



Long QT

Long QT Syndrome

A Guide for Clinicians



Introduction

Long QT syndrome (LQTS) is a genetic heart disorder due to the malfunction of cardiac ion channels that results in 4,000 deaths annually in the United States (Vincent, GM, 1998). LQTS has an estimated prevalence of at least one in 3,000 and occurs in all ethnicities (Lehnart SE et al., 2007). Affected individuals have delayed repolarization, manifested by QT prolongation on the electrocardiogram (ECG), with an increased propensity to syncope, ventricular tachyarrhythmias, and sudden cardiac death. Sudden death is the first and final symptom in 10–15 percent of fatal LQTS events. LQTS has genetic causes in at least 75 percent of individuals diagnosed with this condition, including mutations in 12 different genes. The disorder is usually inherited as an autosomal dominant trait, although a rare subtype with autosomal recessive inheritance (Jervell and Lange-Nielsen syndrome) has been reported.

Clinical Diagnosis

LQTS is diagnosed based on clinical history, ECG findings, and family history.

• Clinical History

The disorder typically manifests in patients younger than 40 years of age, and sometimes as early as in infancy. Patients often have a history of syncope in the absence of any other causes, such as medications, cardiomyopathies, myocardial ischemia, or electrolyte imbalances.

The circumstances under which syncope occurs (with exercise, with auditory stimulation, at rest) may further suggest a particular subtype of LQTS. In some patients, syncope may be mistakenly diagnosed as seizures. Patients may also experience presyncope or palpitations. In some patients, sudden cardiac death occurs without any preceding symptoms and without an identifiable cause at autopsy.

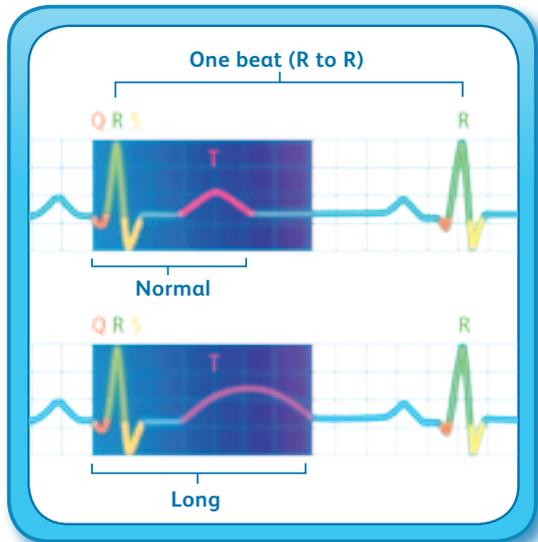


Figure 1: Illustration showing prolonged QT interval on an electrocardiogram (ECG)

TABLE 1: SUGGESTED BAZETT-CORRECTED QTc VALUES (in ms) FOR DIAGNOSING QT PROLONGATION

| RATING | 1–15 YRS | ADULT MALE | ADULT FEMALE |
|------------|----------|------------|--------------|
| Normal | < 440 | < 430 | < 450 |
| Borderline | 440–460 | 430–450 | 450–470 |
| Prolonged | > 460 | > 450 | > 470 |

Goldenberg I et al., J Cardiovasc Electrophysiol, 2006.

• Electrocardiogram

An accurate measurement of the QT interval is critical for diagnosing LQTS. The QT interval should be calculated as a mean value from three to five cardiac cycles, from the beginning of the QRS complex to the end of the T wave. The QT interval is usually corrected for heart rate using the Bazett formula QT/\sqrt{RR} . The longest QTc should be used in evaluating for the LQTS. Table 1 shows the normal values for the corrected QT (QTc) used to diagnose LQTS.

The diagnosis is unequivocal when the QTc interval is significantly prolonged, especially when coupled with a supporting clinical history.

• Family History

A detailed family history may identify other family members with syncope, a prolonged QT interval on ECG, or untimely sudden cardiac death, suggesting an inherited form of LQTS.

