

Advances in congenital long QT syndrome

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Purpose of review

Dramatic advances have been made in understanding of both the genetics and the phenotypic expression of congenital long QT syndrome. This paper reviews recent clinically relevant literature.

Recent findings

Long QT syndrome is one of the leading causes of sudden cardiac death. This syndrome, once diagnosed by a clinical profile, has been more clearly defined by specific gene defects causing ion channel abnormalities in the beating heart. Genetic testing for long QT syndrome, once available only through research laboratories, is now commercially available. Diagnosis, risk assessment, and management are increasingly being guided by gene-specific diagnoses. In a family with suspected disease, the genetic test will determine the defect in as many as 75% of subjects. Once the diagnosis is made, the mainstay of therapy continues to be β -blockers. Implantable cardioverter-defibrillators are indicated in patients at high risk for malignant arrhythmias.

Summary

Long QT syndrome is one of the first cardiovascular diseases to see the dramatic changes that bench research can bring to the clinical arena. Future research is needed to determine the gene defect in the remaining 25% of patients with suspected long QT syndrome and in risk stratification.

Keywords

genetics, ion channel, long QT, sudden death

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Abbreviations

ICD	implantable cardioverter-defibrillator
LQTS	long QT syndrome
QTc	corrected QT interval
SIDS	sudden infant death syndrome

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Introduction

Congenital long QT syndrome (LQTS) is estimated to affect one in 5000 persons and is one of the primary causes of sudden cardiac death in the young. LQTS is characterized by prolonged ventricular repolarization (QT interval prolongation) and a propensity for syncope and sudden death secondary to torsades de pointes. Deaths in children with LQTS are heartbreaking, as most of the children seem otherwise healthy and involved in ordinary childhood activities. Since the early 1990s, when it was discovered that cardiac channel mutations resulted in the pathogenic mechanisms for LQTS [1–4], there have been impressive advancements in bringing the genetic basis of LQTS into clinical practice. Within the past several years, genetic testing for LQTS has become available as a commercial diagnostic test [5], making LQTS one of the first genetic cardiovascular diseases that have been translated from the research bench to the clinical bedside. This new availability of genetic testing is changing the face of clinical practice for LQTS in both diagnosis and management, particularly in families in which an index case has been identified.

Genetics of long QT syndrome

Historically, there have been two primary clinical designations of LQTS: Romano-Ward syndrome and the Jervell and Lange-Nielsen syndrome. Two other syndromes, Andersen-Tawil syndrome and Timothy syndrome, are often designated as being in the LQTS family of diseases, although these syndromes have very different clinical manifestations. The primary problem is a defect in a gene(s) encoding a critical ion channel(s) within cardiac muscle cells. The first chromosomal location for a gene defect was established in 1995 [3,4]. Since these initial publications, more than 400 mutations among five cardiac channel genes have been shown to account for a majority of patients with clinical LQTS [1,6,7^{**},8,9,10^{*}], as summarized in Table 1.

Romano-Ward syndrome, with an apparent autosomal dominant pattern of inheritance, is the most common among patients with LQTS. Patients in this group are otherwise healthy except for the cardiac manifestation of propensity toward sudden arrhythmic death secondary to torsades de pointes. Five primary cardiac channel genes have been identified within families with this syndrome: *LQT1* (*KCNQ1*-encoded potassium channel mutations), *LQT2* (*KCNH2*-encoded potassium channel mutations),

Table 1 Molecular basis of congenital long QT syndrome

Type	Locus	Gene	Mode of inheritance	Current	Frequency (%)
Romano-Ward syndrome					
LQT1	11p15.5	<i>KCNQ1/KVLQT1</i>	AD	I _{Ks}	30–35
LQT2	7q35–36	<i>KCNH2/HERG</i>	AD	I _{Kr}	30–35
LQT3	3p21–p24	<i>SCN5A</i>	AD	I _{Na}	5–10
LQT4	4q25–q27	<i>ANKB</i>	AD	Na/Ca	<1
LQT5	21q22.1	<i>KCNE1/mink</i>	AD	I _{Ks}	<1
LQT6	21q22.1	<i>KCNE2/MIRP1</i>	AD	I _{Ks}	<1
Jervell and Lange-Nielsen syndrome					
JLN1	11p15.5	<i>KCNQ1/KVLQT1</i>	AR	I _{Ks}	80
JLN2	21q22.1	<i>KCNE1/mink</i>	AR	I _{Ks}	20
Andersen-Tawil syndrome					
ATS1	17q23	<i>KCNJ2</i>	AD	IK1	50
Timothy syndrome					
TS1	1q42–q43	<i>CACNA1C</i>	Sporadic	I _{CaL}	?

