A novel variant in *KCNQ1* associated with short QT syndrome

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Introduction

Short QT syndrome (SQTS) is a rare and relatively recently discovered cardiac channelopathy associated with atrial and ventricular fibrillation and sudden cardiac death. A short QT interval on electrocardiogram (ECG) is particularly rare in the pediatric population, with a reported incidence of 0.05%.[1] This autosomal dominant condition has been associated with 20 different variants in 9 different genes.[1] Associated genes include those encoding potassium channels (*KCNH2, KCNQ1, KCNJ2*) and cation channels (*SCN5A*), genes encoding L-type calcium channel subunits (*CACNA1C, CACNB2b, CACNA2D1*), and, less commonly, anion exchanger mutations such as *SLC4A3*.[1] There are, however, a substantial number of patients clinically diagnosed with SQTS for whom no causative genetic mutation is identified. We present a case of ventricular fibrillation cardiac arrest with a suspiciously short but initially nondiagnostic QTc (383 ms). Clinical genetic testing revealed a novel variant in the *KCNQ1* gene, which we believe likely represents a novel variant associated with SQTS.

Case report

A previously healthy 10-year-old girl was vacationing with her family on the beach when she experienced a ventricular fibrillation sudden cardiac arrest. She told her father she felt nauseous and then collapsed and became unconscious. She received bystander cardiopulmonary resuscitation and had an automated external defibrillator placed, which recorded ventricular fibrillation. She converted to pulseless electrical activity after a 120 joule shock, and subsequently to an organized rhythm (Figure 1). She had return of spontaneous circulation after 10 minutes and was transferred to a local hospital. She had no history of syncope or palpitations. She was active in sports and able to keep up with other children her age without difficulty. The patient's mother, maternal grandmother, and maternal great-grandmother all had a history of atrial fibrillation. Her mother ultimately underwent ablation for her atrial fibrillation as a teenager, but had not followed up with a cardiologist in a number of years. A paternal first cousin died suddenly at 4 months of age of an

KEY TEACHING POINTS

- Short QT syndrome remains a rare and fairly recently discovered cardiac channelopathy, and there are still a substantial number of patients for whom no causative genetic mutation is identified. Owing to the still relatively small patient cohort, it is important to investigate new, potentially pathologic variants to contribute to the understanding of the disease.
- In cardiac channelopathies, variants of uncertain significance (VUS) should be interpreted in close conjunction with the clinical context. If there is sufficient clinical suspicion of a given disease, a genetic test result alone should not be the decisive diagnostic factor. Likewise, a genetic variant alone should typically not be used to confirm a diagnosis in the absence of sufficient clinical evidence. Depending on the index of clinical suspicion, the potential clinical significance of a VUS may require further investigation, including family and functional studies when possible.
- Short QT syndrome remains a rare diagnosis with continued investigation into the clinical and genetic associations. Given the relatively small cohort, patients with suspected short QT syndrome should undergo rigorous clinical and genetic evaluation to help refine diagnostic criteria.

KEYWORDS Atrial fibrillation; *KCNQ1*; Short QT syndrome; Sudden cardiac arrest; Ventricular fibrillation
(Heart Rhythm Case Reports 2021;7:650–654)

Funding Sources: The authors have no funding sources to disclose. Disclosures: The authors have no conflicts of interest to disclose. **Address reprint requests and correspondence:** Dr David Spar, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, MLC 2003, Cincinnati, OH 45229. E-mail address: David.Spar@cchmc.org.

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https://doi.org/10.1016/j.hrcr.2021.04.017

