M.J. Ackerman, M.D., PhD.

GENETICS OF LONG QT SYNDROME

David J. Tester, B.S.; Michael J. Ackerman, M.D., Ph.D.
Mayo Clinic, Rochester, Minnesota

Abstract

Long QT syndrome (LQTS) is a potentially life-threatening cardiac arrhythmia characterized by delayed myocardial repolarization that produces QT prolongation and increased risk for torsades des pointes (TdP)-triggered syncope, seizures, and sudden cardiac death (SCD) in an otherwise healthy young individual with a structurally normal heart. Currently, there are three major LQTS genes (*KCNQ1, KCNH2*, and *SCN5A*) that account for approximately 75% of the disorder. For the major LQTS genotypes, genotype-phenotype correlations have yielded gene-specific arrhythmogenic triggers, electrocardiogram (ECG) patterns, response to therapies, and intragenic and increasingly mutation-specific risk stratification. The 10 minor LQTS-susceptibility genes collectively account for less than 5% of LQTS cases. In addition, three atypical LQTS or multisystem syndromic disorders that have been associated with QT prolongation have been described, including ankyrin-B syndrome, Anderson-Tawil syndrome (ATS), and Timothy syndrome (TS). Genetic testing for LQTS is recommended in patients with either a strong clinical index of suspicion or persistent QT prolongation despite their asymptomatic state. However, genetic test results must be interpreted carefully.

Introduction

With an estimated incidence as high as 1 in 2,000 persons, congenital LQTS is characterized by delayed repolarization of the ventricular myocardium, QT prolongation (QTc > 480 ms as the 50th percentile among LQTS cohorts), and increased risk for torsades des pointes (TdP)-mediated syncope, seizures, and sudden cardiac death (SCD) in an otherwise healthy young individual with a structurally normal heart.[1] While LQTS is rarely inherited recessively and characterized by a severe cardiac phenotype and sensorineural hearing loss,[2] it is typically inherited as an autosomal-dominant trait.[3] Sporadic de novo germline mutations may account for nearly 5% to 10% of LQTS. At the molecular level, LQTS comprises a collection of several distinct cardiac channelopathies. To date, there are three major LQTS genes and 10 minor LQTS-susceptibility genes that account for nearly 80% of the disorder (Table 1). In addition, three atypical LQTS or multisystem syndromic disorders associated with either QT or QTU prolongation have been described, namely ankyrin B syndrome (formerly LQT4), Andersen-Tawil syndrome (ATS, formerly LQT7), and Timothy syndrome (TS, formerly LQT8).

The Major LQTS Genotypes

The Big Three: KCNQ1, KCNH2, and SCN5A

Approximately 75% of patients with a clinically certain LQTS diagnosis have mutations in one of three major LQTS-susceptibility genes that encode for ion channel α subunits and are critically responsible for the orchestration of the cardiac action potential: *KCNQ1*-encoded I_{Ks} ($K_v7.1$) potassium channel, *KCNH2*-encoded I_{Kr} ($K_v11.1$) potassium channel, or *SCN5A*-encoded I_{Na} ($Na_v1.5$) sodium channel.[4-6] Loss-of-function mutations in *KCNQ1* cause about 35% of LQTS type 1 (LQT1), while loss-of-function *KCNH2* mutations contribute approximately 30% of LQTS (LQT2). Gain-of-function *SCN5A* mutations underlie roughly 10% of LQTS (LQT3). About 5% to 10% of LQTS patients host multiple mutations in these genes and typically present at a younger age with a more severe phenotype.[4] The vast majority of mutations are single nucleotide substitutions or small insertion/deletions.[4-6] However, a few large gene rearrangements resulting in single or multiple whole exon deletions/duplications have been described.[7-9]

