# Long QT Panel, Sequencing and Deletion/Duplication

Long QT syndrome (LQTS) is characterized by prolongation of the QTc interval and T-wave abnormalities on an electrocardiogram (ECG) in the absence of specific conditions known to lengthen it, such as QT-prolonging drugs. LQTS is associated with tachyarrhythmias, often torsade de pointes (TdP), which may result in syncope, ventricular fibrillation, or sudden cardiac death. Cardiac events may occur from infancy to middle age but are most common in preteens and young adults. Common triggers for cardiac events include exercise, loud noises, emotional stress, or sleep. Not all individuals with a pathogenic variant in an LQTS-associated gene have ECG abnormalities or cardiac symptoms. Syndromic forms of LQTS associated with additional noncardiac features include Andersen-Tawil syndrome, Timothy syndrome, and Jervell and Lange-Nielsen syndrome (JLNS). Molecular confirmation of LQTS in symptomatic individuals or at-risk family members is useful to initiate treatment to prevent syncope or sudden death.

## Tests to Consider

### Long QT Panel, Sequencing and Deletion/Duplication 3001603

**Method:** Massively Parallel Sequencing / Exonic Oligonucleotide-based CGH Microarray

- Use to confirm diagnosis of LQTS in symptomatic individuals.
- Use for presymptomatic testing in individuals with family history of LQTS or sudden cardiac death.

### Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication 2010183

**Method:** Massively Parallel Sequencing

Preferred test to assess for hereditary form of cardiomyopathy or arrhythmia.

### Familial Mutation, Targeted Sequencing 2001961

**Method:** Polymerase Chain Reaction/Sequencing

- Assess for a familial sequence variant previously identified in a family member.
- A copy of the relative's genetic laboratory report documenting the familial variant is required.

## Disease Overview

### Clinical Findings

- Syncope
- Cardiac arrest/sudden cardiac death
- ECG abnormalities
  - Prolonged QTc interval on ECG
  - Torsade de pointes
  - T wave alternans
  - Notched T wave
  - Low heart rate for age
- Syndromic forms of LQTS:
  - Andersen-Tawil syndrome
    - Characteristic facial features
    - Periodic paralysis/muscle weakness
  - Timothy syndrome
    - Characteristic facial features
    - Cutaneous syndactyly of hands/feet
    - Neurodevelopmental disorder
  - JLNS
    - Congenital sensorineural hearing loss

## Genetics

### Genes

Sequencing and deletion/duplication: *CACNA1C*, *CAV3*, *KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNQ1*, *SCN5A*

Sequencing only: *CALM1*, *CALM2*

### Etiology

Pathogenic germline variants in genes associated with LQTS[1]

Commonly implicated genes with estimated contribution to congenital LQTS:

- *KCNQ1* (30-35%)
- *KCNH2* (25-30%)
- *SCN5A* (5-10%)

### Penetrance

Variable, influenced by gene involved

Of individuals with a pathogenic variant in an LQTS-associated gene:

- An estimated 25% do not show QTc prolongation on ECG
- Approximately 50% or less have clinical symptoms

### Prevalence

1:2,500 for congenital LQTS

### Inheritance

Typically, autosomal dominant with incomplete penetrance

Autosomal recessive inheritance for JLNS

## Test Description

### Clinical Sensitivity

60-75%[2]

### Limitations

- A negative result does not exclude a heritable form of LQTS.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted genes
  - Regulatory region and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Deletions/duplications of *CALM1* and *CALM2*
  - Noncoding transcripts
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Deletions/duplications less than 1kb in the targeted genes
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants
  - Single exon deletions/duplications in the following exons:
    - *KCNH2* (NM_000238) 13
    - *KCNQ1* (NM_000218) 16
    - *KCNQ1* (NM_181798) 1

### Analytical Sensitivity

For massively parallel sequencing:

| Variant Class | Analytical Sensitivity (PPA) Estimate[a] (%) | Analytical Sensitivity (PPA) 95% Credibility Region[a] (%) |
|---|---|---|
| SNVs | 99.2 | 96.9-99.4 |
| Deletions 1-10 bp | 93.8 | 84.3-98.2 |
| Deletions 11-44 bp | 99.9 | 87.8-100 |
| Insertions 1-10 bp | 94.8 | 86.8-98.5 |
| Insertions 11-23 bp | 99.9 | 62.1-100 |

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

| Genes Tested | | | |
|---|---|---|---|
| Gene | MIM # | Associated Disorder(s) | Inheritance |
| *CACNA1C* | 114205 | LQTS 8<br>Timothy syndrome | AD |
| *CALM1* | 114180 | LQTS 14<br>CPVT 4 | AD |
| *CALM2* | 114182 | LQTS 15 | AD |
| *CAV3* | 601253 | LQTS 9 | AD |
| *KCNE1* | 176261 | JLNS2 | AR |
| | | LQTS 5 | AD |
| *KCNE2* | 603796 | Familial atrial fibrillation 4<br>LQTS 6 | AD |
| *KCNH2* | 152427 | LQTS 2<br>SQTS 1 | AD |
| *KCNJ2* | 600681 | Andersen-Tawil syndrome<br>SQTS 3<br>Familial atrial fibrillation 9 | AD |
| *KCNQ1* | 607542 | Familial atrial fibrillation 3<br>SQTS 2<br>LQTS 1 | AD |
| | | JLNS 1 | AR |
| *SCN5A* | 600163 | Progressive/nonprogressive heart block<br>Brugada syndrome 1<br>Dilated cardiomyopathy 1E<br>Familial atrial fibrillation 10<br>Familial ventricular fibrillation 1<br>LQTS 3 | AD |
| | | Sick sinus syndrome 1 | AR |

AD, autosomal dominant; AR, autosomal recessive; CPVT, catecholaminergic polymorphic ventricular tachycardia; SQTS, short QT syndrome

## References


1. Adler A, Novelli V, Amin AS, et al. An international, multicentered, evidence-based reappraisal of genes reported to cause congenital long QT syndrome. Circulation. 2020;141(6):418-428. PubMed

2. Alders M, Bikker H, Christiaans I. Long QT syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2021. [Last Update: Feb 2018; Accessed: Feb 2021]


## Related Information

Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication


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