# 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*

## 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:

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 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 Combined Cardiac Panel is available as a separate test if the Arrhythmia 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; *TTN*, sequencing of exons 1-171 and 199-363 only. For *PKP2*, sequencing of exon 6 is not performed. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: *GATA5, HCN4* and *SCN1B* genes, 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, |
| *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 |
| *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 |

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| *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 |

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| *PKP2* | PLAKOPHILIN 2 | AD | ARVC, BrS |
| *PLN* | PHOSPHOLAMBAN | AD | ARVC , DCM, HCM |
| *PPA2* | PYROPHOSPHATASE, INORGANIC, 2 | AR | SCD, mitochondrial disease |
| *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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