Brugada Syndrome Panel

Panel Gene List:

ABCC9, CACNA1C, CACNA2D1, CACNB2, GPD1L, HCN4, KCND3, KCNE3, KCNH2, KCNJ8, PKP2, SCN10A, SCN1B, SCN2B, SCN3B, SCN5A, TRPM

Clinical Features:

Brugada syndrome (BrS) is a genetic heart dis order due to abnormal ion channel function characterized by ST segment elevation on ECG (leads V1-3) in the absence of structural heart disease.[1-3] It is associated with increased risk for syncope, ventricular tachyarrhythmia and sudden cardiac death. In individuals with an apparently normal heart, Brugada syndrome accounts for up to 20% of unexpected sudden deaths and is suspected to account for 4-12% of all unexpected sudden deaths.[4] Brugada syndrome occurs worldwide and is estimated to affect 5 per 10,000 individuals of all ethnicities, with some regional differences.[3]

The diagnosis of BrS is based on clinical history, ECG findings, and family history. Typically, the disorder manifests in patients between ages 20 to 40, but symptoms have been reported from infancy through late life. Most individuals with BrS are asymptomatic. The most common clinical symptoms are syncope and cardiac arrest that occur at rest, during sleep, or with high fever. In some patients, symptoms of BrS will develop after taking certain medications such as sodium channel blockers. Sudden cardiac death may occur without preceding symptoms and without an identifiable cause at autopsy.

Additionally, many symptoms of BrS are similar to those of other heart conditions, such as arrhythmogenic right ventricular cardiomyopathy (ARVC), atypical right bundle branch block, left ventricular hypertrophy, early repolarization, acute myocardial infarction, and acute pericarditis.

Inheritance Pattern/Genetics:

Autosomal Dominant

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 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

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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 BrS 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. For the CACNA1C, sequencing of exons 1-42 only. For PKP2, sequencing of exon 6 is not performed. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: HCN4 and *SCN1B gene(s),* only whole gene deletions or duplications may be detected.; SCN5A gene, exon level coverage for exons 2-12 and 21-28 only.

Gene	Protein	Inheritance	Disease Association(s)
ABCC9	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 9	AD	DCM, BrS, ERS, Cantu syndrome and related disorders
CACNA1C	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, L TYPE, ALPHA-1C SUBUNIT	AD	BrS (with short QTc), Timothy syndrome, LQTS
CACNA2D1	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, ALPHA-2/DELTA SUBUNIT 1	AD	BrS, Epilepsy
CACNB2	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, BETA-2 SUBUNIT	AD	BrS (with short QTc)
GPD1L	GLYCEROL-3-PHOSPHATE DEHYDROGENASE 1-LIKE	AD	BrS
HCN4	HYPERPOLARIZATION-ACTIVATED CYCLIC NUCLEOTIDE-GATED POTASSIUM CHANNEL 4	AD	BrS, SSS, AF, AV block, Bradycardia, Tachycardia, LVNC
KCND3	POTASSIUM CHANNEL, VOLTAGE-GATED, SHAL-RELATED SUBFAMILY, MEMBER 3	AD	BrS, AF, SIDS, Spinocerebellar ataxia
KCNH2 (HERG)	POTASSIUM CHANNEL, VOLTAGE-GATED, SUBFAMILY H, MEMBER 2	AD	BrS, LQTS, SQTS
KCNE3	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED SUBFAMILY, MEMBER 3	AD	BrS
KCNJ8	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 8	AD	BrS, VF, SIDS, Cantu syndrome
PKP2	PLAKOPHILIN 2	AD	ARVC, BrS
SCN1B	SODIUM CHANNEL, VOLTAGE-GATED, TYPE I, BETA SUBUNIT	AD	BrS, CCD, Epilepsy
SCN2B	SODIUM CHANNEL, VOLTAGE-GATED, TYPE II, BETA SUBUNIT	AD	BrS, AF

SCN3B	SODIUM CHANNEL, VOLTAGE-GATED, TYPE III, BETA SUBUNIT	AD	BrS, AF, VF, SIDS
SCN5A	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT	AD, AR	BrS, ARVC/ARVC-like disease, DCM, HB, LQTS, SIDS, SSS
SCN10A	SODIUM CHANNEL, VOLTAGE-GATED, TYPE X, ALPHA SUBUNIT	AD	BrS, LQTS, AF, painful small-fiber peripheral neuropathy
TRPM4	TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL, SUBFAMILY M, MEMBER 4	AD	HB, BrS

Abbreviations: AD – Autosomal dominant; AF – Atrial fibrillation; AR – Autosomal recessive; ARVC- Arrhythmogenic right ventricular cardiomyopathy; AV – Atrioventricular; BrS – Brugada syndrome; CCD – Cardiac conduction defect; DCM – Dilated cardiomyopathy; ERS – Early repolarization syndrome; HB – Heart block; LQTS – Long QT syndrome; SIDS – Sudden infant death syndrome; SSS – Sick sinus syndrome; SIDS – Sudden infant death syndrome; VF – Ventricular fibrillation

References:

1. Brugada R, Campuzano O, Brugada P, et al. Brugada Syndrome. 2005 Mar 31 [Updated 2014 Apr 10]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1517/
2. Hedley et al. (2009) Human Mutation 30 (9):1256-66 (PMID: 19606473)
3. Fowler et al. (2009) Current Opinion In Cardiology 24 (1):74-81 (PMID: 19102039)
4. Antzelevitch et al. (2002) Circ. Res. 91 (12):1114-8 (PMID: 12480811)

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