Long QT Syndrome (LQTS)

Also Known As: Ventricular fibrillation with prolonged QT interval, Romano-Ward syndrome (RWS), or Jervell and Lange-Nielsen syndrome (JLNS)

Long QT Syndrome (LQTS) testing provides efficient and rapid genetic testing for all reported long QT syndrome subtypes (LQT1-15) using Next Generation Sequencing (NGS) technology. The panel includes 15 genes that are definitively associated with LQTS or other inherited arrhythmia disorders that may present with clinical features similar to LQTS (**Table 1**). Many of these genes code for ion channel proteins of the heart muscle that help regulate the movement of sodium, potassium and calcium ions in and out of cardiac cells, as well as their associated regulatory factors and interacting proteins (2).

Table 1: Genes Associated with Long QT Syndrome (1).

Gene	Disease Associations	Inheritance	No. Pathogenic Variants Reported
AKAP9	LQTS type 11	AD	1
ANK2	LQTS type 4, Arrhythmia	AD	More than 20
CACNA1C	LQTS type 8, BrS, TS	AD	Only a few
CALM1	LQTS type 14, CPVT	AD	Only a few
CALM2	LQTS type 15, CPVT	AD	Only a few
CAV3	LQTS type 9, HCM, LGMD, RMD, TDM, SIDS	AD, AR	5 probable
KCNE1	LQTS type 5, JLNS	AD, AR	More than 36
KCNE2	LQTS type 6	AD	More than 20
KCNH2	LQTS type 2, SQTS	AD	More than 700
KCNJ2	LQTS type 7, ATS, SQTS, AF	AD	More than 70
KCNJ5	LQTS type 13, Hyperaldosteronism	AD	2
KCNQ1	LQTS type 1, SQTS, JLNS	AD, AR	More than 500
SCN4B	LQTS type 10, AF	AD	2
SCN5A	LQTS type 3, BrS, DCM, ARVC, HB, SSS, SIDS	AD, AR	More than 200
SNTA1	LQTS type 12	AD	3

Abbreviations: AD - Autosomal dominant; AF - Atrial fibrillation; AR - Autosomal recessive; ARVC - Arrhythmogenic right ventricular cardiomyopathy; ATS – Andersen-Tawil syndrome; BrS - Brugada syndrome; CPVT - Catecholaminergic polymorphic ventricular tachycardia; DCM - Dilated cardiomyopathy; HB - Heart block; JLNS - Jervell and Lange-Nielsen syndrome; LGMD - Limb girdle muscular dystrophy; LQTS - Long QT syndrome; RMD - Rippling muscle disease; SIDS - Sudden infant death syndrome; SQTS - Short QT syndrome; SSS - Sick sinus syndrome; TDM - Tateyama-type distal myopathy; TS - Timothy syndrome.

Considerations for Testing

- Individuals with clinical symptoms of LQTS may benefit from diagnostic genetic testing to establish or confirm diagnosis, clarify risks, or inform management.
- Asymptomatic members of a family with a known LQTS pathogenic variant may also benefit from risk assessment by avoiding activities and medications that can trigger symptoms.
- Differentiation of hereditary LQTS from acquired (non-genetic) causes of LQTS.
- Genetic counseling and recurrence risk calculation.
- Prenatal diagnosis in families with a known disease-associated variant.

Clinical Characteristics

Long QT syndrome is a cardiac disorder resulting from abnormal ion-channel functions leading to prolonged repolarization of cardiac muscle characterized by long QT interval and T-wave abnormalities on the electrocardiogram (ECG) and the ventricular tachycardia *torsade de pointes* (TdP). The most common symptom in individuals with LQTS is unexpected fainting (syncope). Syncope typically occurs during exercise and high emotions, less frequently at rest or during sleep, and usually without warning. In some cases, TdP can lead to ventricular arrhythmias and sudden cardiac death in patients with structurally normal hearts. Sudden death can be the first symptom in 10% - 15% of LQTS patients. While cardiac events may occur from infancy through middle age, they are most common from the pre-teen years through the 20s. Young patients may be asymptomatic and experience sudden cardiac death (SCD) without warning (2). LQTS may be present even in the absence of any clinical symptoms and, in some patients, sudden cardiac death occurs without any preceding symptoms and without an identifiable cause at autopsy. Inherited LQTS may underlie up to 10% - 15% of sudden infant death syndrome (SIDS) cases. Therefore, careful monitoring is necessary, and preventive implantable cardioverter-defibrillators (ICD) placement is often warranted.

Approximately 75% of cases of LQTS are due to known genetic causes. About 50% of individuals with a pathogenic variant in one of the genes associated with LQTS usually experience cases of unexpected fainting. Some types of LQTS are associated with a phenotype extending beyond cardiac arrhythmia. In addition to the prolonged QT interval, associations include muscle weakness and facial dysmorphism in Andersen-Tawil syndrome (LQTS type 7), hand/foot, facial, and neurodevelopmental features in Timothy syndrome (LQTS type 8) and profound sensorineural hearing loss in Jervell and Lange-Nielson syndrome (4).

