

Long QT Panel, Sequencing and Deletion/Duplication

Content Review: May 2022 Last Update: January 2024

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.

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*, *CALM1*, *CALM2*, *CALM3*, *KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNQ1*, *SCN5A*, *TRDN*

Etiology

Pathogenic germline variants in genes associated with LQTS¹

Commonly implicated genes with estimated contribution to congenital LQTS:

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

Featured ARUP Testing

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Method: Massively Parallel Sequencing

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

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the [Laboratory Test Directory](#) for additional information.

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 Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing, or NGS) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- The pipeline includes an algorithm for the detection of large deletions and duplications.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Clinical Sensitivity

60-75%²

Analytic Sensitivity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate ^a (%) and 95% Credibility Region	Analytic Specificity (NPA)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp ^b	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp ^b	94.8 (86.8-98.5)	>99.9
Exon-level ^c deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [Single exon]	>99.9

^aGenes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

^bVariants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

^cIn most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

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

Variant Class	Analytic Sensitivity (PPA) Estimate ^a (%) and 95% Credibility Region	Analytic Specificity (NPA)
Exon-level ^c duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

^aGenes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

^bVariants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

^cIn most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

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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 the targeted genes
 - Regulatory region and deep intronic variants
 - Breakpoints of large deletions/duplications
- The following may not be detected:
 - Deletions/duplications/insertions of any size by massively parallel sequencing
 - Large duplications less than 3 exons in size
 - Noncoding transcripts
 - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
 - Low-level somatic variants
 - Duplications in the following genes: *CAV3*, *KCNE1*, *KCNE2*

Genes Tested

Gene	MIM #	Associated Disorder(s)	Inheritance
<i>CACNA1C</i>	114205	LQTS 8 Timothy syndrome	AD
<i>CALM1</i>	114180	LQTS 14 CPVT 4	AD
<i>CALM2</i>	114182	LQTS 15	AD
<i>CALM3</i>	114183	LQTS 16	AD
<i>KCNE1</i>	176261	JLNS2	AR
		LQTS 5	AD
<i>KCNE2</i>	603796	Familial atrial fibrillation 4 LQTS 6	AD
<i>KCNH2</i>	152427	LQTS 2 SQTS 1	AD
<i>KCNJ2</i>	600681	Andersen-Tawil syndrome SQTS 3 Familial atrial fibrillation 9	AD
<i>KCNQ1</i>	607542	Familial atrial fibrillation 3	AD

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

		SQTS 2	
		LQTS 1	
		JLNS 1	AR
<i>SCN5A</i>	600163	Progressive/nonprogressive heart block Brugada syndrome 1 Dilated cardiomyopathy 1E Familial atrial fibrillation 10 Familial ventricular fibrillation 1 LQTS 3	AD
		Sick sinus syndrome 1	AR
<i>TRDN</i>	603283	Cardiac arrhythmia syndrome, with or without skeletal muscle weakness	AR

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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.
2. Alders M, Bikker H, Christiaans I. [Long QT syndrome.](#) In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2021. [Updated: Feb 2018; Accessed: Mar 2022]

Related Information

[Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication](#)

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