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Long QT Syndrome Overview

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Summary

The purpose of this overview is to increase the awareness of clinicians regarding genetic causes of long QT syndrome (LQTS), inform (when possible) medical management of LQTS based on genetic cause, and inform risk assessment and surveillance of at-risk relatives for early detection and treatment of LQTS.

The following are the goals of this overview.

Goal 1

Briefly describe the clinical characteristics of LQTS.

Goal 2

Review the genetic causes of LQTS.

Goal 3

Review the differential diagnosis of LQTS with a focus on genetic conditions.

Goal 4

Provide an evaluation strategy to identify the genetic cause of LQTS in a proband (when possible).

Goal 5

Review management of LQTS including targeted pharmacologic treatment.

Goal 6

Inform risk assessment and evaluation of at-risk relatives for early detection and treatment of LQTS.

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1. Clinical Characteristics of Long QT Syndrome

Long QT syndrome (LQTS) is characterized by QT prolongation and T wave abnormalities on EKG. LQTS predisposes individuals to a significant risk of life-threatening arrhythmic events, especially in young individuals. Molecular genetic testing identifies a genetic cause in ~80% of affected individuals, most often in genes associated with autosomal dominant LQTS. Subsequent cascade genetic testing allows for identification of at-risk relatives who can benefit from tailored therapeutic management strategies to reduce morbidity and mortality.

The initial scoring system for a clinical diagnosis of LQTS was updated by Schwartz & Crotti [2011] and mainly relied on EKG findings, of which a prolonged corrected QT interval was the most prominent. This scoring system did not account for genetic test results. Nevertheless, the detection of a pathogenic variant proven to cause LQTS is also sufficient to establish a diagnosis of LQTS [Priori et al 2013]. This idea is incorporated in the LQTS diagnostic scoring system proposed in the European Society of Cardiology guidelines for management of LQTS [Zeppenfeld et al 2022] (see Table 1). A LQTS risk score of >3.0 in the absence of a secondary cause for QT prolongation is sufficient for a diagnosis of LQTS.

Table 1. Long QT Syndrome: Scoring System for Clinical Diagnosis

Findings			Points
EKG [1]	QTc [2]	≥480 ms	3.5
		460-479 ms	2
		450-459 ms (in males)	1
		≥480 ms during 4th minute of recovery from exercise stress test	1
	Torsade de pointes [3]		2
	T wave alternans		1
	Notched T wave in 3 leads		1
	Low heart rate for age [4]		0.5
Clinical history	Syncope [3]	With stress	2
		Without stress	1
	Congenital deafness		0.5
Family history	Family member(s) with clinical or molecular diagnosis of LQTS [5]		1
	Unexplained sudden cardiac death at age <30 years in immediate family [5]		0.5
Genetic finding	Pathogenic variant in a gene known to cause LQTS		3.5
Total points: ≤1.0 = low probability of LQTS; 1.5-3.0 = intermediate probability of LQTS; >3.0 = clinical diagnosis of LQTS			

Adapted from Schwartz & Crotti [2011] with modification in Zeppenfeld et al [2022]
LQTS = long QT syndrome; QTc = corrected QT
1. In the absence of medications or disorders known to affect these electrocardiographic features
2. QTc is calculated by the Bazett formula, where QTc = QT/√RR.
3. Mutually exclusive
4. Resting heart rate <2nd centile for age
5. The same family member cannot be used for both criteria.

Cardiac Features

T wave abnormalities include T wave alternans, notched T wave, broad-based and flattened T waves (see Adler et al [2020] and Wilde et al [2022] for concise examples and Tardo et al [2023] for a comprehensive review) and are associated with tachyarrhythmias, typically the ventricular tachycardia torsade de pointes (TdP). TdP is

usually self-terminating and may cause palpitations, dizziness, or syncope, the most common symptom in individuals with LQTS. Syncope is typically precipitous and without warning. A careful evaluation of medical history can help distinguish LQTS-associated syncope from common vasovagal and orthostatic forms of syncope in which presyncope and other warning symptoms occur. Absence of aura, incontinence, and postictal findings help differentiate LQTS-associated syncope from seizures. The number of syncopal events in symptomatic individuals ranges from one to hundreds, averaging just a few. In some instances, TdP degenerates to ventricular fibrillation and aborted cardiac arrest (if the individual is defibrillated) or sudden death.

Cardiac events (i.e., syncope, cardiac arrest, or sudden cardiac death) may occur from infancy through middle age but are most common from the preteen years through the 20s, with the risk generally diminishing throughout that time period. The usual age range of events differs somewhat for each genotype. Cardiac events are uncommon after age 40 years; when present, they are often triggered by administration of a QT-prolonging drug or hypokalemia. Cardiac events in individuals over age 40 years are more likely associated with *SCN5A*-related LQTS.

