

Combined Cardiac Panel

Panel Gene List: *ABCC9, ACTC1, ACTN2, AKAP9, ALMS1, ALPK3, ANK2, ANKRD1, BAG3, BRAF, CACNA1C, CACNA2D1, CACNB2, CALM1, CALM2, CALM3, CASQ2, CAV3, CHRM2, CRYAB, CSRP3, DES, DMD, DOLK, DSC2, DSG2, DSP, DTNA, EMD, FHL1, FKRP, FKTN, GATAD1, GLA, GPD1L, HCN4, HRAS, ILK, JPH2, JUP, KCND3, KCNE1, KCNE2, KCNE3, KCNE1L (KCNE5), KCNH2 (HERG), KCNJ2, KCNJ5, KCNJ8, KCNQ1, KRAS, LAMA4, LAMP2, LDB3, LMNA, MAP2K1, MAP2K2, MIB1, MTND1, MTND5, MTND6, MTTD, MTTG, MTTT, MTTI, MTTK, MTTL1, MTTL2, MTTM, MTTQ, MTTTS1, MTTTS2, MURC, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOZ2, MYPN, NEBL, NEXN, NKX2-5, NRAS, PDLIM3, PKP2, PLN, PRDM16, PRKAG2, PTPN11, RAF1, RANGRF, RBM20, RIT1, RYR2, SCN10A, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SGCD, SNTA1, SOS1, TAZ, TCAP, TGFB3, TMEM43, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TRDN, TRPM4, TTN, TTR, TXNRD2, VCL*

Additional genes from our cardiology test menu may be added to this panel by selecting test code 935C.

Clinical Features:

Cardiac arrhythmias occur due to disruption of the heart's natural rhythm and cardiomyopathy is defined as disease of the heart muscle. In some individuals or families, the clinical picture may be complex or features of both these conditions may be present, in which case a broader approach to genetic testing may be helpful. Both phenotypes are genetically heterogeneous and have many different clinical presentations.

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 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.^{1,12-15}

Several risk factors may also contribute towards development of a cardiomyopathy, including genetic disorders, hypertension, ischemic heart disease and infection. There are several different genetic cardiomyopathies. **Hypertrophic cardiomyopathy (HCM)** is characterized by myocardial hypertrophy and myocyte disarray in the absence of other cardiac or systemic causes.¹⁶⁻¹⁸ **Dilated cardiomyopathy (DCM)** usually presents with one or more of the following: i) heart failure with symptoms of congestion (edema, orthopnea or paroxysmal dyspnea), ii) reduced cardiac output resulting in fatigue or dyspnea on exertion, arrhythmias and/or conduction system disease and iii) thromboembolic disease or stroke, mainly from left ventricular mural thrombus. However, some individuals with a DCM pathogenic variant may also be asymptomatic.^{15,19} **Left ventricular non-compaction (LVNC)** is characterized by abnormal trabeculations in the left ventricle, most frequently at the apex, and can share the same clinical presentation as DCM, ranging from asymptomatic disease to progressive deterioration of cardiac function, arrhythmias, thromboembolic events, or sudden cardiac death.^{19,20} **Noonan syndrome (NS)** is a relatively common multi-system disorder that may include HCM, facial dysmorphism, congenital heart defects, short stature, skeletal malformations, motor delay, learning disabilities, and impaired blood clotting ability.²¹ Cardiomyopathy can also be a presenting feature of other inherited disorders, such as Danon disease, Fabry disease, mitochondrial myopathy, or muscular dystrophy¹⁵⁻¹⁹.

