Genotype-phenotype-guided medical and surgical intervention in long QT syndrome

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Introduction

Long QT syndrome (LQTS) is an inherited cardiac arrhythmia disorder characterized by QT prolongation and/or abnormal T-wave morphology on the electrocardiogram (ECG) and symptoms including syncope, cardiac arrest, and sudden cardiac death.[1] Beta-blockers have long been accepted as the first line of treatment, and are highly effective, especially in patients with LQTS type 1. This type of LQTS is related to abnormalities in the KvLQT1, which controls the slow delayed rectifier potassium current of cardiac repolarization, where cardiac events are typically triggered by adrenergic stimulation.[2] An alternative antiadrenergic treatment strategy is the use of left cardiac sympathetic denervation (LCSD), initially advocated as an effective treatment in addition to beta-blockade for those with recurrent symptoms and appropriate implantable cardioverter-defibrillator discharges, but more recently used in patients who are intolerant to beta-blockade.[3] The effects of LCSD are to both interrupt the main source of myocardial norepinephrine, thereby limiting the catecholaminergic activation of dysfunctional KvLQT1 channels, and to increase myocardial refractoriness and fibrillatory threshold.[4] This report details patient-specific treatment strategies used in a child with LQTS type 1 who had complications on beta-blocker therapy. The strategies were based on genetic results and continual assessment of the phenotype.

Case report

A 4-year-old boy was diagnosed with LQTS after an episode of syncope while climbing out of a swimming pool. His corrected QT interval (QTc) was reportedly measured between 480 and 520 ms at an external institution, although the original ECGs were unavailable for review. He was treated with mexiletine until genetic testing exposed a maternally inherited truncating Swedish founder mutation in the C-terminal of *KCNQ1* (c.1552C>T; p.R518X) (Figure 1). Mexiletine was discontinued and he was treated with nadolol.[5] He remained asymptomatic for many years, and was reviewed at our institution at the age of 11 when his family relocated. At this time, on a daily dose of 20 mg of nadolol (0.74 mg/kg), the QTc on a resting ECG was 407 ms. In the family, he is the second child of nonconsanguineous parents. The *KCNQ1* variant was inherited from his asymptomatic mother with normal QT intervals on repeated ECGs. The proband's 21-year-old asymptomatic brother also carries the same variant. Additionally, the family history is significant for sudden cardiac death in a 49-year-old maternal great uncle who died while shoveling snow and a 28-year-old maternal grandfather who died in a construction accident. The deceased relatives were not genotyped and no further details were available (Figure 2). An exercise test was performed on our patient,

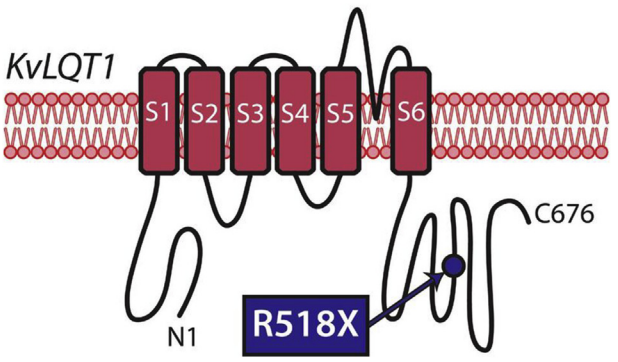

Figure 1 A depiction of the potassium channel, KvLQT1, encoded by the gene *KCNQ1*, is shown with 6 transmembrane domains (S1–S6) seen spanning the cardiomyocyte membrane. The site of the pathogenic variant identified in the proband—KCNQ1 c.1552C>T; p.R518X—is depicted by the blue circle in the C-terminus.

KEYWORDS Arrhythmia; Electrophysiology; Left cardiac sympathetic denervation; Long QT syndrome; Sudden cardiac death
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KEY TEACHING POINTS

- Comprehensive phenotyping and deep knowledge of the underlying genotype guide successful management in complex long QT syndrome.
- Left cardiac sympathetic denervation may be a successful option for long QT patients who cannot tolerate beta blockade.
- Competing risks in complex patients with long QT syndrome require a personalized, patient-centered approach to medical management.

which demonstrated a peak heart rate of 173 beats per minute and a QTc measured within the normal limits during the recovery period from exercise (Figure 3A). He was continued on the same dose of nadolol and reviewed annually.

At the age of 11 he presented to the Emergency Department after 3 days of anxiety and suicidal ideation, prompted by an encounter with a sexual predator in an online video game chat room, necessitating nadolol discontinuation. Psychiatric evaluation reported an unspecified anxiety disorder with moderately severe suicidal ideation and recommended an inpatient admission with 24-hour surveillance and discontinuation of nadolol. On further questioning regarding his psychological status, his parents reported that he was asymptomatic prior to starting nadolol and during early treatment, but had noted marked personality changes 6–8 months before this acute psychotic reaction, including fatigue, depression, and anxiety.

