Long QT Panel, Sequencing and Deletion/Duplication

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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.

Featured ARUP Testing

Long QT Panel, Sequencing and Deletion/Duplication 3001603

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.

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 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 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
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]Genes 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).

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In 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

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
  - SNVs and small deletions/insertions will not be called in the following exons due to technical limitations of the assay:
    - CALM1 (NM_001363670) exon(s)[1]
- 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
CACNA1C	114205	LQTS 8 Timothy syndrome	AD
CALM1	114180	LQTS 14 CPVT 4	AD
CALM2	114182	LQTS 15	AD
CALM3	114183	LQTS 16	AD
KCNE1	176261	JLNS2	AR
		LQTS 5	AD
KCNE2	603796	Familial atrial fibrillation 4 LQTS 6	AD
KCNH2	152427	LQTS 2 SQTS 1	AD
KCNJ2	600681	Andersen-Tawil syndrome SQTS 3 Familial atrial fibrillation 9	AD
KCNQ1	607542	Familial atrial fibrillation 3 SQTS 2 LQTS 1	AD
		JLNS 1	AR
SCN5A	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

Gene	MIM #	Associated Disorder(s)	Inheritance
TRDN	603283	Cardiac arrhythmia syndrome, with or without skeletal muscle weakness	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.

2. Alders M, Bikker H, Christiaans I. Long QT syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews.* University of Washington, Seattle. Updated Feb 2018; accessed Mar 2022.

Related Information

Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication

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