Genetics

Cardiac arrhythmia can be caused by genetic disorders, trauma, infection and structural abnormalities. Hereditary cardiac arrhythmia can be inherited in an autosomal dominant or autosomal recessive manner. As seen in **Table 1**, variants in a single gene may be associated with different types of arrhythmia (clinical heterogeneity). Conversely, variants in different genes can cause a similar arrhythmia phenotype (genetic heterogeneity).

Romano-Ward syndrome (RWS), which accounts for the majority of LQTS is usually inherited in an autosomal dominant manner, and an affected individual with a disease-causing variant has a 50% chance of transmitting this variant to a child. Most individuals diagnosed with LQTS and carrying a pathogenic variant have an affected parent. Autosomal recessive inheritance has only been described in LQTS cases associated with sensorineural deafness (known as Jervell and Lange-Nielsen syndrome). Cases of LQTS caused by a *de novo* pathogenic variant are small.

Diagnosis/Testing

Diagnosis of LQTS is established clinically by the presence of prolongation of the QTc interval in the absence of specific conditions known to lengthen it (for example, QT-prolonging drugs) and/or by molecular genetic testing that identifies pathogenic variant(s) in one or more of the 15 genes known to be associated with LQTS, of which KCNQ1 (LQT1), KCNH2 (LQT2) and SCN5A (LQT3) are the most common (**Table 2**). Approximately 20% of families meeting clinical diagnostic criteria for LQTS do not have detectable pathogenic variants in one of the above genes.

LQTS-associated with biallelic pathogenic variants 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 (1).

Management (1, 3)

- LQT1 and LQT2 patients benefit the most from beta blocker therapy.
- The benefit of beta blocker therapy is less clear in LQT3 patients.
- Implantable cardioverter-defibrillators (ICDs) indicated:
  - If the patient presents as SCD survivor or aborted cardiac arrest.
  - If beta blockers are not effective in preventing cardiac events.
- Agents/circumstances to avoid:
  - Certain drugs may provoke life-threatening arrhythmias in LQTS patients.
  - Competitive sports/activities associated with intense physical activity and/or emotional stress for most individuals.
- Evaluation of at-risk relatives:
  - Presymptomatic diagnosis and treatment is warranted in at-risk relatives to prevent syncope and sudden death.
- Surveillance:
  - Regular assessment of beta blocker dose for efficacy and adverse effects in all individuals with LQTS, especially children during rapid growth.
  - Regular periodic evaluations of ICDs for inappropriate shocks and pocket or lead complications.

Test Methodology

Using genomic DNA obtained from a blood or mouthwash specimen, 241 coding exons and their flanking splice junctions of 15 genes are sequenced simultaneously by massively parallel sequencing (next-generation sequencing). The sequence data is assembled and compared to the published genomic reference sequence. Capillary dideoxy DNA Sanger sequencing is used to confirm the presence of potentially disease-associated variants and to obtain sequence for regions that do not reach NGS quality standards (e.g., less than 20x coverage). The Long QT Syndrome test has an analytical sensitivity and specificity of greater than 99.9% after confirmation with Sanger sequencing.

Variants are classified through the utilization of the most current ClinVar databases as pathogenic, likely pathogenic, variants of uncertain significance, likely benign or benign. Finally, the test report is issued to the appropriate genetic counselor, physician and/or health care provider for ultimate dissemination to the patient, such that the appropriate clinical care may be provided.

This sequencing test will not detect large chromosomal aberrations and deletions, insertions, or rearrangements greater than or equal to 5 base pairs. Approximately 10% of patients with LQTS and no sequence abnormality in one of the common LQTS genes have been found to have a large deletion or duplication.

Test Code

- **1267 Long QT Syndrome by Next Generation Sequencing** (KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP9, SNTA1, ANK2, CALM1, CALM2, KCNJ5)

Turnaround time

- Up to 14 days

Specimen Requirements

- Whole Blood (Yellow top tube-ACD solution A)
- Mouthwash

References:

1. **Alders M, Mannens MMAM:** Romano-Ward Syndrome. In GeneReviews. Edited by RA Pagon, MP Adam, HH Ardinger, et al: University of Washington, Seattle. 1993-2014. 2003 Feb 20 (Updated 2012 May 31). Available at http://www.ncbi.nlm.nih.gov/books/NBK1129/
2. **Fernandez-Falgueras A, Sarquella-Brugada G, Brigda J, et al.** 2017. Cardiac Channelopathies and Sudden Death: Recent Clinical and Genetic Advances. *Biol* **6(1)**:7.
3. **Goldenberg I, Zareba W, Moss AJ.** 2008. Long QT Syndrome. *Curr Probl Cardiol* **33**:629-694.
4. **Priori SG, Napolitano C.** 2004. Genetics of Cardiac Arrhythmias and Sudden Cardiac Death. *Ann N Y Acad Sci* **1015**:96-110.

Table 2: Characteristics of Long QT Syndrome Types 1, 2 and 3 (1).

Phenotype	Gene	Average QTc	ST-T-Wave Morphology	Incidence of Cardiac Events	Cardiac Event Trigger	Sudden Death Risk
LQTS type 1	KCNQ1	480 msec	Broad-base T-wave	63%	Exercise, Emotion	6% - 8%
LQTS type 2	KCNH2		Bifid T-wave	46%	Emotion, Exercise, Sleep	
LQTS type 3	SCN5A	~ 490 msec	Long ST, Small T	18%	Sleep	