AD, autosomal dominant; AR, autosomal recessive. Reproduced with permission from [7**].

LQT3 (*SCN5A*-encoded sodium channel mutations), and *LQT5* and *LQT6* (*KCNE1*-encoded or *KCNE2*-encoded potassium channel β -subunit mutations). In addition, *LQT4* has been defined as mutations in the *ANKB*-encoded ankyrin B, the first noncardiac channel gene to be identified in LQTS [1,6,7**,8,9,10*].

The Jervell and Lange-Nielsen syndrome has the clinical feature of congenital deafness in addition to the prolonged QTc (corrected QT interval). It displays an apparent autosomal recessive pattern of inheritance and reported cases depend on homozygous or compound heterozygous mutations in one of two genes, *KCNQ1* and *KCNE1*. *KCNQ1* is also the gene responsible for *LQT1* disease, the most common form of the Romano-Ward syndrome above. *KCNE1* is associated with *LQT5*. A recent multicenter study [11**] has focused on the genetic and clinical aspects of this rare form of LQTS and has shown that this form of LQTS is a severe variant with early onset, major QT prolongation, in which β -blockers have limited efficacy.

Andersen-Tawil syndrome is sometimes designated as *LQT7*, although some authors have argued that it should be simply designated as a separate entity, AT-1. The syndrome is associated with multiorgan system involvement in which the electrocardiographic findings are only a part of the overall syndrome. Rather than a long QTc measurement, patients with this syndrome have a normal QTc, but an abnormal QU measurement. These electrocardiographic findings are predictive of the *KCNJ2* defects [12*].

Timothy syndrome is associated with syndactyly and a long QT measurement and is sometimes designated as *LQT8*. This syndrome is associated with mutations in the *CACNA1C*-encoded L-type calcium channel α -subunit [7**].

Commercially available genetic testing

In May 2004, the first commercial genetic test to detect cardiac channel mutations was announced [5,13**]. The diagnostic test provides comprehensive mutational analysis of five cardiac channel genes implicated in LQTS. Genetic testing for Andersen-Tawil syndrome or Timothy syndrome is available only through research laboratories. The available diagnostic test can determine the molecular basis of LQTS in up to 75% of families with a suspected channelopathy [5,13**,14**]. The remaining 25% of families with a strong clinical probability of LQTS will have a negative genetic test result. Thus, the testing will be most useful in families in which a gene defect can be identified in the index cases and then subsequent family members can be evaluated to confirm or exclude that specific defect. In families in which a gene defect is not identified, a negative test result cannot fully exclude the diagnosis of LQTS. Tester *et al.* [14**] recently showed that the yield of genetic testing correlated significantly with the QTc and the clinical diagnostic score, ranging from 0% when QTc was less than 400 ms to 62% when QTc was greater than 480 ms. Among those with the highest clinical probability, the yield was 72%.

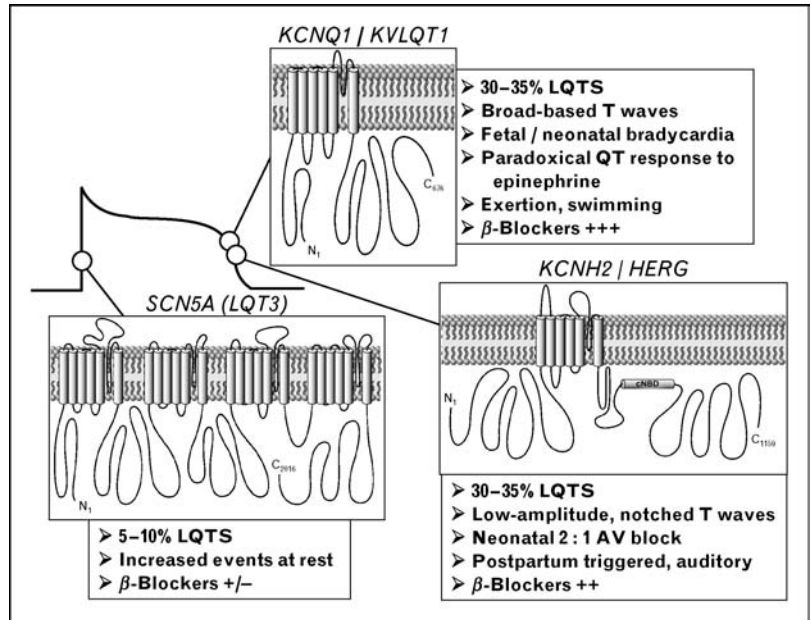
One of the concerns in genetic testing is the overall cost of screening multiple family members, as an extensive amount of DNA must be analyzed. A recent cost-effectiveness analysis of genetic testing [15*] versus no testing, given multiple assumptions about the population and relevant probabilities and costs, showed favorably for testing. The benefit of testing is to more accurately diagnose and treat individuals based on a combination of clinical information and genetic test results.