Pathogenic variants in *KCNH2*, *KCNQ1*, and *SCN5A* account for 90% of individuals with an identified molecular cause of LQTS. Three clinical phenotypes are recognized in individuals with pathogenic variants in these genes (see Table 2).

Table 2. Long QT Syndrome: Phenotype Correlations by Gene

Gene	Average QTc [1]	ST & T Wave Morphology [2]	All Cardiac Events [3]	Syncope [4]	Aborted Cardiac Arrest [5]	SCD	Cardiac Event Trigger [6]
KCNH2	480 ms	Bifid (notched) T waves, low-voltage T wave alternans (biphasic)	49%	36%	6%	5%	Auditory stimuli, emotion, exercise, sleep
KCNQ1		Broad-based T wave	44%	37%	4%	3%	Exercise, emotion
SCN5A	474 ms	Long ST; high-amplitude & narrow T wave	41%	23%	8%	9%	Sleep

SCD = sudden cardiac death

1. Average values from 807, 879, and 237 individuals with *KCNH2*-, *KCNQ1*-, and *SCN5A*-related LQTS, respectively [Kutyifa et al 2018].

2. Tardo et al [2023]

3. Cumulative probability of a cardiac event (syncope, aborted cardiac arrest, or sudden death) at age 50 years in a cohort of individuals with *KCNH2*-, *KCNQ1*-, and *SCN5A*-realted LQTS, including 14%-20% of probands and their relatives [Kutyifa et al 2018].

4. Percentage of individuals with one or more syncopal events [Kutyifa et al 2018]

5. Percentage of individuals with one or more aborted cardiac arrest(s) [Kutyifa et al 2018]

6. Schwartz et al [2001]

Although incidence of syncopal events is highest in those with *KCNQ1*-related LQTS and lowest in *SCN5A*-related LQTS, the incidence of sudden cardiac arrest or death was highest in individuals with *SCN5A*-related LQTS in a cohort of individuals with an identified genetic cause from the LQTS Registry receiving treatment (see Table 2). Of individuals who die of complications of LQTS, death is the first sign of the disorder in an estimated 10%-15%.

The risk of sudden cardiac death is dependent on history of syncope, proband status (i.e., being the first in the family in whom the genetic cause for LQTS has been identified), QTc interval, treatment, age, and gender. The age and sex dependency differs between the three main molecular causes of LQTS. Overall, boys are at relatively

high risk before onset of adolescence, and girls after the onset of adolescence (age 13 to 14 years) [Wang et al 2022].

- ***KCNH2*-related LQTS.** Increased mortality occurred especially in women older than age 12 to 13 years, particularly up to nine months postpartum [Kutyifa et al 2018, Skinner et al 2019]. The risk for males aged one to 13 years can also be high [Wang et al 2022]. A common trigger is sudden arousal (e.g., auditory stimuli).
- ***KCNQ1*-related LQTS.** Severely increased mortality was observed for boys age five to 15 years [Kutyifa et al 2018, Skinner et al 2019], although the risk for girls age 13 to 20 years can also be high [Wang et al 2022]. Most sudden cardiac deaths occur during exercise (e.g., swimming) and emotion [Wilde et al 2022].
- ***SCN5A*-related LQTS.** Increased mortality is observed from childhood (especially in boys) throughout adulthood (both genders) [Wang et al 2022]. In contrast to *KCNQ1*- and *KCNH2*-related LQTS, QT prolongation in *SCN5A*-related LQTS is more pronounced during slow heart rate and events usually occur during sleep or rest.

Table 3. Cumulative Probability of Cardiac Events by Age

Gene	% of Persons with ≥1 Cardiac Event [1] by Age [2]				
	Age 10 years	Age 20 years	Age 30 years	Age 40 years	Age 50 years
KCNH2	9%	29%	42%	46%	49%
KCNQ1	15%	32%	38%	42%	44%
SCN5A	7%	23%	29%	37%	41%

1. Cardiac events include syncope, aborted cardiac arrest, and sudden cardiac death.
2. Studies from the LQTS Registry including individuals with clinical manifestations, 14%-20% probands and family members with a pathogenic variant (most individuals were on treatment; 52%-60% with beta-blockers) [Kutyifa et al 2018]

LQTS exhibits incomplete penetrance for EKG changes and symptoms. Approximately 25% of individuals with an identified molecular cause of LQTS have a normal QTc (<440 ms) on baseline EKG. The percentage of individuals with a normal QTc was higher in those with *KCNQ1*-related LQTS (36%) than in those with *KCNH2*-related LQTS (19%) or *SCN5A*-related LQTS (10%) [Priori et al 2003, Goldenberg et al 2011]. With appropriate treatment, at least 56% of individuals with *KCNQ1*-related LQTS, 51% of those with *KCNH2*-related LQTS, and 59% of those with *SCN5A*-related LQTS remain asymptomatic (assessed at age 50 years) [Kutyifa et al 2018].