For the cases in which a clear clinical diagnosis of LQTS cannot be established, a clinical scoring system has been developed based on personal and family history, symptomatology, and ECG findings. Table 2 shows this Schwartz-Moss scoring system.

TABLE 2: DIAGNOSTIC CRITERIA FOR LQTS

| FINDING | SCORE |
|--|-------|
| ELECTROCARDIOGRAPHIC[†] | |
| Corrected QT interval, msec | |
| ≥ 480 | 3 |
| 460–470 | 2 |
| 450 (in males) | 1 |
| Torsades de pointes [†] | 2 |
| T-wave alternans | 1 |
| Notched T-wave in 3 leads | 1 |
| Low heart rate for age [§] | 0.5 |
| CLINICAL HISTORY | |
| Syncope [†] | |
| With stress | 2 |
| Without stress | 1 |
| Congenital deafness | 0.5 |
| FAMILY HISTORY[¶] | |
| Family members with definite LQTS | 1 |
| Unexplained SCD in immediate family members < 30 yrs old | 0.5 |

[†] Findings in the absence of medications or disorders known to affect these electrocardiographic findings.

[‡] Torsades de pointes and syncope are mutually exclusive.

[§] Resting heart rate below the second percentile for age.

[¶] The same family member cannot be counted in both categories.

| SCORE | PROBABILITY OF LQTS |
|-------|---------------------|
| ≤ 1 | Low |
| 2–3 | Intermediate |
| ≥ 4 | High |

Schwartz et al., Circulation, 1993.

TABLE 3: HIGH-RISK SUBSETS FOR ABORTED CARDIAC ARREST OR SUDDEN CARDIAC DEATH BY AGE

| AGE-GROUP | HIGH RISK SUBSETS |
|------------------------------|--|
| Childhood (1–12 years) | Males with prior syncope and/or QTc > 500 msec |
| | Females with prior syncope |
| Adolescence (13–20 years) | Males and females with either 1 or 2 or more of the following: <ul style="list-style-type: none"> • QTc ≥ 530 msec • ≥ 1 episode of syncope in the past 1 year • ≥ 2 episodes of syncope in the past 2–10 years |
| Adulthood (21–40 years) | Either 1 or more of the following: <ul style="list-style-type: none"> • Female gender • Interim syncope after age 18 years • QTc ≥ 500 msec |
| 41–60 years | Either 1 or more of the following: <ul style="list-style-type: none"> • Female gender • Syncope in the past 10 years • QTc ≥ 500 msec • LQT3 genotype |
| 61–75 years | Syncope in the past 10 years |

Moss et al., Curr Probl Cardiol, 2008.

Clinical Course

The clinical course of LQTS is quite variable, even within the same family. Patients with LQTS may be asymptomatic or present with syncope, life-threatening ventricular tachyarrhythmia (e.g., torsade de pointes), aborted cardiac arrest, or sudden death. Some cases of sudden infant death syndrome (SIDS) are due to unrecognized LQTS. The clinical variability is influenced by incomplete penetrance of the underlying mutation, functional status of interacting genes, age, gender, environmental factors, and therapeutic interventions.

Using the Long QT Syndrome Registry, Moss et al., have delineated risk factors for adverse outcomes in patients with LQTS (e.g., aborted cardiac arrest and sudden cardiac death). The most powerful predictor of subsequent life-threatening cardiac events in LQTS patients is a history of syncope, whereby timing and frequency of previous syncopal events are crucial factors. Recent or recurrent syncopal events are associated more frequently with subsequent malignant events. A QTc duration of > 500 msec has consistently been associated with a worse prognosis. Additionally, there is an age-dependent effect of gender on the clinical course of LQTS. Before 15 years of age, males have a higher risk of cardiac events such as syncope or sudden cardiac death compared to females. Over age 15, the risk reverses and females have a higher risk than males. Table 3 depicts subjects at a high risk of sudden cardiac death categorized by age group.

