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

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]

Jervell and Lange-Nielsen syndrome (JLNS) is an autosomal recessive disorder characterized by profound bilateral congenital sensorineural deafness and severe prolongation of the QT interval[1] . JLNS is due to homozygous or compound heterozygous variants in the *KCNQ1* and *KCNE1* genes[4,5,6]. The typical presentation of this disorder is a child with congenital deafness and syncopal episodes.[5,6]

Inheritance Pattern/Genetics:

Autosomal Dominant or Autosomal Recessive

Test Methods:

Genomic DNA is extracted directly from the submitted specimen or, if applicable, from cultured fibroblasts. The DNA is enriched for the complete coding regions and splice junctions of the genes on this panel using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons at the exon-level; however, technical limitations and inherent sequence properties effectively reduce this

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resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Sequence variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Copy number variants are reported based on the probe coordinates, the coordinates of the exons involved, or precise breakpoints when known. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request. Available evidence for variant classification may change over time and reported variant(s) may be reclassified according to the ACMG/AMP Standards and Guidelines (PMID: 25741868), which may lead to issuing a revised report.

Sequencing and deletion/duplication analysis of the remaining genes on the Arrhythmia Panel is available as a separate test if the LQTS Panel is negative.

Test Sensitivity:

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. The following gene specific information applies. CACNA1C, sequencing of exons 1-42 only, AKAP9, sequencing of the KCNQ1-binding domains only including Ser1570 residue. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: SCN5A gene, exon level coverage for exons 2-12 and 21-28 only.

Gene	Protein	Inheritance	Disease Associations
AKAP9	A-KINASE ANCHOR PROTEIN 9	AD	LQTS
ANK2	ANKYRIN 2	AD	Arrhythmia, LQTS, CPVT
CACNA1C	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, L TYPE, ALPHA-1C SUBUNIT	AD	BrS (with short QTc), 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, AF

SCN4B	SODIUM CHANNEL, VOLTAGE-GATED, TYPE IV, BETA SUBUNIT	AD	LQTS, AF
SCN5A	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT	AD, AR	LQTS, ARVC/ARVC-like disease, BrS, DCM, HB, SIDS, SSS
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:

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5. Schwartz et al. (2006) Circulation 113 (6):783-90 (PMID: 16461811)
6. Tranebjærg L, Samson R, Green GE. Jervell and Lange-Nielsen Syndrome. 2002 July 02 [Updated 2014 Nov 20]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1405/

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