Non-Cardiac Features

Some types of LQTS are associated with a phenotype extending beyond cardiac arrhythmia.

- Andersen-Tawil syndrome, caused by a heterozygous pathogenic variant in *KCNJ2*, is associated with prolonged QT interval, episodic muscle paralysis, muscle weakness, facial dysmorphism, dental anomalies, and small hands and feet.
- Jervell and Lange-Nielsen syndrome, caused by biallelic *KCNQ1* or *KCNE1* pathogenic variants, is associated with congenital profound sensorineural hearing loss and QTc usually >500 ms.
- Timothy syndrome, caused by a heterozygous pathogenic variant in *CACNA1C*, is a multisystem disorder where QTc prolongation causes a high risk of arrhythmic events in neonates. Extracardiac features include hand/foot syndactyly, neurodevelopmental features including autism spectrum disorder and intellectual disability, and characteristic facial appearance.

Biallelic Pathogenic Variants / Digenic Inheritance

LQTS associated with biallelic pathogenic variants (in genes associated with autosomal dominant LQTS) or heterozygosity for pathogenic variants in two different genes (i.e., digenic pathogenic variants) is generally associated with a more severe phenotype with longer QTc interval and a higher incidence of cardiac events [Schwartz et al 2003, Westenskow et al 2004, Tester et al 2005, Itoh et al 2010, Mullally et al 2013].

Nomenclature

The designation "acquired long QT syndrome" may be used to distinguish QT interval prolongation associated with non-heritable causes and conditions from heritable predisposition to QTc prolongation. Of note, gene-environment interactions occur, and drug exposures and conditions associated with acquired LQTS may also be cardiac event triggers in individuals with a genetic predisposition to QT prolongation.

Prevalence

The prevalence of LQTS has been estimated at 1:2,500 [Schwartz et al 2009, Giudicessi & Ackerman 2013, Lieve & Wilde 2015].

2. Genetic Causes of Long QT Syndrome

Using the ClinGen Gene Curation Framework, the Clinical Genome Resource Long QT Syndrome Gene Curation Expert Panel has categorized reported long QT syndrome (LQTS)-related genes into definitive, strong, moderate, and limited clinical validity classification levels for LQTS, acquired LQTS, and LQTS-associated phenotypes (see Table 4) [Adler et al 2020].

Table 4. Long QT Syndrome: Genetic Causes

Gene [1]	% of LQTS Attributed to Pathogenic Variants in Gene [2]	Gene Validity Classification [3]	LQTS Phenotype(s)	Comment	OMIM Phenotype
KCNQ1	30%-35%	Definitive	LQTS w/broad-based T waves [4] w/ or w/o atrial fibrillation	Note: Biallelic variants in *KCNQ1* cause Jervell and Lange-Nielsen syndrome	192500
KCNH2	25%-30%	Definitive	LQTS w/bifid T waves [4]		613688
SCN5A (GoF variants)	5%-10%	Definitive	LQTS w/long horizontal ST segment [4]		603830
CACNA1C (GoF variants)	<1%	Definitive	LQTS	Some persons have additional features consistent w/Timothy syndrome.	601005
CALM1	<1%	Definitive	LQTS or LQTS-CPVT overlap [5]		616247
CALM2	<1%	Definitive			616249
CALM3	<1%	Definitive			618782

Table 4. continued from previous page.

Gene [1]	% of LQTS Attributed to Pathogenic Variants in Gene [2]	Gene Validity Classification [3]	LQTS Phenotype(s)	Comment	OMIM Phenotype
CAV3	<1%	Definitive	LQTS	Caveolinopathy is assoc w/a broad spectrum of phenotypes. [6]	123320 192600 606072 611818 614321
KCNJ2	<1%	Definitive	LQTS	Some persons have additional features consistent w/Andersen-Tawil syndrome.	170390
TRDN	<1%	Definitive [7]	CPVT-LQTS overlap syndrome [8]		615441
KCNE1 [9]	<1%	Strong	Susceptibility to acquired LQTS [6]	Note: Biallelic variants in *KCNE1* cause Jervell and Lange-Nielsen syndrome	613695
		Limited	LQTS		
KCNE2	<1%	Strong	Susceptibility to acquired LQTS [3]		613693

