Long QT Syndrome Panel

Disorder also known as: Ventricular fibrillation with prolonged QT interval; Romano-Ward syndrome (RWS); Jervell and Lange-Nielsen syndrome (JLNS)

Panel Gene List: *AKAP9, ANK2, CACNA1C, CALM1, CALM2, CALM3, CAV3, KCNE1, KCNE2, KCNH2 (HERG), KCNJ2, KCNJ5, KCNQ1, SCN4B, SCN5A, SNTA1, TRDN*
Additional genes from our cardiology test menu may be added to this panel by selecting test code 727C.

Clinical Features:

Long QT syndrome (LQTS) is due to abnormal cardiac ion channel function and characterized by prolongation of the QT interval on ECG. Approximately seventy-five percent of cases of LQTS are due to known genetic causes. LQTS is associated with increased risk for syncope, ventricular arrhythmia, and sudden cardiac death in young adults with normal heart structure. Sudden death is the first and final symptom in 10-15% of individuals with this diagnosis. LQTS has an estimated prevalence 1 in 2000 individuals[1], occurs in all ethnicities, and results in approximately 4000 deaths annually in the US.[2]

The diagnosis of LQTS is based on clinical history, ECG findings, genetic testing, and family history. Typically, the disorder manifests in patients younger than 40 years of age and may present as early as infancy. Patients often have a history of syncope or palpitations in the absence of any other causes, such as medications, structural heart abnormalities, myocardial ischemia, or electrolyte imbalances. In some patients, syncope may be mistakenly diagnosed as seizures. 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.[3]

Inheritance Pattern/Genetics: Autosomal Dominant or Autosomal Recessive

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the 17 genes (Only exons 1-44 for *CACNA1C*, only the *KCNQ1*-binding domains including Ser1570 residue for *AKAP9*) are enriched using a proprietary targeted capture system developed by GeneDx. These targeted regions are sequenced simultaneously by massively parallel (NextGen) sequencing on an Illumina platform with paired-end reads. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing is used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 15 reads are achieved by NextGen sequencing. Concurrent deletion/duplication testing is performed for the genes in the panel using exon-level oligo array CGH (ExonArrayDx), except for *CALM1*. Data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. The array is designed to detect most intragenic deletions and duplications. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat array CGH

analysis. Sequence and array CGH alterations are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Benign and likely benign variants, if present, are not included in this report but are available upon request.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the 17 genes included in the LQTS Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined LQTS and a family history of disease. The technical sensitivity of the sequencing test is estimated to be 98%. The sequencing panel will not reliably detect deletions, insertions, or rearrangements greater than or equal to five base pairs (bp). Deletions or duplications of less than 500 bp are not reliably detected by array CGH.

Gene	Protein	Inheritance	Disease Associations
AKAP9	A-KINASE ANCHOR PROTEIN 9	AD	LQTS
ANK2	ANKYRIN 2	AD	Arrhythmia, LQTS
CACNA1C	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, L TYPE, ALPHA-1C SUBUNIT	AD	BrS, Timothy syndrome, LQTS
CALM1	CALMODULIN 1	AD	LQTS, CPVT
CALM2	CALMODULIN 2	AD	LQTS, CPVT
CALM3	CALMODULIN 3	AD	LQTS, CPVT
CAV3	CAVEOLIN 3	AD, AR	HCM, LQTS, LGMD, Rippling muscle disease, Tateyama-type distal myopathy, SIDS
KCNE1	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED SUBFAMILY, MEMBER 1	AD, AR	LQTS, JLNS
KCNE2	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED SUBFAMILY, MEMBER 2	AD	LQTS
KCNH2 (HERG)	POTASSIUM CHANNEL, VOLTAGE-GATED, SUBFAMILY H, MEMBER 2	AD	LQTS, SQTS
KCNJ2	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 2	AD	Andersen-Tawil syndrome, SQTS, AF
KCNJ5	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 5	AD	LQTS, Hyperaldosteronism
KCNQ1	POTASSIUM CHANNEL, VOLTAGE-GATED, KQT-LIKE SUBFAMILY, MEMBER 1	AD, AR	JLNS, LQTS, SQTS
SCN4B	SODIUM CHANNEL, VOLTAGE-GATED, TYPE IV, BETA SUBUNIT	AD	LQTS, AF
SCN5A	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT	AD, AR	BrS, DCM, ARVC, HB, LQTS, SSS, SIDS
SNTA1	ALPHA SYNTROPHIN	AD	LQTS
TRDN	TRIADIN	AR	CPVT, LQTS

Abbreviations: AD – Autosomal dominant; AF – Atrial fibrillation; AR – Autosomal recessive; ARVC- Arrhythmogenic right ventricular cardiomyopathy; 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; SIDS – Sudden infant death syndrome; SQTS – Short QT syndrome; SSS – Sick sinus syndrome

References:

1. Lehnart et al. (2007) Circulation 116 (20):2325-45 (PMID: 17998470)
2. Vincent, et al. (1998) Annual Review Of Medicine 49 :263-74 (PMID: 9509262)
3. Arnestad et al. (2007) Circulation 115 (3):361-7 (PMID: 17210839)4. Ackerman MJ et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Europace : European Pacing, Arrhythmias, And Cardiac

Electrophysiology : Journal Of The Working Groups On Cardiac Pacing, Arrhythmias, And Cardiac Cellular Electrophysiology Of The European Society Of Cardiology. 2011 13(8):1077-109.21810866