

# Familial long QT syndrome and late development of dilated cardiomyopathy in a child with a KCNQ1 mutation: A case report



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## Introduction

Congenital long QT syndrome (LQTS) is an inherited cardiac channelopathy characterized by prolongation of the QT interval on electrocardiogram (ECG), and is associated with an increased risk of life-threatening ventricular arrhythmias. Mutations in over a dozen distinct genes have been implicated in the pathogenesis of this group of disorders.<sup>1</sup> LQTS type 1 (LQT1), the most prevalent LQTS subtype, is characterized by a heterozygous loss-of-function mutation in the KCNQ1 gene, which codes for the  $\alpha$ -subunit of the delayed rectifier inward potassium ion channel. The association of LQTS with dilated cardiomyopathy (DCM) is rare but has been reported in the presence of sodium channel gene mutations, as seen in LQTS type 3. In this case report, we describe a patient with familial LQT1 (KCNQ1 mutation) identified in infancy who was subsequently diagnosed with severe DCM later in childhood.

## Case report

A 2-day-old male infant underwent cardiology evaluation owing to a family history of LQTS. Evaluation of the extended family had previously been remarkable for multiple family members, including his mother, having a prolonged QTc on ECG screening. The patient's ECG demonstrated a QTc of 495 msec and abnormal T-wave morphology (Figure 1A). He was admitted to the hospital for initiation of propranolol. Genetic testing of the patient and multiple first- and second-degree maternal relatives identified the presence of a deleterious genetic mutation, KCNQ1 Ser 349 Ter, consistent with LQT1. The patient's older brother, who had previously been thought to be unaffected, was also found to be positive for the mutation and started on medication. The patient was maintained on propranolol until 4 years of age,

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and nadolol thereafter. Throughout this time he was clinically well, without palpitations, syncope, or documented arrhythmias, although his QTc remained prolonged on serial ECG evaluations. He underwent formal exercise testing at 7 years of age, which was notable for a prolonged QTc throughout exercise and recovery. There were no arrhythmias and he had a normal oxygen consumption of 40.5 mL/kg/min. He was active in multiple recreational sports, including basketball, lacrosse, and baseball; an automated external defibrillator was available for emergency use. Repeat exercise testing was performed at 8 years of age, which again demonstrated a prolonged QTc without ventricular ectopy. Oxygen consumption was not measured, but his physical working capacity was described as low (work rate 67 watts).

At 9 years of age, the patient was admitted to the hospital complaining of several days of diffuse abdominal pain, vomiting, diarrhea, and fatigue. He was admitted to the general pediatric service with a presumed diagnosis of viral gastroenteritis and discharged home the following day after receiving intravenous hydration. He presented to the emergency room 1 week later with continued gastrointestinal symptoms, as well as worsening fatigue and dyspnea. The initial physical examination was notable for tachypnea and intermittent retractions. On auscultation, a 1/6 holosystolic murmur was heard at the apex, with no other abnormalities. Hepatomegaly with tenderness to palpation was present. The initial laboratory evaluation was notable for an elevated B-type natriuretic peptide of 8578 pg/mL. A chest radiograph showed increased interstitial markings without pulmonary edema or cardiomegaly. His ECG showed new T wave changes and voltage criteria for left ventricular (LV) hypertrophy, but no evidence of arrhythmia (Figure 1B). A transthoracic echocardiogram was performed and demonstrated severely diminished LV ejection with a markedly dilated left atrium, a mildly dilated left ventricle, and moderate to severe mitral regurgitation. The LV ejection fraction (EF), as estimated by Simpson's rule (biplane), was 15%. Right ventricular (RV) ejection was decreased as well, but not as markedly as that of the left ventricle. There was