Based on Adler et al [2020] and ClinGen
CPVT = catecholaminergic polymorphic ventricular tachycardia; GoF = gain-of-function; LQTS = long QT syndrome
1. Genes are organized first by frequency of causation of LQTS, then strength of ClinGen classification, and then alphabetically.
2. Up to 25% of individuals with LQTS do not have a detectable pathogenic variant in one of the genes in table 4 [Ingles & Semsarian 2020].
3. Gene validity classifications indicate the evidence level for association with the indicated phenotypes. Some genes have different classifications when associated with different phenotypes. Although *KCNE2* was reported to have disputed evidence of association with LQTS, it was included in Table 4 because its association with acquired LQTS was strong [Adler et al 2020].
4. Tardo et al [2023]
5. *CALM1*-, *CALM2*-, and *CALM3*-related LQTS is associated with an overlap with catecholaminergic polymorphic ventricular tachycardia (CPVT). The OMIM disease entries include both LQTS and CPVT. These phenotypes have been evaluated by ClinGen expert panels as definitive and moderate, respectively [Adler et al 2020, Walsh et al 2022].
6. During a ClinGen evaluation of gene-disease validity by an expert panel for muscular dystrophies and myopathies, the panel decided to lump all indicated OMIM disease entities as "caveolinopathy" because they found no significant difference in phenotype, inheritance pattern, or molecular mechanism. See *CAV3* ClinGen and He et al [2022].
7. See *TRDN* ClinGen.
8. Biallelic variants in *TRDN* cause a LQTS-CPVT overlap syndrome. It has been proposed that TRDN-related LQTS be referred to as triadin knockout syndrome because of its recognizable features [Altmann et al 2015].
9. There is limited evidence for LQTS caused by *KCNE1* variants in absence of additional QT-prolonging factors, but strong evidence for an association with acquired LQTS (i.e., provoked by non-heritable factors or in combination with pathogenic variants causing QT interval prolongation) [Adler et al 2020].

3. Differential Diagnosis of Long QT Syndrome

Other causes of QTc interval prolongation to be considered:

- Drug-induced QT prolongation (See drugs at CredibleMeds®; free registration required.)
- Hypokalemia
- Certain neurologic conditions including subarachnoid bleed
- Structural heart disease

Other causes of syncope or sudden death to be considered in children and young adults:

- Sudden infant death syndrome (SIDS), commonly defined as unexpected sudden death within the first year of life. Death during the first year of life in families with long QT syndrome (LQTS) appears to be rare, yet infants with SIDS have been shown to have pathogenic variants in one of the genes listed in Table 4 [Ackerman et al 2001, Schwartz et al 2001, Arnestad et al 2007]. While it seems probable that these pathogenic variants were the cause of the SIDS, the association is uncertain, and the frequency of pathogenic variants in infants with SIDS has been questioned [Wedekind et al 2006].
- Vasovagal (neurally mediated) syncope, orthostatic hypotension
- Seizures. Absence of aura, incontinence, and postictal findings help differentiate LQTS-associated syncope from seizures.
- Familial ventricular fibrillation
- Subtle cardiomyopathies (HCM, DCM, ARVC)
- Catecholaminergic polymorphic ventricular tachycardia
- Calcium release deficiency syndrome [Ormerod et al 2022]
- Brugada syndrome
- Anomalous coronary artery

4. Evaluation Strategies to Identify the Genetic Cause of Long QT Syndrome in a Proband

Establishing a specific genetic cause of long QT syndrome (LQTS):

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, family history, and genomic/genetic testing.

Clinical history. Clinical history in individuals with syncope or a cardiac arrest can reveal specific triggers for the cardiac event that can be gene specific. On rare occasions LQTS is accompanied by gene-specific extracardiac features.

Physical examination. The great majority of individuals with LQTS do not have associated physical features. On rare occasions, LQTS is accompanied by gene-specific extracardiac features. Individuals with EKG characteristics suggestive of a specific LQTS-associated syndrome (e.g., EKG with T-U patterns characteristic of Andersen-Tawil syndrome) can be assessed for physical features of that syndrome.

Family history. A three-generation family history should be taken, with attention to relatives with manifestations of LQTS – including syncope, aborted cardiac arrest, or sudden death in a child or (young) adult – and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing and EKG recordings. Specific focus should also be on triggers of events in relatives, as well as epilepsy (LQTS-associated syncopes may have been attributed to epilepsy). In such instances, review of medical records should include EEG recordings, accompanied by an EKG, which can show QTc prolongation in affected family members.

