Arrhythmia Panel

Panel Gene List: *ABCC9, AKAP9, ANK2, CACNA1C, CACNA2D1, CACNB2, CALM1, CALM2, CALM3, CASQ2, CAV3, CTNNA3, DES, DSC2, DSG2, DSP, FLNC, GATA4, GATA5, GATA6, GJA5, GNB5, GPD1L, HCN4, JUP, KCNA5, KCND3, KCNE1, KCNE2, KCNE3, KCNE1L (KCNE5), KCNH2 (HERG), KCNJ2, KCNJ5, KCNJ8, KCNQ1, LDB3, LMNA, MYL4, NKX2-5, PKP2, PLN, PPA2, RANGRF, RYR2, SCN10A, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SNTA1, TECRL, TGFB3, TMEM43, TRDN, TRPM4, TTN*

Additional genes from our cardiology test menu may be added to this panel by selecting test code 695C.

Clinical Features:

Cardiac arrhythmias occur due to disruption of the heart's natural rhythm. Several risk factors can predispose an individual to develop an arrhythmia, including genetic disorders, trauma, electrolyte imbalance and structural abnormalities of the heart. There are several different genetic arrhythmia disorders. **Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC)** affects the cardiac desmosome, which is a protein complex that maintains cell-to-cell connections and provides mechanical attachments between adjacent cells. ARVC is characterized by myocyte death and replacement by fat and fibrous tissue in the right ventricle, predisposing to ventricular tachyarrhythmia and sudden cardiac death.[1,2] **Brugada syndrome (BrS)** is caused by abnormal ion channel function and is characterized by ST segment elevation on ECG (leads V1-3) in the absence of structural heart disease. BrS is associated with increased risk for syncope, ventricular tachyarrhythmia and sudden cardiac death.[3-5] **Catecholaminergic polymorphic ventricular tachycardia (CPVT)** is characterized by cardiac calcium channel dysfunction that is precipitated by stress-induced release of catecholamines.[6-8] **Long QT syndrome (LQTS)** is characterized by prolongation of the QT interval on ECG and is associated with increased risk for syncope, ventricular arrhythmia, and sudden cardiac death in individuals with normal heart structure.[9-11] **Short QT syndrome (SQTS)** is characterized by shortening of the QT interval on ECG and paroxysmal atrial and ventricular tachyarrhythmias, and is associated with an increased risk of atrial fibrillation and sudden cardiac death.[12-14] Genetic predisposition to a cardiac arrhythmia may occur as an isolated feature or may be part of a multisystemic disorder, such as Jervell and Lange-Nielsen syndrome, Timothy syndrome, Andersen-Tawil syndrome, Naxos disease, Carvajal syndrome and muscular dystrophy.[1,15-18]

Inheritance Pattern/Genetics: Autosomal Dominant, Autosomal recessive, or X-linked

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, only the KCNQ1-binding domains including Ser1570 residue for AKAP9, and excluding exon 6 of the PKP2 gene and the following genomic regions of the TTN gene:

chr2:179527692-179527782, 179523898-179523982, 179523731-179523815). 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. Reported clinically significant variants are confirmed by an appropriate orthogonal method. 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 Combined Cardiac Panel is available as a separate test if the Arrhythmia Panel is negative.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in the Arrhythmia Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined arrhythmia 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 specific exclusions for exon-level deletion/duplication testing for this panel are: CALM1, GATA5, and SCN1B only whole gene deletions or duplications may be detected.

Gene	Protein	Inheritance	Disease Association(s)
ABCC9	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 9	AD	DCM, BrS, ERS, Cantu syndrome and related disorders,
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
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)
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, AR	HCM, LQTS, LGMD, Rippling muscle disease, Tateyama-type distal myopathy, SIDS

