Short QT Syndrome Panel

Panel Gene List: *CACNA1C, CACNB2, KCNH2 (HERG), KCNJ2, KCNQ1*
Additional genes from our cardiology test menu may be added to this panel by selecting test code J551C.

Clinical Features:

Short QT syndrome (SQTS) is a heart disorder that affects the cardiac rhythm due to abnormal functioning of ion channel proteins. It is characterized by shortening of the QT interval on ECG and paroxysmal atrial and ventricular tachyarrhythmias. SQTS is associated with an increased risk of atrial fibrillation and sudden cardiac death, resulting from an accelerated cardiac atrial and ventricular repolarization.[1-3] Fewer than 200 cases of short QT syndrome have been published since the condition was first described in 2000.[4]

The diagnosis of SQTS is based on clinical history, ECG findings and family history. The disorder may manifest in any stage of life, sometimes as early as infancy. Patients may have a history of atrial fibrillation, or less likely, syncope. SQTS 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. Autosomal dominant SQTS may also underlie some cases of sudden infant death syndrome (SIDS).[5]

Inheritance Pattern/Genetics: Autosomal Dominant

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV) (Only exons 1-44 for CACNA1C). 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. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. 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. Sequencing and deletion/duplication analysis of the remaining genes on the Comprehensive Arrhythmia Panel is available as a separate test if the SQTS Panel is negative.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in the SQTS Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined SQTS and a family history of disease. 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.

Gene	Protein	Inheritance	Disease Association(s)
CACNA1C	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, L TYPE, ALPHA-1C SUBUNIT	AD	BrS (with short QTc), Timothy syndrome, LQTS
CACNB2	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, BETA-2 SUBUNIT	AD	BrS (w/ short QTc)
KCNH2 (HERG)	POTASSIUM CHANNEL, VOLTAGE-GATED, SUBFAMILY H, MEMBER 2	AD	LQTS, SQTS, BrS
KCNJ2	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 2	AD	Andersen-Tawil syndrome, SQTS , AF
KCNQ1	POTASSIUM CHANNEL, VOLTAGE-GATED, KQT-LIKE SUBFAMILY, MEMBER 1	AD, AR	JLNS, LQTS, SQTS, AF

Abbreviations: AD – Autosomal dominant; AF – Atrial fibrillation; AR – Autosomal recessive; BrS – Brugada syndrome; JLNS – Jervell and Lange-Nielsen syndrome; LQTS – Long QT syndrome; SQTS – Short QT syndrome

References:

1. Napolitano C, Priori SG, Bloise R. Catecholaminergic Polymorphic Ventricular Tachycardia. 2004 Oct 14 [Updated 2016 Oct 13]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1289/
2. Liu et al. Progress In Cardiovascular Diseases 51 (1):23-30 (PMID: 18634915)
3. Priori et al. (2002) Circulation 106 (1):69-74 (PMID: 12093772)
4. Mazzanti et al. (2017) J Cardiovasc Electrophysiol 28 (10):1226-1236 (PMID: 28569435)
5. Nyegaard et al. (2012) American Journal of Human Genetics 91 (4):703-12 (PMID: 23040497)