EKG evaluation. The corrected QT (QTc) values on resting EKG and ST-T wave morphology can suggest a specific genetic cause of LQTS (see Table 2). Additional tests can be helpful to unmask QTc prolongation in individuals with borderline QTc values on resting EKG [Priori et al 2013]:

- **Exercise EKG,** which commonly shows failure of the QTc to shorten normally and even prolongation of the QTc interval [Jervell & Lange-Nielsen 1957, Vincent et al 1991, Swan et al 1998, Horner et al 2011, Sy et al 2011]. Many individuals develop characteristic T wave abnormalities [Zhang et al 2000]. The U wave should not be included in the QT assessment [Bains et al 2023].

- **QTc interval measurement** during change from supine to standing position [Viskin et al 2010, Zeppenfeld et al 2022]
- **Intravenous pharmacologic provocation testing** (e.g., with epinephrine), which may demonstrate inappropriate prolongation of the QTc interval [Ackerman et al 2002]. However, it is not recommended to do this as routine diagnostic testing, as reproducibility is modest [Churet et al 2019, Zeppenfeld et al 2022]. With the small risk of induction of arrhythmia, such provocative testing is best performed in laboratories experienced in arrhythmia induction and control [Shimizu et al 2004, Vyas et al 2006].

Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing, genome sequencing). Single-gene testing is currently uncommon in LQTS and requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing with analysis of a multigene panel does not. For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **A LQTS multigene panel** that includes the genes listed in Table 4 is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype.

  Depending on the sequencing method used and copy number variant detection tools, exon or whole-gene deletions/duplications may not be detected. Exon or multiexon deletions or duplications in *KCNH2 or KCNQ1* have been identified in approximately 3% of individuals with LQTS [Barc et al 2011]. More rarely, a homozygous deletion of exon 2 in *TRDN* was described in an individual with QTc prolongation (490 ms), although this individual also had a variant of uncertain significance in *RYR2* that was inherited from an unaffected father [O'Callaghan et al 2018].

  Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

- **Single-gene testing.** Molecular genetic testing based on the individual's phenotype (T wave pattern and triggers of syncope), which has been shown to predict the genotype [Zhang et al 2000, Van Langen et al 2003] (see Table 2), can be performed if a multigene panel is not available or does not contain a specific gene of suspicion.

5. Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with long QT syndrome (LQTS), the main focus in the management of individuals with LQTS is to identify the subset of individuals at high risk for cardiac events. For this risk stratification the following evaluations are recommended if not performed as part of the evaluation that led to the diagnosis:

- **EKG evaluation.** Individuals with a QTc interval >500 ms are at higher risk for a cardiac event; individuals with QTc interval >600 ms are at extremely high risk [Priori et al 2003, Goldenberg et al 2008]. Overt T wave alternans, especially when present despite proper beta-blocker therapy, is also associated with a higher risk for cardiac events [Priori et al 2013]. Individuals with a pathogenic variant who have a normal QTc interval are at low risk [Priori et al 2013].

- **Medical history.** Individuals with syncope or cardiac arrest in the first year of life [Schwartz et al 2009, Spazzolini et al 2009] or younger than age seven years [Priori et al 2004] are at higher risk for an event. These individuals may not be fully protected by pharmacologic treatment. Individuals with arrhythmic events while on proper pharmacologic treatment are also at higher risk [Priori et al 2013]. Asymptomatic individuals with pathogenic variants or individuals with prolonged QT intervals who have been asymptomatic at a young age (age <40 years) are at low risk for events later in life, although females remain at risk after age 40 years [Locati et al 1998].
- To aid in risk stratification, an **online calculator** named 1-2-3-LQTS-Risk was validated for clinical use [Mazzanti et al 2022], predicting the risk of life-threatening cardiac events in five-year intervals. The prediction accounts for age, gender, QTc interval, history of syncope, and genotype (limited to the three most common genetic causes of LQTS). Further improvement of risk prediction using machine learning and functional imaging has been proposed [Marathe et al 2022].

Consultation with a clinical geneticist, certified genetic counselor, or certified advanced genetic nurse is recommended to inform affected individuals and their families about the nature, mode of inheritance, and implications of LQTS in order to facilitate medical and personal decision making.

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Asymptomatic Individuals

Beta-blockers are clinically indicated in all asymptomatic individuals, including those who have a pathogenic variant on molecular genetic testing with a normal QTc interval [Priori et al 2004, Schwartz et al 2009]. Males who have a pathogenic variant and who have been asymptomatic before age 40 years are at low risk for cardiac events. In these individuals the necessity of beta-blockers can be discussed [Locati et al 1998].