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

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the 120 genes (Only exons 1-44 for *CACNA1C*, only the *KCNQ1*-binding domains including Ser1570 residue for *AKAP9*, excluding exon 6 of the *PKP2* gene and the following genomic regions of the *TTN* gene: chr2:179527692-179527782, 179523898-179523982, 179523731-179523815) are enriched using a proprietary targeted capture system developed by GeneDx. These targeted regions are sequenced simultaneously by massively parallel (NextGen) sequencing on an Illumina platform with paired-end reads. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing is used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 15 reads are achieved by NextGen sequencing. Concurrent deletion/duplication testing is performed for the genes in the panel using exon-level oligo array CGH (ExonArrayDx), except for *CALM1*, *HRAS*, *FKRP*, and the 14 mitochondrial genes. *EMD*, *KCNE1L* (*KCNE5*), *SCN1B* and *TAZ* have gene level resolution; exon level events may not be detected. Data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. The array is designed to detect most intragenic deletions

and duplications. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat array CGH analysis. Sequence and array CGH alterations are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Benign and likely benign variants, if present, are not included in this report but are available upon request.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the 120 genes included in the Combined Cardiac Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined cardiomyopathy and/or arrhythmia and a family history of disease. The technical sensitivity of the sequencing test is estimated to be 98%. The sequencing panel will not reliably detect deletions, insertions, or rearrangements greater than or equal to five base pairs (bp). Deletions or duplications of less than 500 bp are not reliably detected by array CGH.

Gene	Protein	Inheritance	Disease Association(s)
<i>ABCC9</i>	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 9	AD	DCM, BrS, Cantu syndrome and related disorders
<i>ACTC1</i>	ACTIN, ALPHA, CARDIAC MUSCLE	AD	CHD, DCM, HCM, LVNC
<i>ACTN2</i>	ACTININ, ALPHA-2	AD	DCM, HCM
<i>AKAP9</i>	A-KINASE ANCHOR PROTEIN 9	AD	LQTS
<i>ALMS1</i>	CENTROSOME AND BASAL BODY ASSOCIATED PROTEIN	AR	Alstrom syndrome, infantile DCM
<i>ALPK3</i>	ALPHA-KINASE 3	AR	Pediatric Cardiomyopathy
<i>ANK2</i>	ANKYRIN 2	AD	Arrhythmia, LQTS
<i>ANKRD1</i>	ANKYRIN REPEAT DOMAIN-CONTAINING PROTEIN 1	AD	HCM, DCM
<i>BAG3</i>	BCL2-ASSOCIATED ATHANOGENE 3	AD	DCM, myofibrillar myopathy
<i>BRAF</i>	V-RAF MURINE SARCOMA VIRAL ONCOGENE HOMOLOG B1	AD	Noonan/CFC/Costello
<i>CACNA1C</i>	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, L TYPE, ALPHA-1C SUBUNIT	AD	BrS, Timothy syndrome, LQTS
<i>CACNA2D1</i>	CALCIUM CHANNEL, VOLTSGE-DEPENDENT ALPHA-2/DELTA SUBUNIT 1	AD	BrS
<i>CACNB2</i>	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, BETA-2 SUBUNIT	AD	BrS
<i>CALM1</i>	CALMODULIN 1	AD	LQTS, CPVT
<i>CALM2</i>	CALMODULIN 2	AD	LQTS, CPVT
<i>CALM3</i>	CALMODULIN 3	AD	LQTS, CPVT
<i>CASQ2</i>	CALSEQUESTRIN 2	AR	CPVT
<i>CAV3</i>	CAVEOLIN 3	AD, AR	HCM, LQTS, LGMD, Tateyama-type distal myopathy, SIDS, rippling muscle disease
<i>CHRM2</i>	M2-MUSCARINIC ACETYLCHOLINE RECEPTOR	AD	DCM
<i>CRYAB</i>	CRYSTALLIN, ALPHA-B	AD, AR	DCM, myofibrillar myopathy
<i>CSRP3</i>	CYSTEINE- AND GLYCINE-RICH PROTEIN 3	AD	HCM, DCM
<i>DES</i>	DESMIN	AD	DCM, ARVC, myopathy, AV block, LGMD
<i>DMD</i>	DYSTROPHIN	XL	DMD, BMD, DCM
<i>DOLK</i>	DOLICHOL KINASE	AR	DCM, congenital disorder of glycosylation type Im
<i>DSC2</i>	DESMOCOLLIN	AD, AR	ARVC, ARVC+skin and hair findings, DCM
<i>DSG2</i>	DESMOGLEIN	AD	ARVC, DCM
<i>DSP</i>	DESMOPLAKIN	AD, AR	ARVC, DCM, Carvajal syndrome
<i>DTNA</i>	DYSTROBREVIN, ALPHA	AD	LVNC, CHD

