Case Presentation
A 34-year-old female who is 4 months postpartum presents after a nocturnal seizure. She was awakened at night by an alarm clock to feed her baby, spoke briefly with her husband, and suddenly lost consciousness, appearing to have epileptic-type movements before spontaneously recovering. On further questioning, she reported several syncopal events over the past 15 years, once when standing suddenly, also thought at the time to be a seizure. Previous neurological investigations were normal. A 12-lead ECG (Figure 1A) revealed a corrected QT interval of 550 ms with low-amplitude, notched T-waves.

Background and Prevalence
Long QT syndrome (LQTS) is an inherited cardiac condition caused by genetically encoded abnormalities in cardiac ion channels, characterized clinically by palpitations, syncope, and sudden cardiac death, with varying degrees of QT prolongation and T-wave morphological abnormalities on the surface ECG. Advances in molecular and genetic cardiology over the past 20 years, coupled with increasing awareness of inherited conditions in the etiology of sudden cardiac death, have moved LQTS from the periphery to mainstream clinical medicine. A recent clinical and genetic analysis of 45,000 neonates suggests the prevalence to be in the range of 1:2000–2500.¹

Genetic and Molecular Mechanism of Long QT Syndrome
LQTS typically displays autosomal dominant Mendelian inheritance with variable penetrance² and rarely is inherited in a recessive fashion associated with sensorineural deafness. De novo variants of particularly severe forms are now being recognized. Linkage analysis first identified the potassium ion channel proteins KvLQT1 (KCNQ1) and HERG (KCNH2) as the basis for LQT types 1 and 2, and the sodium channel protein NaV1.5 (SCN5A) for type 3. Approximately 70% of patients with a clinical diagnosis will have identifiable mutations in 1 of the 12 genes now associated with the condition, with most located in genes encoding varying components of the potassium channel.³

Depolarization (phase 0) of the cardiac action potential results from rapid sodium influx (I Na⁰), whereas repolarization (phases 2 and 3) is driven by potassium efflux via the slow (I Kr) and delayed rectifier current (I Kr), components of the delayed rectifier current (Figure 2A). LQT1 and LQT2 result from mutations within α subunits of I Na⁰ and I Kr, respectively, that reduce net potassium current and delay repolarization. Importantly, heterozygous loss of function mutations do not reproduce the LQTS 1 and 2 phenotypes, suggesting more complex effects at the genomic, RNA, or protein level. LQT3 results from gain of function in I Na⁰, leading to persistent late, slow sodium influx (Figure 2B). Arrhythmia in LQT is thought to result from variable ion channel function and transmural dispersion of repolarization (TDR) across the ventricular myocardium, initiating an increase in calcium influx, sodium-calcium exchange current, and calcium overload. This triggers further fluxes in transmembrane gradient manifest as early afterdepolarizations (EADs) during phase 2/3, initiating torsades de pointes (TdP), the hallmark arrhythmia of LQTS. Subendocardial focal triggers generate scrolls of rotating excitation which bifurcate and terminate as a result of functional conduction block, explaining both the classical ECG appearance and high propensity for TdP to spontaneously terminate (Figure 1B).
Early analysis of families with LQTS assumed a penetrance of close to 100%, until genotyping identified a number of asymptomatic family members considered unaffected on clinical evaluation who nevertheless harbored familial mutations, with an average penetrance (ie, the ratio of clinically affected to the total number of mutation carriers) of 25%. The highly variable penetrance of LQTS within families is now established, necessitating detailed and sequential clinical and genetic analysis.