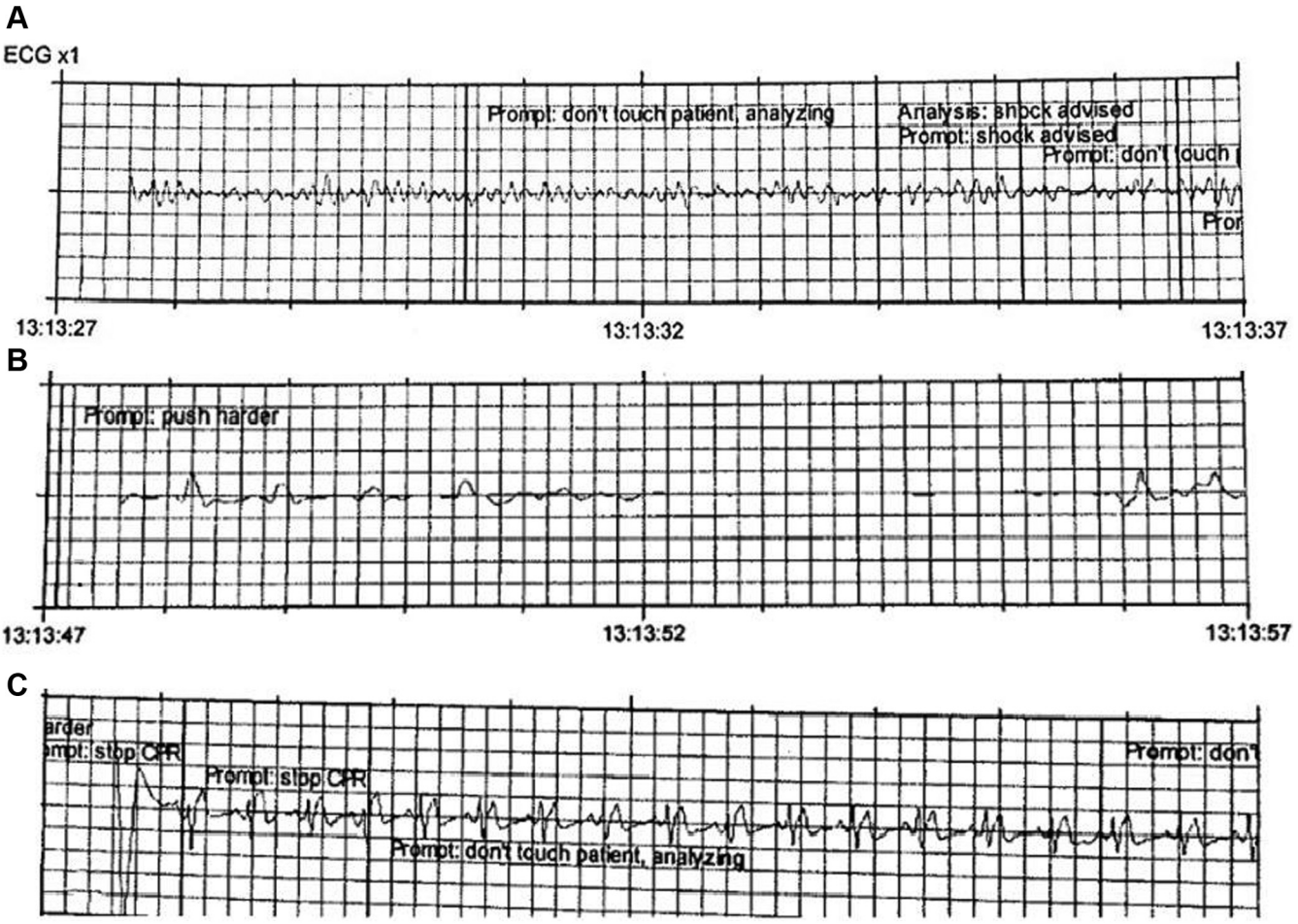

Figure 1 Electrocardiogram strips from the automated external defibrillator showing **A:** the initial rhythm of ventricular fibrillation, **B:** rhythm after a shock showing pulseless electrical activity during a pause in cardiopulmonary resuscitation (CPR), and **C:** rhythm after shock and several minutes of CPR showing an organized rhythm during a pause in CPR.

unknown etiology that was ultimately attributed to sudden infant death syndrome.

Her initial physical examination was unremarkable and remained so throughout her hospitalization. An initial transthoracic echocardiogram performed the day of her arrest was notable for an ejection fraction of 35% with a structurally normal heart. Her initial ECG showed normal sinus rhythm at 103 beats/min with a QT of 292 ms and a QTc of 383 ms calculated using Bazett's formula (Figure 2). There were no electrolyte abnormalities and a repeat echocardiogram the following day demonstrated normal function with an ejection fraction of 55%. Cardiac magnetic resonance imaging showed no evidence of myocarditis or cardiomyopathy. Telemetry monitoring and serial ECGs were significant for a short QT interval with a minimal QTc of 344 ms (Figure 2). Our patient's minimal QT interval was 82% of her predicted QT interval of 369 ms (calculated as proposed by Rautaharju)[2] and while her T_{peak}-T_{end} was within the normal range at 72 ms, her $T_{p\text{-}e}$/QT ratio was slightly elevated at 0.26. Graded exercise testing demonstrated a lack of adaptation of the QT interval to exercise and increasing heart rates, with a baseline QTc of 361 ms and a shortest QTc of 353 ms seen at peak exercise. There was also a blunted adaptation of the QT interval in recovery and decreasing heart rates, with a QTc of 321 ms at 1 minute into recovery and a QTc of 372 ms at 7 minutes into recovery. A subcutaneous implantable cardioverter-defibrillator (ICD) was placed for secondary prevention. During the procedure defibrillation threshold testing was performed, ventricular fibrillation was induced, and the ICD delivered a successful shock with return to sinus rhythm. She has been doing well since discharge, with complete cardiovascular and neurologic recovery at 6 month follow-up, no symptoms, and no ICD therapies.