Implantable cardioverter-defibrillator (ICD). In general, an ICD is **not** indicated for asymptomatic individuals with LQTS who have not tried beta-blocker therapy. Prophylactic placement of an ICD can be considered for asymptomatic individuals suspected to be at very high risk, such as asymptomatic individuals with two or more pathogenic variants (in genes associated with autosomal dominant LQTS) on molecular genetic testing [Priori et al 2013]. LQTS-related sudden death in a close relative is not an indication for an ICD in an asymptomatic individual [Kaufman et al 2008].

Symptomatic Individuals

All symptomatic persons should be treated [Priori et al 2013]. Complete cessation of symptoms is the goal. Management is focused on the prevention of syncope, cardiac arrest, and sudden death.

Beta-blockers are the mainstay of therapy for LQTS, including asymptomatic individuals with prolonged QT intervals and individuals who have a pathogenic variant on molecular genetic testing with a normal QTc interval [Priori et al 2004, Schwartz et al 2009]. Some individuals have symptoms despite the use of beta-blockers [Moss et al 2000]. However, a majority of cardiac events that occur in individuals with *KCNQ1*-related LQTS reported to be treated with beta-blockers are not caused by failure of the medication but failure to take the medication (non-compliance) and/or the administration of QT-prolonging drugs [Vincent et al 2009]. It is therefore important to:

- Avoid inadequate beta-blocker dosing by regular adjustments in growing children, with evaluation of the efficacy of dose by assessment of the exercise EKG or ambulatory EKG;
- Administer beta-blockers daily, and have strategies in place in case of missed doses;
- Use long-acting agents (e.g., nadolol) to increase compliance and avoid use of short-acting metoprolol [Chockalingam et al 2012];
- Administer QT-prolonging drugs (see Agents/Circumstances to Avoid) to individuals with LQTS **ONLY** after careful consideration of risk versus benefit by the individual(s) and physician(s).

ICD is recommended in individuals with LQTS resuscitated from a cardiac arrest because of the high recurrence risk even when on beta-blocker therapy, although children with *KCNQ1*-related LQTS with an arrest while not receiving beta-blockers can be treated with beta-blockers or with left cardiac sympathetic denervation [Alexander et al 2004, Vincent et al 2009, Jons et al 2010]. An ICD can be useful for an individual with beta-blocker-resistant syncopes, ventricular arrhythmias, or a contraindication for beta-blocker therapy (e.g., severe asthma) [Zareba et al 2003, Priori et al 2013, Zeppenfeld et al 2022].

Left cardiac sympathetic denervation (LCSD) is recommended for high-risk individuals with LQTS in whom ICD therapy is refused or contraindicated and/or in whom beta-blockers are either not effective, not tolerated, not accepted, or contraindicated [Schwartz et al 2004, Priori et al 2013, Zeppenfeld et al 2022]. LCSD can be useful in individuals who experience events while on therapy with beta-blockers or ICD [Priori et al 2013].

Sodium channel blockers (e.g., mexiletine) can be useful as additional pharmacologic therapy for individuals with selected pathogenic variants in *SCN5A* and a QTc interval >500 ms in whom sodium channel blockers are shown to shorten the QTc interval by >40 ms [Priori et al 2013, Zeppenfeld et al 2022].

Note: Most affected individuals live normal lives. Education of affected adults and the parents of affected children, especially about beta-blocker compliance, is an important aspect of management.

Supportive Care

Assess for asthma, orthostatic hypotension, depression, and diabetes mellitus, because these disorders may be exacerbated by treatment with beta-blockers.

Electrolyte imbalances may lengthen the QTc interval; identification and correction of electrolyte abnormalities is important. These imbalances can occur as a result of diarrhea, vomiting, metabolic conditions, and unbalanced diets used for weight loss.

Although the incidence of arrhythmias during elective interventions such as surgery, endoscopies, childbirth, or dental work is low, it is prudent to monitor the EKG during such interventions and to alert the appropriate medical personnel in case intervention is needed.

Lifestyle modifications are advised based on genotype (see Agents/Circumstances to Avoid).

Surveillance

Beta-blocker dose should be regularly assessed for efficacy and adverse effects; doses should be altered as needed. Dose adjustment including efficacy testing is especially important in growing children.

Individuals with an ICD should have regular, periodic evaluations of the ICD for inappropriate shocks and pocket or lead complications.

Agents/Circumstances to Avoid

Drugs that cause further prolongation of the QT interval or provoke torsade de pointes should be avoided for all individuals with LQTS. See CredibleMeds® (free registration required) for a complete and updated list.