Figure 1. Electrocardiographic traces from leads II and V5 (A–F) and lead II (B) in patients with long QT syndrome. A, ECG traces from the initial patient described showing low-amplitude, notched T-waves characteristic of LQT2. B, Alternating T-wave axis and morphology (T-wave alternans) leading to an episode of torsades de pointes (TdP) triggered by a ventricular ectopic beat. C, Traces from a previously asymptomatic individual who suffered significant QT prolongation (QTc 570 ms) and ventricular fibrillation following a head injury and intracranial hemorrhage. D, On recovery his QT interval normalized (QTc 440 ms), but (E) showed marked prolongation 2 minutes into recovery on exercise testing (QTc 550 ms). Genetic analysis identified deletion of 10 amino acid residues in KCNQ1. F, Severe QT prolongation (QTc 740 ms) in a 9-year-old child presenting with nocturnal seizures. Despite propranolol therapy he continued to have short runs of TdP and underwent primary prevention ICD implantation. A functionally deleterious missense mutation previously associated with severe phenotype was identified in SCN5A (c.G1231A; p.V411M).

Genotype–Phenotype Correlation

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genetic screening to identify affected family members (cascade screening). This highly variable penetrance and the paroxysmal nature of the arrhythmias are likely a result of multiple other inherited and acquired factors, most of which have yet to be identified, but which include autonomic innervation, hormonal influences, environmental factors, and even behavioral components. Some of the variation in penetrance may in part be explained by common genetic variants identified in genome-wide association studies. The presence of 2 variants in the NOS1AP gene in 205 South African patients with the same founder LQT mutation (KCNQ1: A431V) has been associated with significantly longer QT intervals and a greater probability of symptoms.4

Clinical Manifestations
LQTS may present at any time from fetal life onward. However, many individuals will be asymptomatic life-long. The natural history of 647 untreated patients aged >28 years found 13% suffered a cardiac arrest or sudden death before the age of 40.3 Clinical events may be precipitated by specific triggers, in a broadly but not exclusively type-specific manner, such as exercise and specifically swimming in LQT1, emotion and auditory stimulation especially on waking in LQT2, and rest in LQT 3. As seizure activity attributable to cerebral anoxia during ventricular arrhythmias is relatively common, LQTS continues to be misdiagnosed as epilepsy,5 although there may be discrete forms of LQTS associated with independent neurological phenotypes with specific seizure disorders. Symptomatic QT prolongation may be acquired secondary to severe electrolyte disturbance, medications, cerebral trauma, and myocardial disease. Differentiation between true secondary QT prolongation and unmasking of otherwise quiescent congenital LQTS have important implications for the individual and family (Figure 1C).

Figure 2. Cardiac action potentials displayed with corresponding QRS-T wave complex on surface ECG (ECG). A, In the normal situation sodium influx ($I_{Na}$) initiates cellular depolarization during phase 0 (blue arrows) and potassium efflux via $I_{Kr}$ and $I_{Ks}$ determines repolarization in phases 2 and 3 (red arrows). B, In long QT syndrome persistent sodium channel influx or reduced potassium efflux leads to prolongation of both action potential duration and QT interval. C, QT prolonging agents further inhibit $I_{Na}$ function leading to greater degrees of QT prolongation and often unmask otherwise quiescent LQTS.

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The risk of cardiac events relates to many interconnected factors which facilitate risk stratification:

- **QT interval** - Longer QT intervals represent enhanced electric instability within the myocardium and hence greater arrhythmic risk. Patients who carry disease-causing mutations yet have normal QT intervals have a significantly lower risk compared to those with QT prolongation (4% versus 15% by the age of 40), yet their event rate remains 10-fold that of unaffected family members.

- **Age** - Symptomatic infants represent an extreme end of the disease spectrum, typically with severe QT prolongation, and a significantly higher cumulative event rate in later life. Ion channel mutations with proven functional effect have been associated with >10% of sudden infant death cases, with SCN5A mutations significantly overrepresented (>50%) compared with familial LQTS. Although traditionally associated with younger patients, there is a continued risk of cardiac events in those over 40 years of age.

- **Sex** - Males are typically at higher risk during childhood and females from teenage life onward. The QTc shortens by ≈20 ms in males but not females postpuberty, most likely because of the enhancing effects of testosterone and detrimental effects of estrogen on \( I_{Na} \) current. The inhibitory effect of estrogen is thought contributory to the increased event rate seen in females with LQT2 postpuberty, postpartum, and postmenopause.