During her admission a 114-gene arrhythmia and cardiomyopathy gene panel (Invitae, San Francisco, CA) was ordered and revealed 3 variants of unknown significance in *KCNQ1* (NM_000218.2: c.836T>G, p.Phe279Cys), *RYR2* (NM_001035.2: c.13291G>A, p.Glu4431Lys), and *TTN* (NM_001267550.2: c.101117T>C, p.Val33706Ala). The performing laboratory noted the variant in *RYR2* was predicted to be tolerated by in silico prediction tools. It was noted that the variant had been reported in 1 individual with long QT syndrome[3] and in 1 individual with sudden cardiac death.[4] However, this variant is also present in population databases, including in a European non-Finnish

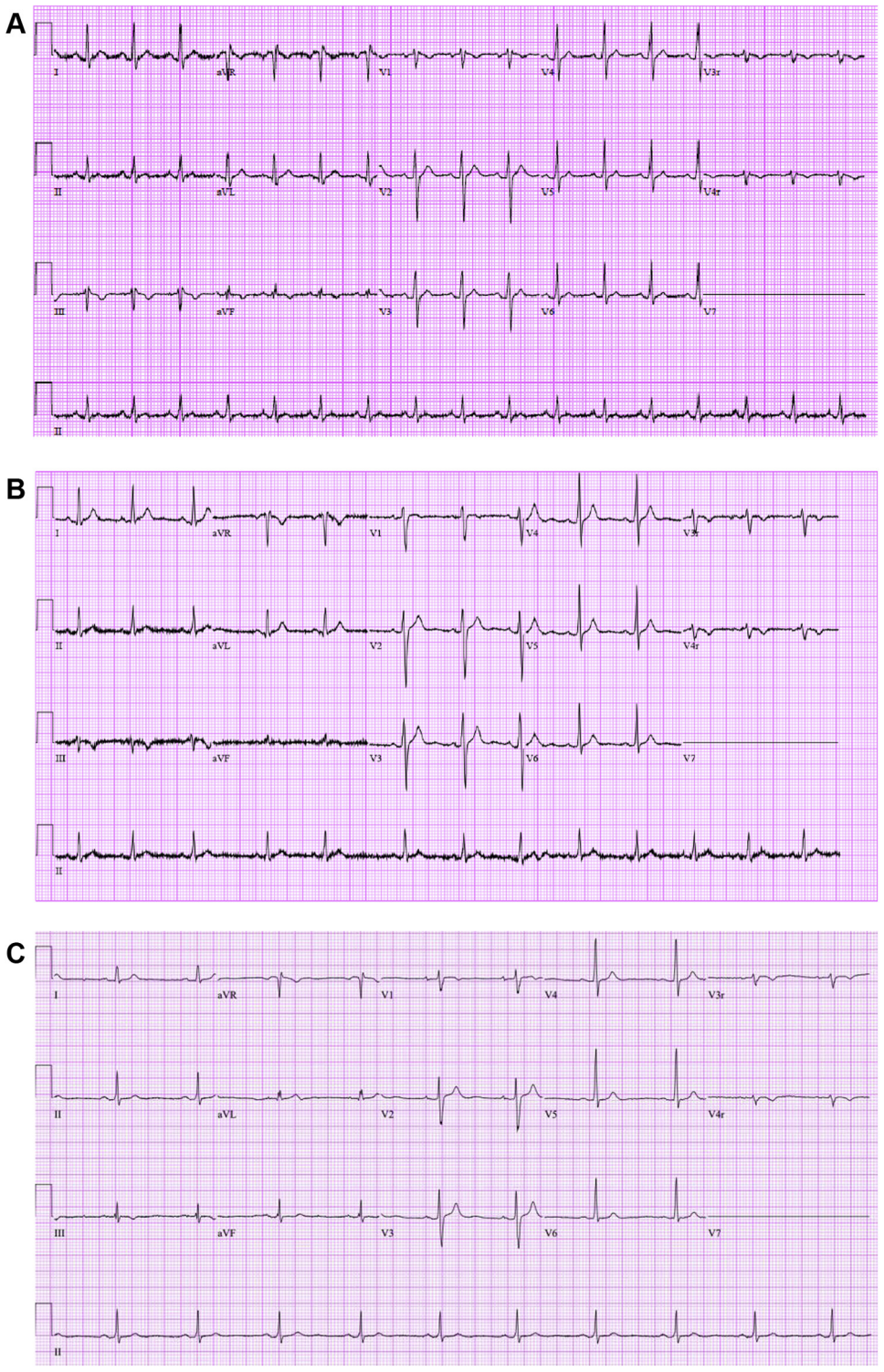

Figure 2 **A:** Initial electrocardiogram (ECG) with QT interval of 292 ms and QTc 383 ms with a heart rate of 103 beats/min. **B:** Follow up ECG with QT interval of 302 ms and QTc 344 ms with a heart rate of 78 beats/min. **C:** Patient's mother's ECG with QT interval of 322 ms and QTc 327 ms with a heart rate of 62 beats/min.

population with an allele frequency of 0.05% (51/106,610 alleles) in gnomAD (Table 1).[5] The *TTN* p.Val33706Ala missense variant occurs in the M band region of the gene and was identified once in gnomAD (allele frequency of 0.0009% in European non-Finnish population); it has not been published in association with disease.

The novel *KCNQ1* p.Phe279Cys variant has not been reported in population databases, and has not been previously published in association with disease. The variant has been shown to impact *KCNQ1* functionality by shifting the voltage dependence of activation in the hyperpolarizing direction.[6] This results in a gain-of-function effect, with a greater

Table 1 Genetic variant data