Relatively gene-specific triggers, ECG patterns, and therapeutic responses have emerged.[10, 11] For example, while swimming and exertion-induced cardiac events are strongly associated with LQT1, auditory triggers and events occurring during the postpartum period usually occur in patients with LQT2, and events occurring during periods of sleep/rest are most common in LQT3. While exceptions to relatively gene-specific T-wave patterns exist, LQT1 is associated with a broad-based T wave and electrocardiographic features, LQT2 with a low-amplitude notched or biphasic T wave, and LQT3 with a long isoelectric segment followed by a narrow-based T wave. Beta blockers are extremely protective in LQT1 patients but are only moderately protective in LQT2 and LQT3.[12, 13] Female LQT2 patients may not be as fully protected with beta blockers as male LQT2 patients. Given the electrophysiological consequence of an LQT3-causing *SCN5A* mutation, late sodium current blockers including mexiletine, flecainide, or ranolazine may represent gene-specific therapeutic options for LQT3.[14, 15] However, the response to sodium channel blockers is mutation-specific, and while there has been clear evidence of the benefit of mexiletine in some LQT3 patients, others have shown no benefit.[11]

GENE	LOCUS	PROTEIN
Long QT Syndrome		
Major LQTS Genes		
KCNQ1 (LQT1)	11p15.5	I_{Ks} potassium channel α subunit (K_vLQT1, K_v7.1)
KCNH2 (LQT2)	7q35-36	I_{Kr} potassium channel α subunit (HERG, K_v11.1)
SCN5A (LQT3)	3p21-p24	Cardiac sodium channel α subunit (Na_v1.5)
Minor LQTS Genes (listed alphabetically)		
AKAP9	7q21-q22	Yotiao
CACNA1C	12p13.3	Voltage gated L-type calcium channel (Ca_v1.2)
CALM1	14q32.11	Calmodulin
CALM2	2p21	Calmodulin
CAV3	3p25	Caveolin-3
KCNE1	21q22.1	K_v7.1 potassium channel beta subunit (MinK)
KCNE2	21q22.1	K_v11.1 potassium channel beta subunit (MiRP1)
KCNJ5	11q24.3	Potassium inwardly-rectifying channel (Kir3.4)
SCN4B	11q23.3	Sodium channel beta 4 subunit
SNTA1	20q11.2	Syntrophin-alpha 1
Ankyrin-B Syndrome		
ANK2	4q25-q27	Ankyrin B
Andersen-Tawil Syndrome		
KCNJ2 (ATS1)	17q23	I_{K1} potassium channel (Kir2.1)
Timothy Syndrome		
CACNA1C	12p13.3	Voltage gated L-type calcium channel (CaV1.2)

Table 1. Summary of long QT syndrome-susceptibility genes.

In general, when the QTc is > 500 ms, LQT2 females and LQT3 males are at higher risk for a cardiac event.[11] In addition, intragenic risk stratification has been realized for LQT1 and LQT2 based upon mutation type, location, and cellular function.[16-21] LQT1 patients with transmembrane-spanning, domain-localizing *KCNQ1* missense mutations and patients with mutations resulting in a greater degree of K_v7.1 loss-of-function (dominant-negative) are at greater risk of an LQT1-triggered cardiac event compared to LQT1 patients with C-terminal region mutations or those with mutations that cause less damage to the biology of the K_v7.1 channel (haploinsufficency), respectively. LQT2 patients with pore region *KCNH2* mutations have a longer QTc, a more severe clinical manifestation of the disorder, and more arrhythmia-related cardiac events occurring at a younger age than those LQT2 patients with non-pore mutations in *KCNH2*.[22] In addition, Shimizu et al. found that LQT2 patients with transmembrane pore region mutations had the greatest risk for cardiac events, those with frame-shift/nonsense mutations in any channel region had an intermediate risk, and those with C-terminus missense mutations had the lowest risk for cardiac events.[21]

The Minor LQTS Genotypes

The 10 minor LQTS-susceptibility genes encode for additional ion channel α subunits (*CACNA1C*, *KCNJ5*), key cardiac potassium-(*AKAP9, KCNE1, KCNE2*) and sodium-channel (*CAV3, SCN4B SNTA1*) interacting proteins, or calcium-binding messenger proteins (*CALM1, CALM2*). Because these additional genes play a minor role in the genetic basis of LQTS, only limited genotype-phenotype correlations have been generated.