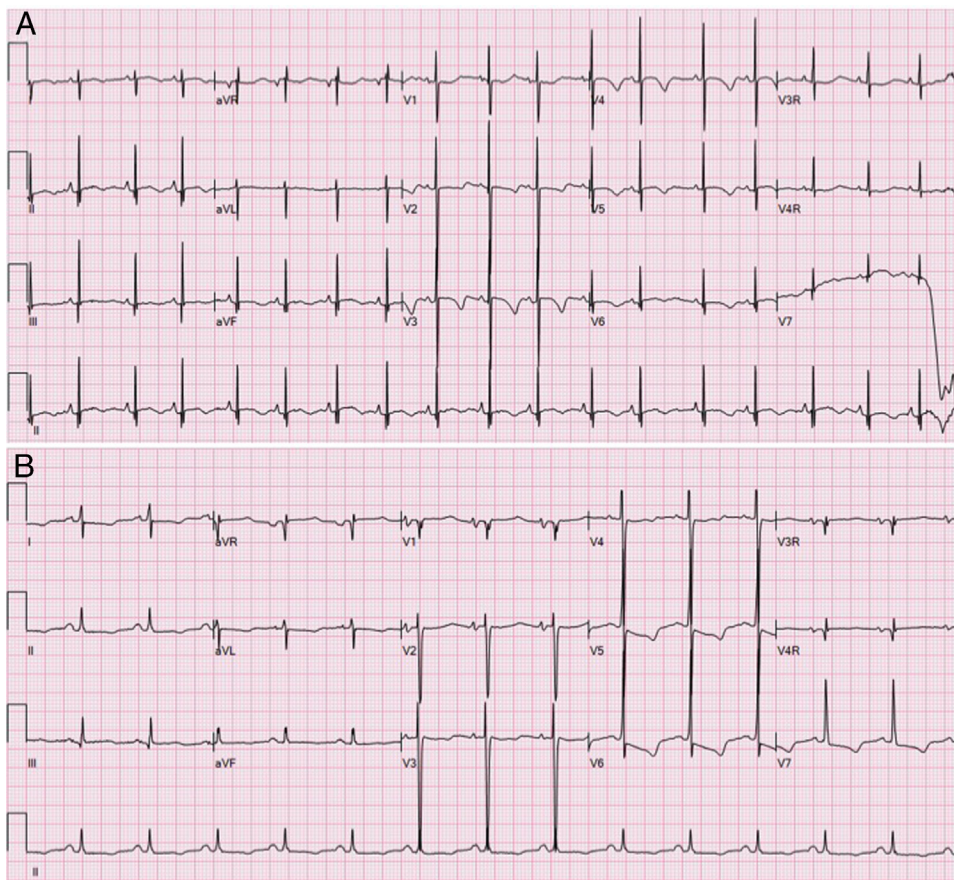
### KEY TEACHING POINTS

- An association between long QT syndrome and dilated cardiomyopathy has been previously described in the presence of SCN5A mutations and may represent a sodium channel “overlap syndrome” between channelopathies and cardiomyopathies.
- It is possible that molecular interaction between potassium channel mutations and other mutations in the cardiac sarcomere and mitochondria may lead to a phenotypic overlap syndrome between long QT syndrome and cardiomyopathy.
- Additional screening for cardiomyopathy may be warranted in patients with a variety of genetic channelopathies.

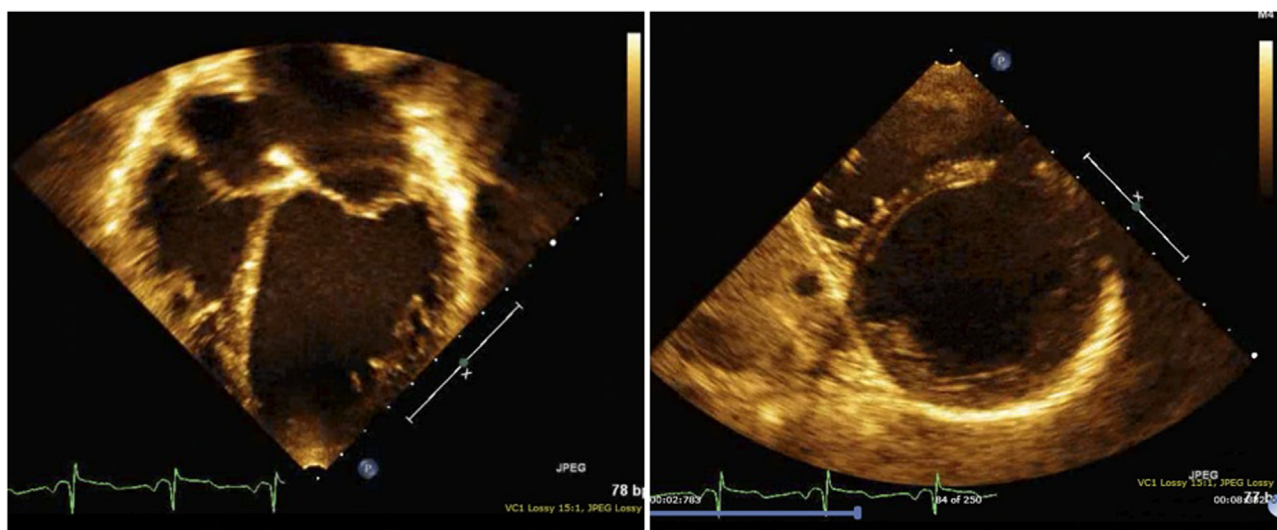
echocardiographic evidence of elevated pulmonary artery pressures with an RV pressure estimate of 38 mm Hg above central venous pressure and a pulmonary artery end-diastolic pressure estimated at 15 mm Hg using the modified Bernoulli equation (Figure 2). An infectious evaluation failed to show any evidence of active viral infection (blood polymerase