Epinephrine given as part of local anesthetics can trigger arrhythmias and is best avoided.

Lifestyle modifications are advised based on genotype:

- Individuals with *KCNQ1*-related LQTS should avoid strenuous exercise, especially swimming without supervision.
- Individuals with *KCNH2*-related LQTS should avoid exposure to loud noises such as alarm clocks and phone ringing.
- Individuals at high risk for cardiac events or with exercise-induced symptoms (as in *KCNH2*- and *KCNQ1*-related LQTS) should avoid competitive sports [Priori et al 2013]. For some individuals, participation in competitive sports may be safe. It is therefore recommended that all individuals with LQTS who wish to engage in competitive sports have their risk evaluated by a clinical expert [Johnson & Ackerman 2012, Priori et al 2013].

Pregnancy Management

The postpartum period is associated with increased risk for a cardiac event, especially in individuals with *KCNH2*-related LQTS. Beta-blocker treatment was associated with a reduction of events in the nine months after delivery [Seth et al 2007]. Recommendations for optimal care during and after pregnancy, including suitability of anti-arrhythmic drugs and surveillance measures, can be found in Roston et al [2020].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

A current study is evaluating the drug ranolazine in individuals with *SCN5A*-related LQTS [Cano et al 2020].

For individuals with *KCNH2*-related LQTS due to a protein trafficking defect, combined treatment with lumacraftor and ivacraftor is under investigation [Schwartz et al 2019].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

6. Genetic Risk Assessment and Evaluations of At-Risk Relatives for Early Detection and Treatment of Long QT Syndrome

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Genetic Risk Assessment

Long QT syndrome (LQTS) without extracardiac features is typically inherited in an autosomal dominant manner. Timothy syndrome (caused by a heterozygous pathogenic variant in *CACNA1C*) and Andersen-Tawil syndrome (caused by heterozygous pathogenic variant in *KCNJ2*), types of LQTS that are associated with a phenotype extending beyond cardiac arrhythmia, are also inherited in an autosomal dominant manner. Jervell and Lange-Nielsen syndrome, a severe form of autosomal recessive LQTS with a high event risk at early age and deafness, is caused by biallelic pathogenic variants in *KCNQ1* or *KCNE1*. Biallelic pathogenic variants in *TRDN* cause another very rare and severe form of autosomal recessive LQTS-catecholaminergic polymorphic ventricular tachycardia (CPVT) overlap syndrome (see Table 5).

Table 5. Long QT Syndrome: Mode of Inheritance

Gene [1]	LQTS Phenotype	Mode of Inheritance
CACNA1C	LQTS w/o extracardiac features (See CACNA1C-Related Disorders.)	AD
	Timothy syndrome (See CACNA1C-Related Disorders.)	
CALM1	LQTS w/o extracardiac features	
CALM2		
CALM3		
CAV3	LQTS w/ or w/o extracardiac features	
KCNE1	LQTS w/o extracardiac features	
	Susceptibility to acquired LQTS	
	Jervell and Lange-Nielsen syndrome	AR
KCNE2	Susceptibility to LQTS	AD
KCNH2	LQTS w/o extracardiac features	
KCNJ2	Andersen-Tawil syndrome	
KCNQ1	LQTS w/o extracardiac features	
	Jervell and Lange-Nielsen syndrome	AR
SCN5A (GoF variants)	LQTS w/o extracardiac features	AD
TRDN	CPVT-LQTS overlap syndrome	AR

AD = autosomal dominant; AR = autosomal recessive; CPVT = catecholaminergic polymorphic ventricular tachycardia; GoF = gain-of-function; LQTS = long QT syndrome
1. Genes are ordered alphabetically

LQTS associated with biallelic pathogenic variants (in genes associated with autosomal dominant LQTS) or heterozygosity for pathogenic variants in two different genes (i.e., digenic pathogenic variants) has also been reported (see Biallelic Pathogenic Variants / Digenic Inheritance).

Risk to Family Members (Autosomal Dominant Inheritance)

A basic view of autosomal dominant LQTS genetic risk assessment is presented in this section; issues that may be specific to a given family or genetic cause of LQTS are not comprehensively addressed. If a proband has a specific syndrome (e.g., Timothy syndrome or Andersen-Tawil syndrome), counseling for that condition is indicated. Genetic risk assessment in families with LQTS with extracardiac features is not discussed further in this section.