	KCNQ1 c.836T>G p.Phe279Cys	*RYR2* c.13291G>A p.Glu4431Lys	*TTN* c.101117T>C p.Val33706Ala
gnomAD frequency			
Total alleles	Absent	54:242,862	1:248,758
European non-Finnish alleles	Absent	51:106,610	1:112,628
In silico tools[†]			
SIFT	Damaging	Tolerated	N/A
PolyPhen-2	Possibly damaging	Benign	N/A
MutationTaster	Disease-causing	Disease-causing	N/A
Species conservation[†,‡]			
Human	Phe	Glu	Val
Rhesus	Phe	Glu	Val
Mouse	Phe	Glu	Val
Dog	Phe	Glu	Val
Elephant	Phe	Glu	Val
Chicken	Phe	=	Val
Xenopus tropicalis	Phe	=	Val
Zebrafish	Phe	Ser	Val
Lamprey	Phe	=	Val

N/A = not available.

Double line (=) indicates unalignable bases in the region.

[†]As assessed through UCSC genome browser (https://genome.ucsc.edu/index.html).[15]

[‡]Species conservation data provided for the wild-type amino acid corresponding to nucleotide position.

fraction of the channels open at a given voltage compared to the wild-type channel. As has been shown in other *KCNQ1* variants associated with gain-of-function mutations, augmentation of these outward repolarizing currents has been shown to decrease the action potential duration and lead to a shorter QT interval. The phenylalanine residue at this position is highly conserved, and in silico prediction tools predict that the variant is likely to be disruptive. Another variant at this position, p.Phe279Ile, has previously been published in association with SQTS in another individual, with functional data demonstrating a gain-of-function effect.[7]

Our patient's father had a normal QT and QTc on his ECG and his genetic testing was negative for our patient's known *KCNQ1* variant. Her mother had a short QT interval on her ECG of 322 ms and a QTc of 327 ms (Figure 2C) at 62 beats/min, and her genetic testing was positive for the same *KCNQ1* variant seen in our patient.