chain reaction assays for adenovirus, influenza, parainfluenza, metapneumovirus, rhinovirus, enterovirus, cytomegalovirus, HHV-6, parechovirus, parvovirus B19, Epstein-Barr virus, and stool polymerase chain reaction assays for common gastrointestinal pathogens were all negative) or systemic inflammation (C-reactive protein <0.5 mg/dL, erythrocyte sedimentation rate 0 mm/h) and the troponin I was 0.01 ng/mL. He was treated with 2 g/kg of intravenous immunoglobulin, without improvement.

A metabolic evaluation (lactate, pyruvate, acylcarnitine profile, blood and urine carnitine levels, plasma amino acids, urine organic acid, and creatine kinase) was negative. Commercial genetic testing consisting of DNA sequencing for 51 known cardiomyopathy genes was performed by the Laboratory for Molecular Medicine (Boston, MA) and was notable for a variant of unknown significance in the titin gene (p.Asn18096Lys). A Combined Mito Genome Plus Mito 140 Nuclear Gene Panel (GeneDx, Gaithersburg, MD) was also performed and showed heterozygosity for a variant of unknown significance in the ACO2 gene (p.Arg142Gln) and heterozygosity for a variant of unknown significance in the NDUFA10 gene (p.Arg337His). Cardiac magnetic resonance imaging (MRI) was obtained and demonstrated moderate to severe LV dilation (end-diastolic volume 165 mL/m<sup>2</sup>), severely diminished LV ejection (EF 21%), and moderately diminished



**Figure 1** A: Twelve-lead electrocardiogram obtained at 2 days of life showing a corrected QT interval of 495 msec and nonspecific T wave abnormalities. B: Twelve-lead electrocardiogram obtained at time of presentation with heart failure at 9 years of age demonstrating new T wave changes and voltage criteria for left ventricular hypertrophy.



**Figure 2** Transthoracic echocardiogram showing severe dilation and systolic dysfunction of the left ventricle.

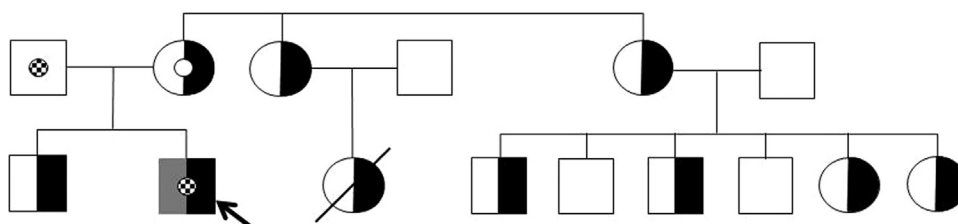
RV ejection (EF 32%) without dilation or hypertrophy. MRI tissue characterization was limited owing to myocardial thinning, but the Lake Louise criteria for MRI diagnosis of myocarditis were not met.<sup>2</sup> Based on these findings, a diagnosis of idiopathic DCM was made. Upon clinical improvement, milrinone was discontinued and he was transitioned to an oral regimen of enalapril, digoxin, nadolol, and enteral diuretics. Owing to his lack of arrhythmias and relative small size, placement of a primary prevention implantable cardioverter-defibrillator was deferred. He was discharged home after approximately 4 weeks, but required readmission for reinitiation of milrinone approximately 1 month later owing to recurrent symptoms of congestive heart failure. A cardiac catheterization was performed during that admission and was notable for preserved cardiac index of 3.6 L/min/m<sup>2</sup> (on milrinone), elevated pulmonary capillary wedge pressure of

14 mm Hg, and normal pulmonary vascular resistance. Based on these findings and clinical status, the patient was listed for heart transplantation. He recently underwent an uncomplicated orthotopic heart transplant. Gross pathologic examination of the explanted heart was consistent with the diagnosis of DCM, with scattered myocyte hypertrophy on microscopic examination.

The patient’s older brother, who also has the LQT1 mutation, was evaluated with screening echocardiography and has normal cardiac chamber size and systolic function. No other family members have been diagnosed with cardiomyopathy (Figure 3).