Genotype and arrhythmia triggers

Strong genotype–phenotype correlations have been identified in patients with clinical LQTS with respect to arrhythmogenic triggers [16] and other clinical manifestations (Figs 1 and 2). Patients with *LQT1* have

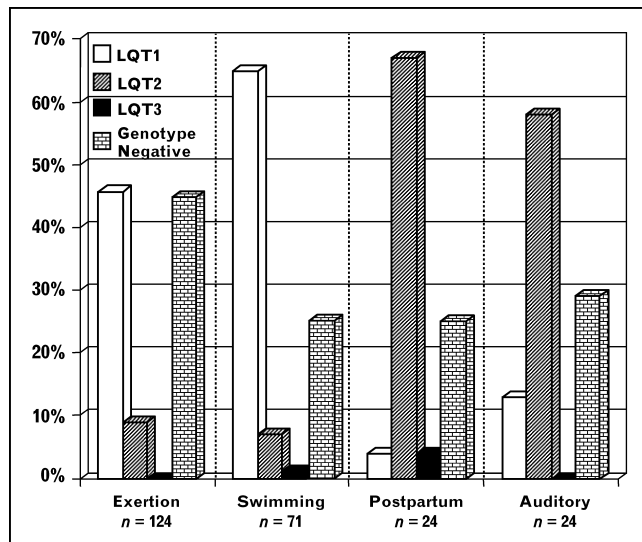
Figure 1 Genotype–phenotype relationships seen in long QT syndrome (LQTS)

The three principal cardiac channels that account for nearly 75% of LQTS cases are superimposed on the cardiac action potential of a ventricular cardiac muscle cell. The inset next to each channel topology summarizes some of the classic clinical findings for the primary LQTS genotypes (*LQT1*, *LQT2*, and *LQT3*). AV, atrioventricular. Reproduced with permission from [7**].



syncopal or sudden death events with exertional activities (e.g. while swimming or other athletic activity); patients with *LQT2* have events in the setting of auditory stimuli (e.g. hearing an alarm clock, telephone, bells); and

Figure 2 Arrhythmogenic triggers and long QT syndrome (LQTS) genotype



The graph summarizes the spectrum and frequency of genotype-positive and genotype-negative status associated with particular arrhythmogenic triggers in a group of 541 consecutive, unrelated patients who were referred for LQTS genetic testing. *LQT1* genotype is indicated as open rectangles, *LQT2* as diagonal-filled rectangles, *LQT3* in black-filled rectangles, and genotype-negative in brick-filled rectangles. None of the patients in this cohort had cardiac events while asleep. Reproduced with permission from [10*].

patients with *LQT3* have syncope, or aborted sudden death during sleep. In addition, fetal bradycardia strongly suggests *LQT1* and neonatal 2:1 atrioventricular block has been shown to be associated with *LQT2* [17]. Postpartum events of torsades de pointes were more often identified in patients with *LQT2* [18]. The initial clinical correlations for arrhythmogenic triggers were made in genotyped families. More recent literature in unrelated patients [10*] has shown that the associations of clinical arrhythmogenic triggers and LQTS genotype persist but that there is much overlap among the LQTS genotypes (Fig. 2). For example, events while swimming (drowning or near-drowning) continue to be strongly correlated with LQTS and specifically *LQT1*. Forty-four percent of patients referred for LQTS genetic testing secondary to exertional syncope, however, did not have a *LQT1–6* gene defect identified. Similarly, in patients with auditory triggers, the most commonly identified genotype was *LQT2* (58%), but almost 30% of the time no LQTS genotype was identified [7**,10*].