- **LQT genotype** - LQT1 is associated with a shorter QT interval (466±44 ms), lower cumulative cardiac event rate (30%), and lower incidence of cardiac arrest or sudden death (0.3%/yr) by 40 years of age compared with either LQT2 (490±49 ms; 46% and 0.6%/yr) or LQT3 (496±49 ms; 42% and 0.56%/yr). A more complex genotype typically confers greater QT prolongation and higher risk of cardiac events, as seen in the autosomal recessive Jervell-Lange Nielsen syndrome and potentially those with compound heterozygosity/digenic inheritance.

- **Time-dependent syncope** - recurrent syncope, particularly in the recent past, is associated with a significantly increased risk of subsequent cardiac arrest independent from other risk factors.

It remains difficult to develop truly robust risk prediction algorithms as a result of the high rate of new mutations in the most penetrant families. Most of the current risk predictors are not clearly corrected for other familial contributions. For example, family history itself has a complex relationship to risk, as the most severe phenotypes are unlikely to have a positive family history. The large families that populate many of the extant clinical studies may be difficult to assess without extensive genetic and clinical characterization of unaffected family members. In practice, risk assessment remains highly dependent on careful evaluation of each family by an expert clinician with genetic insight.

**Investigations**

### Clinical Evaluation

The corrected QT interval on 12-lead ECG forms the basis of investigation, although miscalculation is common leading either to overdiagnosis and inappropriate treatment or a missed diagnosis in an at-risk individual. The 99th percentile for QTc in adult males is 470 ms and in adult females 480 ms, with significant overlap between the normal spectrum and genetically affected individuals with no or only mild QT prolongation. Other supportive ECG features with greater specificity but more subjectivity are T-wave morphological abnormalities and T-wave alternans (Figure 1). Concealed LQTS may be unmasked by either standing, exercise testing, or epinephrine challenge, which may lead to QT prolongation and T-wave morphological abnormalities in a type-specific manner. As with the resting 12-lead, ECG parameters during provocation testing show overlap between LQT patients and the normal population. Repolarization abnormalities are seen in many other forms of inherited heart disease. Therefore, it is important to undertake echocardiography to exclude underlying structural heart disease. Ultimately, the clinical features are best understood in the context of the extended family.

### Genetic Evaluation

Comprehensive genetic testing is an important component of the family evaluation, although careful counseling regarding the potential diagnostic, prognostic, and psychological impact of the test, future issues regarding insurance, and the genetic information nondiscrimination act (GINA) should be conducted before testing. The presence of many genetic variants of unknown significance ensures that ascribing true pathogenicity remains challenging. Segregation of genetic variants with phenotype across kindreds remains perhaps the most powerful predictor, facilitated by detailed familial evaluation within a single cardiovascular genetic center. De novo variants in isolated cases, variants located in highly conserved pore regions absent in large population-based reference sequences, and truncating, indels, or splice variants with concordant disease mechanism all suggest pathogenicity. In vitro demonstration of disease-specific protein dysfunction may provide supportive evidence of variant pathogenicity, although detailed functional analysis cannot be performed for every identified mutation. Importantly, in vitro findings do not always translate to the complex in vivo physiological environment.

Successful identification of disease-causing mutations has important implications for both proband and relatives and is a cost-effective mechanism for familial management. Mutation-specific cascade testing of family members is a highly sensitive and specific mechanism (with rigorously defined pathogenic mutations) to...
identify genetically affected individuals, especially in those with ambiguous clinical findings or nonpenetrant disease.16

**Treatment**

**Anti-Adrenergic Therapy (β-Blockers and Cardiac Sympathectomy)**

Beta-blockers are firmly established as first line therapy in LQTS, particularly nadolol and propranolol.18 This beneficial effect is most pronounced in long QT 1, although it has recently been demonstrated in long QT 3.16 Recurrent symptoms in long QT1 patients appropriately treated are almost exclusively attributable to non-compliance or to the concomitant use of QT prolonging agents.20

 Interruption of the upper thoracic sympathetic chain by left cardiac sympathetic denervation (LCSD) to reduce adrenergic stimulation of the heart has been used in LQTS, either as a mechanism to reduce arrhythmia burden in highly symptomatic individuals receiving repeated ICD therapies as an alternative strategy when β-blockers are contraindicated,18 or for high risk infants with severe QT prolongation. Alternatively, LCSD may be an intermediate step between medical therapy and defibrillator implantation in select patients.