**Discussion**

To our knowledge, this is the first report in the medical literature of an association between LQT1 and DCM. Our patient is unique, as he carries genotypic and phenotypic



**Figure Legend**

- Unaffected Female
- Unaffected Male
- ◐ ◑ Clinically affected with LQT1 (KCNQ1\*)
- ⊖ ⊕ Negative for titin variant
- ⊗ ⊙ Positive for titin variant
- ◼ ◽ Clinically affected with dilated cardiomyopathy
- ⊘ ⊚ Deceased

**Figure 3** Family pedigree demonstrating mutations in the KCNQ1 and titin genes. The KCNQ1 was inherited maternally and multiple first- and second-degree relatives were affected, including a maternal cousin with sudden cardiac death. The titin gene mutation was inherited paternally and no other overlap with the KCNQ1 gene was identified.

characteristics of LQT1 and went on to develop DCM without evidence of frequent ventricular ectopic beats or sustained arrhythmias, making a tachycardia- or PVC-induced cardiomyopathy unlikely. His inflammatory markers and infectious evaluation were negative, and cardiac MRI did not show convincing evidence of myocarditis; therefore, a concurrent myocarditis is highly unlikely. Our patient's presentation, therefore, is more consistent with an idiopathic DCM of subacute onset.

While a cardiac sodium channel "overlap syndrome" between channelopathies and cardiomyopathies has been described related to abnormalities in the SCN5A gene, no such association with DCM has been described with respect to the cardiac potassium channels involved in LQT1. The SCN5A gene encodes the  $\alpha$ -subunit of the voltage-dependent cardiac sodium channel and has been implicated in a number of pathologic cardiac conditions, including LQTS type 3 (LQT3), Brugada syndrome, sick sinus syndrome, conduction system disease, sudden infant death syndrome, and DCM. A study by McNair et al<sup>3</sup> found an SCN5A mutation prevalence of 1.7% in their multicenter cohort of 338 patients with DCM. While none of these patients had QTc prolongation, multiple case reports have described an overlap between ECG evidence of LQTS and DCM in patients with mutations in the SCN5A gene.<sup>4,5</sup> The mechanism of overlap between channelopathy and cardiomyopathy in LQT3 is not well understood, but it has been proposed that ion channel mutations may ultimately result in structural changes to the myocardial tissue via their interaction with cytoskeletal proteins, either directly or as a result of altered ion homeostasis.<sup>6,7</sup> KCNQ1 gene mutations have not previously been described in patients with DCM, but they have been implicated in other types of cardiomyopathies such as hypertrophic cardiomyopathy and LV noncompaction cardiomyopathy.<sup>8,9</sup> The delayed rectifier potassium channel affected in LQT1 is one of several types of potassium channels responsible for reconstitution of the cardiac action potential, whereas the function of the SCN5A channel is absolutely necessary for depolarization and, hence, contractile function.<sup>10,11</sup> It may be that, unlike sodium channel mutations, a single potassium channel mutation is insufficient to cause a significant effect on contractile function without additional abnormalities in cytoskeletal proteins or cardiac metabolism.

Genetic testing of known cardiomyopathy genes revealed genetic variants of unknown significance in mitochondrial genes involved in the electron transport chain and in titin, an autosomal gene coding for a sarcomere protein commonly implicated in DCM. It is possible that normally nonpathogenic variations in the titin gene can become disease-producing via interaction with mutations in other susceptible genes.<sup>12</sup> It has been previously suggested that titin may influence activity of the delayed outward rectifying potassium currents affected in LQT1.<sup>13</sup> While the KCNQ1 mutation was inherited maternally, the titin mutation was inherited paternally, and overlap between the KCNQ1 and titin mutations was not identified in any other maternal family member (Figure 3).

## Conclusions

While a mutation in KCNQ1 has not been previously described as an etiology for DCM, we hypothesize that the potassium ion channel could be involved in the pathogenesis of myocardial dilation and resultant ventricular dysfunction, either in isolation or via molecular interplay with other genetic variants of unknown significance. Similar to SCN5A, it is possible that a potassium channel overlap syndrome may exist. There has been little investigation into the role of the delayed rectifier potassium channel in heart failure.<sup>14</sup> More research is needed into the possible pathogenic manifestations of this mutation within the cardiac myocyte. From a clinical standpoint, patients with known deleterious potassium and sodium channel genetic mutations should be carefully monitored for both QTc prolongation and ventricular dysfunction, irrespective of the presenting phenotype.

## Appendix

### Supplementary data

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.hrcr.2015.10.011>.

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