Genotype and T-wave morphology

Specific genotype–phenotype correlations have been made with respect to the electrocardiographic appearance of T-wave morphology [19–21]. Patients with *LQT1* are generally found to have broad-based T waves; patients with *LQT2* have low-amplitude T waves/G2 notched T waves; and patients with *LQT3* have normal-appearing T waves after a prolonged isoelectric ST segment [7**]. Caution is advised when interpreting these electrocardiographic findings, as T waves on serial electrocardiograms in a single patient may vary considerably. As an example,

an *LQT1* electrocardiogram may mimic the *LQT3*-like electrocardiogram pattern and may lead to more aggressive therapies because, as noted below, *LQT1* disease is more responsive to β -blocker therapy while *LQT3* disease is not [7**].

Provocative testing for borderline long QT syndrome

Experts estimate that 25% of patients with LQTS may have an electrocardiogram showing equivocal or borderline prolonged QT interval [22,23]. Among these patients with 'concealed' LQTS, the largest percentage of genotype-positive individuals will be patients with *LQT1* [7**]. In this group of patients, provocative testing with epinephrine, either as a bolus infusion [24] or as a graded infusion [25], has been shown to unmask LQTS (primarily *LQT1*) by the finding of a paradoxical lengthening of the absolute QT interval seen during administration of low-dose epinephrine [24,25*]. In addition, Khositseth *et al.* [26*] compared the effect of epinephrine on T-wave morphology in patients with *LQT1* and *LQT2* and in control subjects. Epinephrine-induced changes in T-wave morphology are nonspecific, especially with high-dose infusion. Low-dose epinephrine may unmask some patients with concealed *LQT2* disease by noting G2 notched T waves. In these three studies, the epinephrine stress test was only rarely noted to induce nonsustained ventricular arrhythmias.

Exercise testing has also been proposed as a way to identify patients with concealed LQTS [27–29]. The hypothesis is that the QT response to a burst exercise protocol would increase endogenous catecholamines, would better simulate clinical events, and perhaps would distinguish patients with LQTS from control subjects. The findings from these studies show that a marked increase of the QTc measurement from baseline to peak exercise and at 1 minute into recovery was potentially diagnostic for LQTS, particularly *LQT1*. The sensitivity was reported as 85% with a specificity of 86% [29].

The above studies on epinephrine and exercise testing were conducted on a largely adult population and thus caution should be used when extrapolating the data to infants and children. The epinephrine challenge test or the exercise test can be used as additional diagnostic tests in a patient with a suspicious history but with a normal or borderline prolonged QT on baseline electrocardiogram. These tests are probably best utilized while awaiting the more definitive results of genetic testing.

Risk stratification

Whereas there have been great strides in the genetics of LQTS, challenges remain in understanding the variability in disease expression. The Jervell and Lange-Nielson syndrome is clearly more severe than Romano-Ward

syndrome [11**]. Within Romano-Ward, risk stratification is more complex. Priori *et al.* [30] conducted a study of 647 patients genotyped as *LQT1*, *LQT2*, or *LQT3* in order to provide risk stratification according to genotype and other clinical variables. Within their patient cohort, 13% had a cardiac arrest or sudden death before the age of 40 years and before the start of therapy. Patients with *LQT2* and *LQT3* were more likely to have cardiac arrest or sudden death before age 40 years in comparison with patients with *LQT1*. The QTc measurement was an independent predictor of risk among patients with *LQT1* and *LQT2*, but not *LQT3*. There were no gender-related differences when the entire cohort was evaluated together. When differentiated, however, gender did not have an influence among patients with *LQT1*, whereas female patients with *LQT2* had a higher risk than male patients, and for *LQT3* the effect was opposite, with male patients having a higher risk. The authors proposed a schema for risk stratification among patients with LQTS based on genetic defect, QTc measurement, and sex. The risk categories were high ($\geq 50\%$), intermediate (30–49%), and low ($< 30\%$). In order for this schema to be more useful in clinical decision making, the low-risk category should have a much lower associated risk.