Gene (cont.)	Protein	Inheritance	Disease Association(s)
CTNNA3	CATENIN ALPHA 3	AD	ARVC
DES	DESMIN	AD, AR	ARVC, AV block, DCM, myopathy, LGMD
DSC2	DESMOCOLLIN 2	AD, AR	ARVC, ARVC+ skin/hair findings, DCM
DSG2	DESMOGLEIN 2	AD	ARVC, DCM
DSP	DESMOPLAKIN	AD, AR	ARVC, DCM, Carvajal syndrome and related disorders
FLNC	FILAMIN C	AD	RCM, HCM, DCM, ARVC, myopathy
GATA4	GATA-BINDING PROTEIN 4	AD	AF, CHD, cardiomyopathy, SUDS
GATA5	GATA-BINDING PROTEIN 5	AD	AF, CHD, cardiomyopathy
GATA6	GATA-BINDING PROTEIN 6	AD	AF, CHD, pancreatic agenesis, diaphragmatic hernia, diabetes, cardiomyopathy
GJA5	GAP JUNCTION PROTEIN, ALPHA-5	AD	AF, HB, SADS, SIDS, CHD
GNB5	GUANINE NUCLEOTIDE-BINDING PROTEIN, BETA-5	AR	Intellectual developmental disorder with cardiac arrhythmia
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
JUP	JUNCTION PLAKOGLOBIN	AD, AR	ARVC, Naxos disease and related disorders
KCNA5	POTASSIUM CHANNEL, VOLTAGE-GATED, SHAKER-RELATED SUBFAMILY, MEMBER 5	AD	AF
KCND3	POTASSIUM CHANNEL, VOLTAGE-GATED, SHAL-RELATED SUBFAMILY, MEMBER 3	AD	BrS, AF, SIDS, Spinocerebellar ataxia
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, Arrhythmia
KCNE3	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED SUBFAMILY, MEMBER 3	AD	BrS
KCNE1L (KCNE5)	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED FAMILY, MEMBER 1-LIKE	XL	AF, VF
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
KCNJ5	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 5	AD	LQTS, Hyperaldosteronism
KCNJ8	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 8	AD	BrS, VF, SIDS, Cantu syndrome
KCNQ1	POTASSIUM CHANNEL, VOLTAGE-GATED, KQT-LIKE SUBFAMILY, MEMBER 1	AD, AR	JLNS, LQTS, SQTS, AF
LDB3	LIM DOMAIN-BINDING 3	AD	ARVC, DCM, LVNC, LDB3-related myopathies
LMNA	LAMIN A/C	AD, AR	ARVC/ARVC-like disease, DCM, HCM, LMNA-related neuromuscular, lipodystrophy, and premature aging disorders
MYL4	MYOSIN, LIGHT CHAIN 4, ALKALI, ATRIAL, EMBRYONIC	AD, AR	AF
NKX2-5	NK2 HOMEOBOX 5	AD	CHD, CCD
PKP2	PLAKOPHILIN 2	AD	ARVC, BrS
PLN	PHOSPHOLAMBAN	AD	ARVC , DCM, HCM
PPA2	PYROPHOSPHATASE, INORGANIC, 2	AR	SCD, mitochondrial disease

Gene (cont.)	Protein	Inheritance	Disease Association(s)
RANGRF	RAN GUANINE NUCLEOTIDE RELEASE FACTOR	AD	BrS, histiocytoid cardiomyopathy
RYR2	RYANODINE RECEPTOR 2	AD	ARVC, CPVT, LQTS, DCM, SCD, SUDS
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
SCN4B	SODIUM CHANNEL, VOLTAGE-GATED, TYPE IV, BETA SUBUNIT	AD	LQTS, AF
SCN5A	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT	AD, AR	ARVC/ARVC-like disease, BrS, DCM, HB, LQTS, SIDS, SSS
SCN10A	SODIUM CHANNEL, VOLTAGE-GATED, TYPE X, ALPHA SUBUNIT	AD	BrS, LQTS, AF, painful small-fiber peripheral neuropathy
SNTA1	SYNTROPHIN, ALPHA-1	AD	LQTS
TECRL	TRANS-2,3-ENOYL-CoA REDUCTASE-LIKE PROTEIN	AR	CPVT3
TGFB3	TRANSFORMING GROWTH FACTOR, BETA-3	AD	ARVC, Loeys-Dietz syndrome-5
TMEM43	TRANSMEMBRANE PROTEIN 43	AD	ARVC, EDMD
TRDN	TRIADIN	AR	CPVT, LQTS
TRPM4	TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL, SUBFAMILY M, MEMBER 4	AD	HB, BrS, CCD
TTN	TITIN	AD, AR	ARVC, DCM, TTN-related myopathies and muscular dystrophies

Abbreviations: AD – Autosomal dominant; AF – Atrial fibrillation; AR – Autosomal recessive; ARVC- Arrhythmogenic right ventricular cardiomyopathy; AV – Atrioventricular; BrS – Brugada syndrome; CCD – Cardiac conduction defect; CHD – Congenital heart defects; CPVT – Catecholaminergic polymorphic ventricular tachycardia; DCM – Dilated cardiomyopathy; EDMD – Emery Dreifuss muscular dystrophy; ERS – Early repolarization syndrome; HB – Heart block; HCM – Hypertrophic cardiomyopathy; JLNS – Jervell and Lange-Nielsen syndrome; LD-ACM – left dominant arrhythmogenic cardiomyopathy; LGMD – Limb girdle muscular dystrophy; LVNC – left ventricular non-compaction; LQTS – Long QT syndrome; RCM – Restrictive cardiomyopathy; SADS – Sudden arrhythmia death syndrome; SCD - Sudden cardiac death; SIDS – Sudden infant death syndrome; SQTS – Short QT syndrome; SSS – Sick sinus syndrome; SUDEP – sudden unexpected death and epilepsy; SUDS – Sudden unexpected death syndrome; VF – Ventricular fibrillation; XL – X-linked

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