanted given concerns that LQT5 might be the culprit. She has been very active for 9

years (currently a competitive dancer) without recurrent syncope or significant arrhythmias on device interrogations. Maximum QTc was 474 ms. Testing confirmed she did not have the *RYR2* variant. Her remote syncopal episode remains enigmatic; now neither LQT5 nor CPVT are implicated.

Relatives with neither *KCNE1*-p.Asp76Asn nor *RYR2*-p.Lys3997Glu

The proband's mother (I-1) and paternal half-brother (II-4) tested negative for the *KCNE1* variant, were asymptomatic, and had been discharged. Both tested negative for the *RYR2* variant. The proband's father has not undergone genetic testing.

Discussion

This experience illustrates recent evolution in our understanding and approach to managing patients with known or suspected cardiac channelopathies, and the subsequent impact on affected individuals. Every patient and family member should be consistently reassessed for clinical changes, particularly in the context of ongoing progress in understanding these entities. In addition, we propose that this *RYR2* VUS (p.Lys3997Glu) be promoted to likely pathogenic for CPVT, supported by phenotypes of the proband and her children and the variant's location in a genetic "hot spot."³

Unfortunately, diagnosis and management can still be vexing in some patients, particularly for rare subtypes with limited examples, for channelopathy genotypes with overlapping phenotypes, and in patients with discordant clinical and genetic findings.^{1–10} Historically, some clinicians suspected LQTS to be the culprit for arrhythmic events even when ECGs did not show significant QT prolongation.⁷ Medeiros-Domingo and colleagues⁸ described 45 patients with exertional syncope and QTc <480 ms diagnosed with "concealed" LQTS, finding instead that 31% had *RYR2* variants implicating CPVT. The pleiotropy of *SCN5A* variants associated with diverse clinical syndromes has been well established, extended by recent report of a subset of LQT3 patients with Purkinje system hyperexcitability causing PVCs and ventricular tachycardia (VT).¹⁰ Similarly, patients with Anderson-Tawil syndrome type 1 due to *KCNJ2* variants may manifest bidirectional VT and life-threatening arrhythmias, phenotypically overlapping with CPVT.⁹

Twenty years ago, we suspected our proband had CPVT, but available testing at the time identified a *KCNE1* variant associated with a rare form of LQTS (LQT5). These *KCNE1* variants cause loss-of-function in the voltage-gated potassium beta-subunit minK, delaying membrane repolarization and possibly predisposing to arrhythmias.^{11,12} Initial genotype-phenotype correlations were limited, and LQT5 was considered potentially malignant at the time. However, recent large multicenter analysis of LQT5² found ~80% of *KCNE1*-positive patients had QTc <460 ms, and serious arrhythmic events were rare, with <30% occurring during or immediately after exertion. Our family's heterozygous

p.Asp76Asn variant was the most prevalent, and showed low overall penetrance. Indeed, none of our *KCNE1*-positive individuals have had significant QT prolongation, and most with "isolated" LQT5 have been asymptomatic.²

More recent evaluation of the proband for heritable channelopathies using commercially available comprehensive testing revealed an *RYR2*-p.Lys3997Glu variant, heretofore considered a VUS. CPVT1, the most common CPVT subtype, is caused by mutations in the *RYR2*-encoded cardiac ryanodine receptor-2; the most concerning are localized in 1 of 4 "hotspots."^{6,13} Significant arrhythmias typically manifest during periods of elevated sympathetic tone. Stress testing has proven a valuable diagnostic tool, as affected patients typically show progressively frequent ventricular ectopy, from isolated PVCs to bigeminy, polymorphic couplets, and nonsustained VT, often in a bidirectional pattern, resolving during recovery. Our proband and her son showed these findings and experienced PMVT during physical activity (Figure 3). In 2009, an individual was reported with the same *RYR2* variant; although localized to a CPVT hotspot and *in silico* analysis suggested it was damaging,⁸ pathogenicity was uncertain at that time. By applying recent phenotype-enhanced American College of Medical Genetics and Genomics criteria for CPVT¹⁴ to members of this family, we propose that this VUS be upgraded to likely pathogenic.

Implications for clinical management in this family

Our evolving insights into LQT5 and *RYR2* variant readjudication have influenced shared management decisions throughout this family. Asymptomatic "isolated" LQT5 patients with QTc <460 ms, likely to only be at risk for acquired LQTS, will continue to avoid medications contraindicated in LQTS²; some have discontinued beta blockade. We expect to explant the ICD generator in the patient experiencing syncope at ~4 years old, as no arrhythmias have been recorded over 9 years and her QTc values have remained <480 ms.

Individuals with both *KCNE1* and *RYR2* variants will continue LQTS and CPVT precautions and beta blockade; left cervical sympathetic denervation will be considered should they have recurrent PMVT.¹⁵ ICDs are controversial in CPVT patients, given concerns of triggering VT storm,^{6,13} and arrhythmias are usually suppressed with beta blockers, flecainide, and left cervical sympathetic denervation. We note that our patients received ICDs before the *RYR2* variant was discovered, and appropriate ICD shocks terminated PMVT without early recurrence. Finally, our experience with this family also illustrates the good fortune that the *RYR2* variant did not exist in family members discharged from routine follow-up.

Limitations

This analysis was retrospective, and in one family with members having the *RYR2* variant also harboring the *KCNE1* variant. Although LQT5 is usually benign, that is not

universal. Whereas the *RYR2* variant is likely responsible for arrhythmias in our proband and her affected children, and the *KCNE1* variant relatively incidental, we cannot be certain regarding potential pathophysiological interaction.

Conclusions

This 20-year experience with a family whose proband presented with syncope and malignant arrhythmias, early on considered to reflect a rare LQTS subtype after initial genetic testing but later confirmed to be due to CPVT, highlights that providers managing patients with known or suspected inherited arrhythmias should focus primarily on phenotype and consistently reassess contemporary genotype-phenotype correlations to ensure all family members have accurate diagnoses. Intermittent reevaluation of members initially unaffected by the primary genetic variant may be a reasonable practice. Finally, we propose that this *RYR2* VUS (p.Lys3997Glu) be promoted to likely pathogenic for CPVT, supported by patient phenotypes and the variant's location in a genetic "hot spot."³

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