Parents of a proband

- The majority of individuals diagnosed with LQTS have inherited a pathogenic variant from a parent. Due to incomplete penetrance and variable expressivity, a parent who is heterozygous for an LQTS-related pathogenic variant may or may not have LQTS-related EKG changes and symptoms.
- A proband with LQTS may have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with LQTS caused by a *de novo* pathogenic variant is small.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status, inform recurrence risk assessment, and facilitate the use of morbidity- and mortality-reducing interventions for parents found to be heterozygous for an LQTS-related pathogenic variant.

- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism (the incidence of germline mosaicism is very low: 0.1% [Acuna-Hidalgo et al 2015]). Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.
- The family history of some individuals diagnosed with LQTS may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or reduced penetrance. Therefore, an apparently negative family history does not exclude the possibility of an inherited pathogenic variant and molecular genetic testing is indicated.

Note: Biallelic and digenic pathogenic variants have been described. If an individual with LQTS has biallelic or digenic pathogenic variants, the possibility that both parents have pathogenic variants should be considered.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is heterozygous for the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Because LQTS exhibits reduced penetrance, sibs who inherit a pathogenic variant may or may not have symptomatic LQTS. Considerable phenotypic variability within families has also been reported [Giudicessi et al 2018].
- If the proband has a known LQTS-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent; the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Priest et al 2016].
- If the parents do not have signs of LQTS on cardiac evaluation but their genetic status is unknown, the risk to sibs of inheriting an LQTS-related pathogenic variant is estimated to be 50% because a heterozygous parent may be clinically unaffected due to reduced penetrance of LQTS-related EKG changes and symptoms. The likelihood that the proband has LQTS as the result of a pathogenic variant inherited from a heterozygous asymptomatic parent is far greater than the likelihood that the proband has LQTS as the result of a *de novo* pathogenic variant.

Offspring of a proband. Each child of an individual with LQTS has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent is clinically affected and/or has a pathogenic variant, the parent's family members are at risk.

Evaluation of Relatives at Risk

Specific risk issues. With the reduced penetrance of symptoms in individuals with LQTS, careful EKG evaluation including exercise EKG is often necessary to identify affected family members accurately. The absence of a family history of sudden death is common and does not negate the diagnosis or preclude the possibility of sudden death in relatives.

Predictive genetic testing in family members of a proband with a molecular diagnosis of LQTS. If the LQTS-related pathogenic variant(s) has been identified in a proband, it is appropriate to clarify the genetic status of apparently asymptomatic relatives so that individuals found to be heterozygous for an LQTS-related pathogenic variant can benefit as early as possible from prompt initiation of targeted therapy, surveillance, and awareness of agents and circumstances to avoid (e.g., drugs that cause further prolongation of the QT interval and gene-specific cardiac event triggers). Predictive genetic testing is recommended for all at-risk family members of all ages from birth onward and especially for individuals age <18 years because the risk for cardiac events is greatest in childhood [Wilde et al 2022].

Predictive genetic testing can be used to identify relatives who are heterozygous for a familial LQTS-related pathogenic variant and at risk for LQTS-related manifestations but cannot be used to predict disease course (i.e., whether LQTS-related EKG changes and symptoms will occur and, if so, the age of onset and severity).

Evaluation of family members of a proband with a clinical diagnosis of LQTS. If the LQTS-related pathogenic variant in the proband is not known (as is the case in ≤25% of individuals with LQTS who undergo molecular genetic testing for known LQTS-related genes [Ingles & Semsarian 2020]) and the LQTS does not seem to be acquired, first-degree relatives should still be considered to be at risk. These relatives should undergo QTc analysis on resting EKG and, in those with normal QTc on resting EKG, QTc analysis on exercise EKG (the diagnostic accuracy by QTc analysis is considerably improved by evaluation of the exercise EKG in addition to the resting EKG, using the QTc measurements listed in Table 1). To date, there are no clear recommendations on when to repeat the EKG in individuals with normal findings.

Note: Because LQTS exhibits incomplete penetrance for EKG changes and symptoms, the absence of LQTS-related findings on EKG evaluation cannot be used to assess genetic status (i.e., an individual who is heterozygous for an LQTS-related pathogenic variant may have a normal QTc on baseline EKG).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Heart, Lung, and Blood Institute (NHLBI)**
  Long QT Syndrome
- **Canadian Sudden Arrhythmia Death Syndromes (SADS) Foundation**
  Canada
  Email: info@sads.ca
  sads.ca
- **Sudden Arrhythmia Death Syndromes (SADS) Foundation**
  Phone: 801-948-0654
  www.sads.org
- **International Long QT Syndrome Registry**
  Heart Research Follow-Up Program
  Phone: 585-276-0016
  Email: heartajm@heart.rochester.edu
  rarediseases.org/organizations/international-long-qt-syndrome-registry

Chapter Notes

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