CACNA1C–LQTS

In 2012, Boczek and colleagues used a pedigree-based whole exome sequencing and systems biology strategy to identify a novel pathogenic mutation (P857R) within the *CACNA1C*-encoded cardiac L-type calcium channel (LTCC) α subunit that cosegregated with disease in a phenotype-positive/genotype-negative multigenerational nonsyndromic LQTS pedigree.[23] The LTCC is important for excitation-contraction coupling in the heart and mediates an inward depolarizing current in cardiomyocytes. Functional characterization of the mutation using a whole-cell patch-clamp technique in HEK293 cells revealed a gain-of-function with increased $I_{Ca,L}$ and increased cell surface expression of the mutant ion channel compared to wild type. This electrophysiological in vitro phenotype is consistent with the clinical phenotype of QT interval prolongation. Importantly, although *CACNA1C* perturbations had been implicated previously in Timothy Syndrome (TS) and incorrectly given the genotype place holder as LQT8, this was the first demonstration that

CACNA1C was a bona fide LQTS-susceptibility gene, extending the breadth of distinct CACNA1C-related arrhythmogenic phenotypes.

Subsequently, mutational analysis of 103 unrelated LQTS genotype-negative/phenotype-positive patients identified three additional *CACNA1C* missense mutations, suggesting that *CACNA1C* mutations may explain as much as 4% to 5% of genetically elusive LQTS[23] or approximately 1% of LQTS altogether. Interestingly, three of the four mutations (K834D, P857L, and P857R) localized to the same critical PEST-domain in the II-III linker of the LTCC, an amino acid sequence motif that represents an important signal for rapid protein degradation and LTCC channel stability. A fourth mutation (R1906C) localizes near the stromal interaction molecule 1 (STIM1) binding domain in LTCC's C-terminus. STIM1 interacts with the LTCC, resulting in a decrease of LTCC-mediated current, and chronically triggers LTCC internalization. Disruption of this STIM1/LTCC interaction could conceivably result in an increase of cell surface expression of the LTCC, thus leading to an overall increase of $I_{Ca,L}$ and subsequently an increase in cardiac action potential duration and a prolonged QT on ECG.

KCNJ5–LQTS

Yang and colleagues performed a genome-wide linkage and positional candidate gene analysis in a large multigenerational Chinese LQTS pedigree and identified a heterozygote G387R mutation in the *KCNJ5*-encoded G protein-coupled, inwardly rectifying potassium channel subunit Kir3.4.[24] In vitro heterologous expression studies revealed a loss-of-function electrophysiological phenotype associated with reduced plasma membrane expression. All mutation-positive family members experienced recurrent palpitations, 10 of 12 with recurrent syncope, and 5 with either persistent or permanent atrial fibrillation (AF) or atrial tachycardia (AT). While the majority of the mutation-positive individuals were symptomatic, only three had a QTc > 480 ms, all with concomitant AF or AT. *KCNJ5*-mediated LQTS appears to be very uncommon as none of our 500-plus unrelated LQTS probands have been *KCNJ5* positive (data not shown).

Channel Interacting Protein-Mediated LQTS

Importantly, ion channels do not operate in isolation but instead function as macromolecular complexes consisting of the ion channel pore-containing α subunits as well as auxiliary β subunits and other regulatory proteins that interact with and influence ion channel activation and deactivation/inactivation. The *KCNE1*- and *KCNE2*-encoded β subunits minK and MiRP1 were the first auxiliary proteins to be implicated in the pathogenesis of LQTS through their modulatory effect on the $K_v7.1$ (*KCNQ1*, I_{Ks}) and $K_v11.1$ (*KCNH2*, I_{Kr}) potassium channels, respectively.[25, 26] The *AKAP9*-encoded yotiao is an A-kinase-anchoring protein that is critically important to the PKA-dependent phosphorylation state of $K_v7.1$. In 2007, a single mutation identified in a clinically definite unrelated genotype-negative LQTS patient reduced the interaction between $K_v7.1$ and yotiao, eliminated the functional response of the I_{Ks} channel to cAMP, and resulted in action potential prolongation in a computational model of the ventricular cardiomyocte.[27]