Genetics of LQTS

LQTS is a genetic channelopathy of the heart, usually with autosomal dominant inheritance. Therefore, an individual carrying a disease-causing LQTS mutation has a 50 percent chance of transmitting the mutation to a child, either male or female. A recessively inherited genetic syndrome involving LQTS and hereditary deafness (Jervell and Lange-Nielsen Syndrome) is rare. LQTS is a genetically heterogeneous disorder that has been seen in all ethnicities. Mutations in 12 genes have been associated with LQTS, leading either to decreased repolarizing potassium currents or to inappropriate entry of sodium or calcium ions into cardiac myocytes due to defective sodium or calcium ion channels. As shown in Table 4, the vast majority of individuals with heritable LQTS have an identifiable mutation in ion channel genes.

TABLE 4: GENES ASSOCIATED WITH LONG QT SYNDROME

| GENOTYPE | AFFECTED GENE | GENE NAME |
|----------|---------------|--|
| LQT1 | KCNQ1 | KQT-like voltage-gated potassium channel-1 |
| LQT2 | KCNH2 | Potassium channel, voltage gated, H2 |
| LQT3 | SCN5A | Alpha polypeptide of voltage-gated sodium channel type V |
| LQT4 | ANK2 | Ankyrin-B |
| LQT5 | KCNE1 | Voltage-gated potassium channel, Isk-related subfamily, member 1 |
| LQT6 | KCNE2 | Voltage-gated potassium channel, Isk-related subfamily, member 2 |
| LQT7 | KCNJ2 | Inwardly rectifying potassium channel |
| LQT8 | CACNA1C | Calcium channel, L type, alpha-1 polypeptide isoform |
| LQT9 | CAV3 | Caveolin-3 |
| LQT10 | SCN4B | Sodium channel, voltage-gated, type IV beta subunit |
| LQT11 | AKAP9 | A-kinase anchor protein 9 |
| LQT12 | SNTA1 | Syntrophin, alpha-1 |

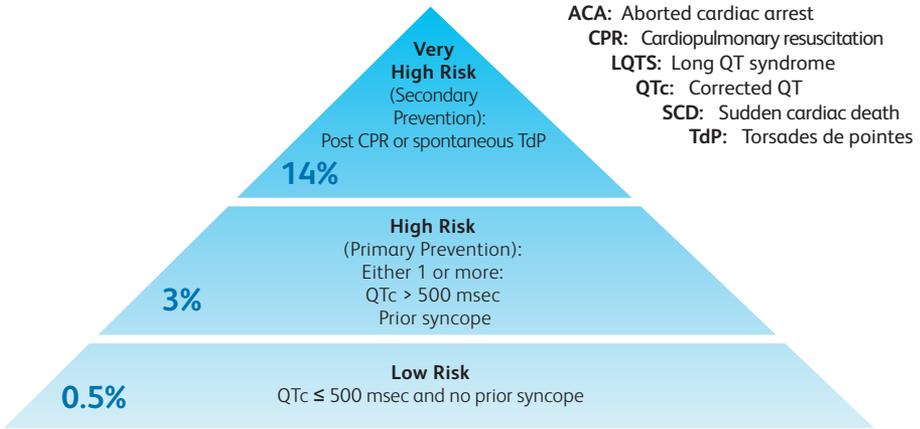
Moss AJ et al., Curr Probl Cardiol, 2008.

● TABLE 5: TRIGGERS ASSOCIATED WITH THE MOST COMMON TYPES OF LQTS

| GENOTYPE | TRIGGER FOR CARDIAC EVENT |
|----------|-----------------------------------|
| LQT1 | Exercise/Vigorous activity |
| LQT2 | Sleep arousal/Startling condition |
| LQT3 | Resting state |

Genotype-phenotype correlations in LQTS have provided improved understanding of the mechanisms of arrhythmia and clinical course in long QT syndrome. For example, the triggers for malignant arrhythmias were found to differ based on the gene involved (Table 5). Patients with LQT1 have an increased risk of cardiac events during vigorous activities such as exercise and competitive sports, whereas LQT2 patients have an increased risk of cardiac events triggered by auditory stimulation, especially during sleep. LQT3 patients usually have arrhythmias during sleep or at rest when they are relatively bradycardic. Moreover, it has been shown that beta-blocker therapy is less effective in LQT3 patients as compared to LQT1 and LQT2 patients.

