Sudden Cardiac Arrest Panel

Panel Gene List:

ANK2, CALM1, CALM2, CALM3, CASQ2, CAV3, KCNE1, KCNE2, KCNH2 (HERG), KCNJ2, KCNQ1, PPA2, RYR2, SCN5A

Clinical Features:

Sudden cardiac arrest (SCA) is a significant cause (10-15%) of mortality in the United States, as only 3-10% of individuals are successfully resuscitated after an out-of-hospital cardiac arrest.[1,2] The majority of sudden cardiac arrest or sudden cardiac death is a result of structural heart disease.[1,3] However, unexplained cardiac arrest in the young (<35y) is a less frequent occurrence and more commonly suggests an inherited form of heart disease.[1,3] The occurrence of unexplained cardiac arrest or sudden cardiac death with no identifiable cause presents a diagnostic problem. An estimated 1/3 of sudden death cases in individuals younger than 20 years do not have an identifiable cause at autopsy, and arrhythmia should be considered in the differential diagnosis.[4] In one study examining 173 individuals with sudden unexplained death and negative autopsy findings, 45 (26%) were subsequently diagnosed with an inherited arrhythmia condition.[5] Long QT syndrome (LQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT) are heritable forms of arrhythmia that frequently manifest symptoms before the age of 50, with some cases occurring in infancy. In each of these conditions, a significant proportion of patients present with sudden death as the first symptom. Other symptoms include palpitations, syncope, and dizziness. The diseases included in this SCA Panel occur in all ethnicities, and prevalence varies from 1 in 2,000 to 1 in 10,000.[6,7,8]

Inheritance Pattern/Genetics:

Autosomal Dominant or Autosomal Recessive

Test Methods:

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested are enriched 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; however, technical limitations and inherent sequence properties effectively reduce this 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.

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

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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. For *SCN5A* gene, exon level coverage for exons 2-12 and 21-28 only.

Gene	Protein	Inheritance	Disease Associations
ANK2	ANKYRIN 2	AD	Arrhythmia, LQTS, CPVT
CALM1	CALMODULIN 1	AD	LQTS, CPVT
CALM2	CALMODULIN 2	AD	LQTS, CPVT
CALM3	CALMODULIN 3	AD	LQTS, CPVT
CASQ2	CALSEQUESTRIN 2	AR	CPVT
CAV3	CAVEOLIN 3	AD 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 , 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	LQTS, SQTS, AF, JLNS
PPA2	PYROPHOSPHATASE, INORGANIC, 2	AR	SCD, mitochondrial disease
RYR2	RYANODINE RECEPTOR 2	AD	ARVC, CPVT, LQTS, DCM
SCN5A	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT	AD, AR	ARVC/ARVC-like disease, BrS, DCM, HB, LQTS, SIDS, SSS

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; SCD - Sudden cardiac death; SIDS – Sudden infant death syndrome; SQTS – Short QT syndrome; SSS – Sick sinus syndrome

References:

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