Work is being conducted to risk stratify patients within the primary LQT groupings (*LQT1–3*) based on the genetic defect. For example, in a recent report, Brink *et al.* [31] showed that the *KCNQ1-A341V* mutation is associated with an unusually severe phenotype, most likely caused by the dominant negative effect of the mutations in a founder population in South Africa. Also proposed are the concepts of compound mutations or the presence of modifier genes that could potentially explain clinical severity [32*]. Westenskow *et al.* [33] showed that compound mutations could potentially be an explanation for clinical severity. Crotti *et al.* [34*] showed that *KCNH2-K897T* mutations are a genetic modifier of latent LQTS.

In addition to evaluating clinical risk based on LQTS genotype, two studies have suggested prognostic value based on the location of a particular mutation. Moss *et al.* [35] reported that patients with mutations involving the pore of the *KCNH2*-encoded potassium channel (*LQT2*) did more poorly than patients with mutations in the C-terminus. Similarly, Shimizu *et al.* [36] more recently showed that patients with mutations in the *KCNQ1*-encoded potassium channel (*LQT1*) were more likely to have LQTS-related cardiac events and were more sensitive to sympathetic stimulation than were those with C-terminal mutations. Because of the great variability among patients with LQTS, however, this malignant domain concept is unlikely to have significant clinical relevance.

Long QT syndrome and sudden infant death syndrome

Sudden infant death syndrome (SIDS) continues to be the leading cause of death within the first year of life. There are several pathophysiologic mechanisms proposed, including disorders of fatty acid oxidation pathways [37], deficits in serotonergic pathways in the brainstem [38,39], and the contribution of prone sleep position [40]. Ventricular dysrhythmia from LQTS has been implicated in SIDS over the past 30 years [41–45]. In a recent review, it was estimated that 5–10% of SIDS cases are due principally to defective cardiac ion channels [46^{••}]. The observations are complex and a full discussion of the role of LQTS in SIDS is beyond the scope of this review. Further study is needed in this area as there are significant clinical implications, such as the recommendation to screen or not to screen all infants for LQTS with baseline electrocardiograms [46^{••},47].

Current treatments

In general, there are three accepted therapies for all patients with LQTS: β -blockers, restriction from competitive athletics, and placement of an internal cardioverter-defibrillator. In addition, all family members should be evaluated and screened for LQTS. In the past, all patients with LQTS were treated in a similar manner. With the current availability of genetic testing, gene-specific tailored decision making is possible.

β -Blockers remain the mainstay of therapy for LQTS. They have been shown to be extremely effective in *LQT1* disease and moderately effective in patients with *LQT2* but they may not offer reliable protection in patients with *LQT3* [48–50]. In addition, in-vitro studies suggest that β -blockers could potentially be proarrhythmic in *LQT3* disease [51]. For the most part, propranolol or nadolol are the β -blockers of choice, although other β -blockers, such as atenolol, have been used [52].

Implantable cardioverter-defibrillator (ICD) therapy is becoming more commonplace for both secondary (after a cardiac arrest or aborted sudden death) and primary (prophylaxis in a high-risk individual) treatment. Due to specific device-related issues such as lead fracture or vein occlusion, a patient's age, weight, and future growth must be taken into account when deciding to place an ICD. A cardiac arrest or aborted sudden death while a patient is on therapy is a clear indication for implantation of an ICD. A presentation of a syncopal event prior to diagnosis and thus prior to β -blockers could result in medical treatment and further clinical monitoring, without the placement of an ICD (secondary to the information that patients with *LQT1* are susceptible to β -blocker therapy). Patients with *LQT3* are problematic as they are not responsive to β -blockers, yet placing ICDs in

asymptomatic young children has potential for increasing device-related complications. Simple pacing may provide some benefit [53].

Exercise restriction is generally recommended for all patients with LQTS. Patients with *LQT3* do not fit the same profile as those with *LQT1* and *LQT2*, as those with *LQT3* primarily have their cardiac events occur during sleep and not during strenuous activity. The American Heart Association [54] has published guidelines for physical activity and recreational sports in young patients with genetic cardiovascular diseases.

Conclusion

Over the past several years, there have been significant advances in the diagnosis and treatment of LQTS, specifically in translating genetic evaluation from the research laboratories to the clinic. With the advent of a commercially available test for LQTS, gene-specific diagnoses, clinical profiles, risk stratification, and treatments have been developed. The available genetic test can determine the genetic defect in 75% of families with suspected LQTS. Future research is needed to further define the genetic defect in the remaining 25% of families.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 576–577).

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