FIGURE 2: FIVE-YEAR KAPLAN-MEIER RATES OF ACA OR SCD



Goldenberg I et al., *J Am Coll Cardiol*, 2008.

Figure 2: Risk stratification scheme for life-threatening events such as aborted cardiac arrest or sudden cardiac death in LQTS patients

Risk Stratification

LQTS can be classified into three risk categories based on published data on rates of aborted cardiac arrest followed by repeat arrest or sudden cardiac death within five years.

High risk (> 10%): Patients who have a history of aborted cardiac arrest and/or episodes of life-threatening ventricular arrhythmias documented on ECG should be considered at high risk of experiencing a life-threatening cardiac event.

Intermediate risk (~3–10%): Patients with a history of syncope within the last two years, especially if recurrent, and/or QTc prolongation > 0.50 sec should be considered at intermediate risk of having a cardiac event.

Low risk (< 1%): Affected individuals without a history of prior syncope and with QTc duration ≤ 0.50 sec can be assigned a low risk of having a cardiac event in future.

However, these risk groups represent a simplified approach, because risk factors in LQTS are time dependent and age specific. Figure 2 shows the suggested risk stratification for aborted cardiac arrest and sudden cardiac death ACA/SCD in LQTS patients.

Management

There are a variety of management strategies available to patients with LQTS.

- **Pharmacologic Therapy:** Medical therapy with beta-blockers is first-line prophylactic therapy. Beta-blockers should be administered to all intermediate or high-risk affected individuals and considered on an individual basis in low-risk patients. Beta-blocker therapy is associated with a significant reduction in the risk of life-threatening cardiac events in high-risk LQTS patients. However, despite these beneficial effects, cardiac events have been reported in patients receiving beta-blocker therapy. Therefore, patients who remain symptomatic despite treatment with beta-blockers should be considered for other, more invasive, therapies.
- **Implantable cardioverter defibrillators (ICD):** Implanted defibrillators in combination with beta-blockers are indicated for secondary prevention in LQTS patients and for primary prevention in high-risk patients who remain symptomatic despite beta-blocker therapy.
- **Surgical left cervicothoracic sympathetic denervation (LCSD):** LCSD should be considered in patients who are symptomatic (recurrent syncope despite beta-blocker therapy) and in patients who experience arrhythmia storms or shocks with an ICD.
- **Lifestyle restriction:** Avoidance of triggers such as competitive sports, swimming (especially in LQT1 patients), alarm clocks, and QT-prolonging drugs is usually recommended for LQTS patients.
- **Genotype specific treatment:** Knowledge of the LQTS genotype may be used to tailor the treatment plan. For instance, LQT3 patients benefit less from beta-blockers, so a lower threshold should be used for ICD placement in LQT3 patients.

Indications and Utility of Genetic Testing

Genetic testing in a clinically affected patient with LQTS can reveal a disease-causing mutation and determine which of the different LQTS genes is involved, thus confirming the clinical diagnosis. Based on genotype-phenotype correlations, it is then possible to suggest triggers to be avoided. Genetic testing of affected individuals can also assist in the identification of other at-risk family members who will benefit from cardiac treatment and surveillance or, in individuals who test negative for a specific familial mutation, obviates the need for serial cardiac evaluations. Results of genetic testing can also be used for prenatal/preimplantation genetic diagnosis.

Genetic Test Results and What They Mean

Diagnostic genetic testing can be considered for patients who clinically manifest with symptoms and ECGs characteristic of LQTS and for asymptomatic patients with a known familial mutation or positive family history of LQTS. **Testing should initially be performed on the symptomatic family member who has clinical manifestations of LQTS. Preferably, the youngest or most severely affected family member should be tested first.** In some cases, genetic testing can be performed on a deceased individual if the medical examiner has stored blood or tissue that can be used for genetic testing. Testing a symptomatic family member is done to identify the familial mutation, if one can be identified. The three possible outcomes of genetic testing are positive, negative, and variant of unknown clinical significance (VOUS). All patients who undergo genetic testing should receive pre-test and post-test genetic counseling to understand the implications of testing. Genetic counseling services across the country can be found at www.nsgc.org.