Given his prior normal QT response to exercise, a repeat test was performed after 3 days without nadolol therapy, which unmasked an LQTS phenotype in the late recovery period from exercise, with a maximal QTc of 520 ms recorded at 6 minutes (Figure 3B). Detailed consideration of future management was multifactorial, including his personal phenotypic expression, namely a male patient with long QT1 under the age of 12,[6] who had suffered prior symptoms consistent with LQTS, albeit without documented arrhythmia; his documented genotype and the associated phenotype in many carriers of the same variant[7]; and the potential need for QT-prolonging agents in the immediate term vs the risk of recurrent psychosis if beta-blockers were reintroduced. Ultimately, given the phenotypic expression in the absence of beta-blockers, age, and prior symptoms, he underwent LCSD, comprising excision of the lower half of the left stellate ganglion and removal of thoracic ganglia (T1–T5) of the left sympathetic chain with concurrent implantation of a Reveal LINQ loop recorder (Medtronic, Minneapolis, MN). He was started on the selective serotonin reuptake inhibitor escitalopram as the optimal

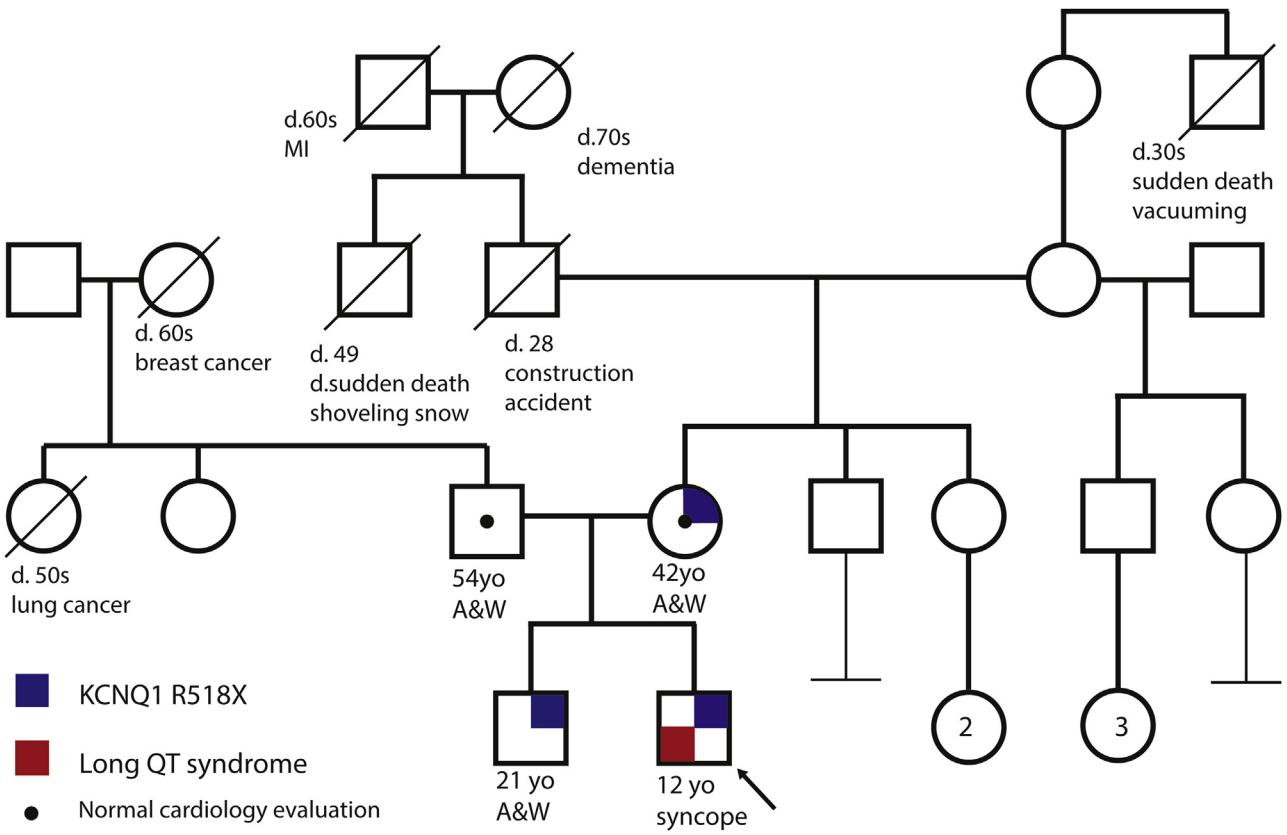

Figure 2 A multigenerational family pedigree with the proband denoted by an arrow. Males are represented by squares and females by circles. Blue quadrants represent the *KCNQ1* R518X genotype, and red quadrants represent long QT syndrome. A&W= alive and well; d. = died; MI = myocardial infarct; yo = years old.