Similarly, the cardiac sodium channel ($Na_v1.5$) encoded by *SCN5A* also forms macromolecular complexes with auxiliary proteins. The *SCN4B*-encoded β4 subunit was implicated in LQTS with the identification of an L179F mutation in a 21-month-old female with intermittent 2:1 atrioventricular block and extreme QT prolongation (QTc, 712 ms).[28] Coexpression of the L179F-SCN4B mutation with wild-type SCN5A led to a significant increase in persistent late sodium current consistent with an LQT3-like electrophysiological phenotype. However, subsequent mutation analysis of *SCN4B* in a cohort of 262 unrelated genotype-negative LQTS patients failed to identify any additional mutations.

The cardiac sodium channel localizes to omega-shaped membrane microdomains called caveolae. Caveolin-3 encoded by *CAV3* is a major scaffolding protein present in caveolae of the heart that may play a role in compartmentalization and regulation of resident ion channels in the caveolae. In 2006, two spontaneous de novo mutations were identified among 905 unrelated LQTS patients referred for genetic testing, thereby demonstrating a pathogenic link between CAV3 mutations and LQTS.[29] Both CAV3 mutations resulted in a significant LQT3-like increase in persistent late sodium current.

Finally, α1-syntrophin (SNTA1) acts as a molecular scaffold between neuronal nitric oxide synthase (nNOS) and the nNOS inhibitor plasma membrane Ca-ATPase subtype 4b (PMCA4b) and interacts with SCN5A to bring the nNOS-PMCA4b complex into close proximity to the cardiac sodium channel.[30] Additionally, an A390V-SNTA1 mutation identified in a clinically definite, unrelated, genotype-negative LQTS patient disrupted SNTA1 binding with PMCA4b, released inhibition of nNOS, caused S-nitrosylation of SCN5A, and was associated with increased late sodium current.[30] In a later study, the identical A257G-SNTA1 mutation was identified in 3 of 39 unrelated genotype-negative LQTS cases and also exhibited an in vitro LQT3-like SCN5A gain of function.[30, 31]

Calmodulin-Mediated LQTS

In 2013, a whole exome sequencing-based strategy elucidated the underlying genetic cause for two unrelated sporadic cases of infantile LQTS with recurrent cardiac arrest and extreme QT prolongation.[32] Both infants hosted sporadic de novo mutations (D130G-CALM1 and D96V-CALM2) in genes (*CALM1* and *CALM2*) that encode for calmodulin, a ubiquitously expressed and essential calcium-signaling protein that is critically involved in a multitude of physiological functions—including as a Ca^{2+} sensor for Ca^{2+}-dependent inactivation of the LTCC ($C_{av}1.2$), inactivation of the cardiac sodium channel ($N_{av}1.5$), and activation of the voltage-gated potassium channel ($K_v7.1$). The calmodulin genes represent an interesting and rare phenomenon in human biology. There are three distinct calmodulin genes with distinct loci (*CALM1*, Chr.14q32.11; *CALM2*, Chr.2p21; and *CALM3*, Chr.19q13.2-q13.3); while they share 76% homology at the DNA nucleotide level, these three genes encode for an identical protein (Calmodulin) of 149 amino acids. All three genes are expressed in cardiac myocytes, with transcript expression levels highest for *CALM3* followed by *CALM2* and *CALM1*.[32]

In a subsequent cohort analysis involving 82 unrelated LQTS cases that remained genetically elusive following analysis of the major LQTS genes, calmodulin mutations were identified in two additional cases.[32] These missense mutations localize to critical EF-hand calcium-binding motifs and reduce calmodulin's calcium-binding affinity by seven-fold. All four calmodulin-positive cases exhibited the common cardiac features of life-threatening ventricular arrhythmias occurring very early in life (three of four during infancy), including frequent T-wave alternans (all cases), markedly prolonged QT intervals (QTc > 600 ms, all cases), and intermittent 2:1 AV block (3 of 4 patients). Ventricular fibrillation was often triggered by adrenergic activation occurring either spontaneously or preceded by a short episode of torsade de pointes

that was not pulse dependent. Additionally, all patients had some degree of neurodevelopmental delay ranging from mild delay in language development to severe cognitive or motor development. Seizures were observed in three cases.