- **A positive result** indicates that a disease-causing mutation was identified in that individual. This finding confirms the diagnosis of LQTS and provides valuable information to the physician and family members. Knowledge of a patient's genotype can help the physician in identifying triggers to avoid and may be useful in stratifying the patient's risk of experiencing a life-threatening cardiac event. All first-degree relatives (children, siblings, parents) of a patient with a positive genetic test result can then be offered predictive genetic testing to clarify the risk for LQTS. If a family member is found to be positive for the familial mutation, this individual is considered to be at risk for LQTS and should be referred for cardiac evaluation, including an ECG. Mutation-positive family members should have a baseline electrocardiogram and annual ECG screening exams. It is important to note that there is variability in symptoms, even within families.

- **A negative result** in an affected individual does not rule out LQTS, and the patient should be managed according to his/her clinical symptoms and ECG. Possible reasons for a negative result could be (1) the patient may have a mutation in a gene not covered in the testing panel, (2) the patient may have a mutation in a part of a LQTS gene that was not covered in the test, or (3) the patient does not have a heritable form of LQTS. Predictive genetic testing of family members when the affected family member testing is negative will not be informative and is not warranted. Family members of a clinically affected individual with negative test results may still be at risk for LQTS and thus should be evaluated by a cardiologist. In addition, cardiac clearance prior to participation in competitive sports is recommended.

If an asymptomatic individual is negative for a mutation identified in a family member, this person is considered a true negative and is not at increased genetic risk for long QT syndrome. LQTS clinical monitoring for this individual is not necessary, but this patient could develop other types of cardiac disease in the future.

If there are no symptomatic members of a LQTS family available for testing, an asymptomatic individual may pursue predictive genetic testing prior to identification of the familial mutation. However, if the asymptomatic family member is found to have a negative test result, this result is considered an uninformative negative result, and this asymptomatic family member should still be evaluated regularly by a cardiologist.

- **A variant of unknown clinical significance (VOUS)** indicates that the pathogenic role of the variant cannot be clearly established. The VOUS has been tested in a large panel of normal individuals and was not identified in any of the normal individuals. To further clarify the clinical significance of this variant, testing of family members is helpful. If an affected relative is found to have the same variant, it is more likely that the variant is disease-causing. The greater the number of affected family members who carry the VOUS, the greater is the likelihood that the VOUS is pathogenic. With consistent linkage of the VOUS with symptomatic family members, the variant found would be reclassified as a family-specific mutation and extended family members can be offered predictive genetic testing.

Resources for Patients

- *Sudden Arrhythmia Death Syndrome (SADS)*: Patient support organization www.sads.org
- *Cardiac Arrhythmias Research and Education Foundation, Inc (C.A.R.E.)*: Patient support organization www.longqt.org
- *The Canadian SADS Foundation*: Patient support organization www.sads.ca
- *Sudden Cardiac Arrest Association*: Patient support organization www.suddencardiacarrest.org
- *National Society of Genetic Counselors*: Search for a counselor/genetic center specializing in cardiology genetics www.nsgc.org

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About GeneDx

GeneDx was founded in 2000 by two scientists from the National Institutes of Health (NIH) to address the needs of patients and clinicians in diagnosing rare inherited disorders. Currently, GeneDx offers testing for more than 300 rare Mendelian disorders, oligonucleotide-microarray-based testing for detecting chromosomal abnormalities, testing for autism spectrum disorders, and gene panels for testing various forms of inherited cardiac disorders. Our highly trained and experienced physicians, geneticists, and genetic counselors work as a team to bring gene discoveries to clinical medicine for use in direct patient care. We invite you to visit our website, www.genedx.com, to learn more about us and the services we offer.

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