Discussion

Our patient presented with a ventricular fibrillation arrest with a structurally normal heart and initial testing that did not identify an obvious diagnosis. As her workup progressed, serial ECGs were obtained and revealed several ECGs with short corrected QT intervals ranging from 344 ms to 383 ms. Although her initial QT interval was in the normal range, subsequent QTc intervals have consistently been less than 360 ms. Her telemetry during her hospitalization was reviewed as part of her investigation and showed a short QT interval at a wide range of heart rates. Her exercise testing also showed abnormal adaptation of the QT interval to exercise, which has been seen in SQTS and may be secondary to enhanced repolarization and limited repolarization reserve.[1] Additionally, her QT interval was less than 88% (2 standard deviations below the predicted value) of her QT_p^2 and her $T_{p\text{-}e}$/QT ratio was elevated compared to controls, with a T_{peak}-T_{end} within the normal range[8]; all of these findings have been seen in SQTS. Owing to the relatively small number of patients with SQTS, there continues to be some debate surrounding the diagnostic criteria. Her testing is consistent with SQTS based on the 2013 HRS/EHRA/APHRS expert consensus statement[9] (QTc less than 360 ms and survival of a ventricular fibrillation episode in the absence of heart disease) and the proposed diagnostic scoring system put forward by Gollob and colleagues[2] (high probability of SQTS with a score of 4: 1 point for QTc less than 370, 2 points for history of sudden cardiac arrest or documented ventricular fibrillation, and 1 point for mutation of undetermined significance in a culprit gene). Genetic testing was performed in accordance with the 2011 HRS/EHRA expert consensus statement[10] based on the patient's clinical history and electrocardiographic phenotype.

To date, a causative variant has been found in less than 20% of patients who have undergone genetic testing for SQTS evaluation,[1] highlighting the importance of continued investigation. The majority of variants described to date are gain-of-function variants in the rapid, inward, and slow delayed rectifier potassium currents, resulting in increased potassium efflux during the plateau phase. This leads to accelerated repolarization and shortened atrial and ventricular action potential duration, increasing arrhythmia susceptibility and sudden death.[11] There have been several variants in patients with SQTS identified in the *KCNQ1* gene, resulting in amino acid changes at 6 different codons.

Our patient had 3 variants classified by the performing laboratory as having uncertain significance. Pathogenic variants in *RYR2* are typically associated with risk for catecholaminergic polymorphic ventricular tachycardia; the *RYR2* variant identified in our patient is present in population databases at an allele frequency far exceeding estimated disease prevalence.[12] Furthermore, our patient had no evidence of catecholaminergic polymorphic ventricular tachycardia on clinical evaluation. Although specific variants in *TTN*, mainly truncating variants in the A band region,[13] have been associated with dilated cardiomyopathy, the *TTN* variant identified in our patient occurs in the M band of *TTN*. Variants in this region are not definitively known to be associated with cardiac disease. It is believed that all individuals have rare missense variants in this gene.[14] Although our patient did have evidence of left ventricular systolic dysfunction immediately after her arrest, she demonstrated quick recovery. It was interpreted that the *TTN* and *RYR2* variants were unlikely to be related to the patient's clinical phenotype. The *KCNQ1* variant, however, is a novel variant, absent from population databases, occurring at the same position as a variant previously reported in association with SQTS, p.Phe279Ile. The Phe279 residue is highly conserved across species. It has been demonstrated that this position is

of functional importance, as the *KCNQ1* Phe279 residue collides with Phe232 in the presence of *KCNE1* and hinders the *KCNQ1* channel from opening.[6] Our patient's variant, p.Phe279Cys, has been shown to impact *KCNQ1* functionality by decreasing the membrane potential—an effect that is enhanced in the presence of *KCNE1*.[6] The authors who reported the p.Phe279Ile variant demonstrated that this variant resulted in altered assembly with *KCNE1*, and induced gain-of-function of slow delayed rectifier potassium channels.[7]

Conclusion

SQTS remains a rare cardiac channelopathy associated with sudden cardiac death. Given the small number of patients, there continues to be investigation into the clinical and genetic associations with the diagnosis. Our patient fulfills diagnostic criteria for SQTS based on the 2013 HRS/EHRA/APHRS consensus statement and Gollob's proposed SQTS diagnostic criteria, and her genetic testing shows a novel variant in a gene known to be associated with SQTS. This variant occurs at a position demonstrated to have relevance to slow delayed potassium channel function, occurs at a position where another missense variant has been published in association with SQTS with supportive functional data, and is consistent with both our patient's and patient's mother's phenotype. This variant is also absent from population databases. As such, though it is currently classified by the performing laboratory as a variant of uncertain significance, we assess that there is strong evidence suggesting that this variant is likely disease-causing.

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