Multisystem Disorders Associated with Either Prolonged QT or QTU Intervals

Ankyrin-B Syndrome (formerly LQT4)

Originally labeled type 4 LQTS (LQT4), this disorder has been renamed more correctly as sick sinus syndrome with bradycardia, or the "ankyrin-B syndrome."[33] The *ANK2* gene encodes ankyrin-B protein, which is involved in anchoring the Na/K-ATPase, Na/Ca exchanger, and InsP3 receptor to specialized microdomains in the cardiomyocyte transverse tubules.[33] Since the discovery of the first human *ANK2* mutation identified in a large, multigenerational French pedigree presenting with "atypical LQTS,"[33] several loss-of-function ankyrin-B mutations have been identified in patients with various arrhythmia phenotypes, including bradycardia, sinus node dysfunction, delayed cardiac conduction/conduction block, idiopathic ventricular fibrillation, AF, drug-induced LQTS, and exercise-induced ventricular tachycardia.

Andersen-Tawil Syndrome (formerly LQT7)

Andersen-Tawil syndrome (ATS) is a rare multisystem disorder characterized by a triad of clinical features including periodic paralysis, dysmorphic features, and ventricular arrhythmias.[34] ATS1 was initially coined type 7 LQTS (LQT7) due to the reported observation of extreme prolongation of the QT interval; however, these measurements erroneously included the prominent U-wave.[35, 36] ATS may manifest with pronounced QTU prolongation, prominent U-waves, and ventricular ectopy, including polymorphic ventricular tachycardia (VT), bigeminy, and bidirectional VT.

Mutations in *KCNJ2*-encoded Kir2.1, a small potassium channel α subunit that is responsible for the inward rectifying cardiac I_{K1} current that plays an important role in setting the heart's resting membrane potential, accounts for two-thirds of ATS. Most ATS1-associated *KCNJ2* mutations are missense mutations that cause a loss of function of I_{K1}.[35] The molecular basis of the remaining third of ATS cases remains genetically and mechanistically elusive.

Timothy Syndrome (formerly LQT8)

Timothy syndrome (TS) is an extremely rare, multisystem, highly lethal arrhythmia disorder associated with extreme QT prolongation, dysmorphic facial features, congenital heart disease, immune deficiency, developmental delay, and often syndactyly.[37] Most TS children have potentially fatal arrhythmias including 2:1 atrioventricular block, torsade de pointes, and ventricular fibrillation.

Remarkably, the same recurrent sporadic de novo missense *CACNA1C* mutation, G406R, in the alternatively spliced exon 8A has been identified in nearly all unrelated TS cases.[37] In addition, two cases of atypical TS have been described with sporadic de novo *CACNA1C* mutations not in exon 8A but in exon 8. One case hosted a G406R mutation in exon 8 that was analogous to the classic TS mutation identified in exon 8a. The other case hosted a G402R missense mutation.[38] These three CACNA1C missense mutations that confer gain-of-function to the LTCC through impaired channel inactivation account for all TS cases analyzed to date.[37, 38]

Genetic Testing in Long QT Syndrome

From a clinical test standpoint, any patient with a strong clinical index of suspicion for a LQTS diagnosis or an asymptomatic patient with an unequivocal prolonged QTc (> 480 ms during pre-puberty, > 500 ms during adulthood) in the absence of other clinical conditions should be offered clinical LQTS genetic testing.[39] However, genetic tests must be understood as probabilistic rather than unconditionally deterministic, and the genetic test results must be interpreted cautiously and incorporated into the overall diagnostic evaluation for these disorders.[3, 39]

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Keywords: long QT syndrome; ion channel; genetics

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