**Implantable Cardioverter-Defibrillators (ICD)**

Given the potential for sudden cardiac death, ICDs are frequently used in the management of LQTS, although the majority of patients will be adequately protected by medical therapy. Based on the findings of a recent European ICD registry,21 the following indications were proposed for ICD implantation: (1) cardiac arrest on therapy, (2) cardiac arrest off therapy (although for LQT1 patients β-blockade may be sufficient),20 (3) syncope on β-blockade where LCSD is unavailable or declined by the patient, (4) compound heterozygous/homozygous patients with syncope on β-blockade, (5) primary prevention in exceptional cases of extreme QT prolongation with other high risk features.

**Lifestyle Modification**

Although LQTS management should be highly individualized, a uniform rule is avoidance of all QT prolonging medications, a comprehensive list of which can be found at www.azcert.org. Pharmacological inhibition of $I_{Ks}$ (Figure 2C) can produce significant QT prolongation and increased risk of life-threatening arrhythmia.20

Disqualification from competitive sports and activities has been the recommendation for the majority of patients. The 36th Bethesda Conference recommends restriction to class 1A activities for all symptomatic individuals irrespective of QTc or genotype, asymptomatic males with QTc >470 ms and females >480 ms, and those with ICDs. Genetically positive patients with normal QT intervals may participate in competitive sports, with the exception of LQT1 patients and competitive swimming. Restriction of an individual from recreational or competitive activities is always a challenging decision, representing a balance between the risk of exertional sudden death and the medical, social, and psychological benefits of sport and exercise. The recent finding of only 2 events in 650 athlete-years follow-up in 60 appropriately counselled and treated LQTS patients (12±7 years; QTc 501±46 ms) is of interest. Both events occurred in the same boy with LQT1 who admitted β-blocker non-compliance on each occasion. This finding may prompt revision of current recommendations regarding inclusion in competitive sports. It also demonstrates the importance of patient/familial autonomy and self-determination on the background of detailed clinical assessment and counseling.22

**Future Developments**

Since the seminal finding that genetically-encoded ion channel variants are associated with LQTS, progress has been made in defining the molecular substrate and improving clinical management. Major challenges remain in accurate and individualized risk stratification and understanding the different mutation-specific, epigenetic, and environmental influences on ion channel gene expression. In vitro modeling of LQTS using induced pluripotent stem cells allows creation of patient-derived cardiomyocytes that recapitulate the LQT phenotype with regard to alterations in transmembrane ion current, prolonged action potential duration, after depolarizations, and arrhythmia. The ability to recreate patient-specific disease models has promise for future studies on the molecular and genetic substrate of LQTS and response to different pharmacological agents.

**Case Presentation: Outcome**

The history, QT interval, and T-wave morphology strongly supported the diagnosis of LQT2. She is currently asymptomatic on nadolol, titrated to a maximal tolerated dose of 120 mg daily. After genetic counseling, she underwent genetic testing. A missense mutation was identified in KCNH2 (c.C1682T; p.A561V), leading to a substitution of the amino acid alanine to valine at codon 561. Alanine at this position is highly conserved across species and on functional analysis, this mutation has detrimental effects on channel function. Cascade screening revealed the patient’s daughter and sister both carried the variant.

**Disclosures**

Dr MacRae holds patents for modeling drug-induced repolarization disorders in the zebrafish. Dr Abrams reports no conflicts.

**References**


Long QT Syndrome
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