Gene (cont.)	Protein	Inheritance	Disease Association(s)
<i>EMD</i>	EMERIN	XL	EMD
<i>FHL1</i>	FOUR-AND-A-HALF LIM DOMAINS 1	XL	HCM, LVH, EMD, skeletal muscle, muscle hypertrophy, Myofibrillar myopathy
<i>FKRP</i>	FUKUTIN RELATED PROTEIN	AR	DCM, muscular dystrophy
<i>FKTN</i>	FUKUTIN	AR	DCM, LGMD, Fukuyama Congenital Muscular Dystrophy
<i>GATAD1</i>	GATA ZINC FINGER DOMAIN-CONTAINING PROTEIN 1	AR	DCM
<i>GLA</i>	GALACTOSIDASE, ALPHA	XL	Fabry disease
<i>GDPII</i>	GLYCEROL-3-PHOSPHATE DEHYDROGENASE 1-LIKE	AD	BrS
<i>HCN4</i>	HYPERPOLARIZATION-ACTIVATED CYCLIC NUCLEOTIDE-GATED POTASSIUM CHANNEL 4	AD	BrS, SSS
<i>HRAS</i>	V-HA-RAS HARVEY RAT SARCOMA VIRAL ONCOGENE HOMOLOG	AD	Costello syndrome
<i>ILK</i>	INTEGRIN-LINKED KINASE	AD	DCM
<i>JPH2</i>	JUNCTOPHILIN 2	AD	HCM
<i>JUP</i>	JUNCTION PLAKOGLOBIN	AD, AR	ARVC, Naxos Disease
<i>KCND3</i>	POTASSIUM CHANNEL, VOLTAGE-GATED, SHAL-RELATED SUBFAMILY, MEMBER 3	AD	BrS, SIDS, Spinocerebellar ataxia
<i>KCNE1</i>	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED SUBFAMILY, MEMBER 1	AD, AR	LQTS, JLNS
<i>KCNE2</i>	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED SUBFAMILY, MEMBER 2	AD	LQTS
<i>KCNE3</i>	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED SUBFAMILY, MEMBER 3	AD	BrS
<i>KCNE1L (KCNE5)</i>	POTASSIUM CHANNEL, VOLTAGE-GATED, ISK-RELATED FAMILY, MEMBER 1-LIKE	XL	BrS, AF, VF
<i>KCNH2 (HERG)</i>	POTASSIUM CHANNEL, VOLTAGE-GATED, SUBFAMILY H, MEMBER 2	AD	LQTS, SQTS
<i>KCNJ2</i>	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 2	AD	Andersen-Tawil syndrome, SQTS
<i>KCNJ5</i>	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 5	AD	LQTS
<i>KCNJ8</i>	POTASSIUM CHANNEL, INWARDLY RECTIFYING, SUBFAMILY J, MEMBER 8	AD	ERS, SIDS
<i>KCNQ1</i>	POTASSIUM CHANNEL, VOLTAGE-GATED, KQT-LIKE SUBFAMILY, MEMBER 1	AD, AR	JLNS, LQTS, SQTS
<i>KRAS</i>	V-KI-RAS2 KIRSTEN RAT SARCOMA VIRAL ONCOGENE HOMOLOG	AD	Noonan/CFC/Costello
<i>LAMA4</i>	LAMININ, ALPHA-4	AD	DCM
<i>LAMP2</i>	LYSOSOME-ASSOCIATED MEMBRANE PROTEIN 2	XL	Danon disease
<i>LDB3</i>	LIM DOMAIN-BINDING 3	AD	DCM, LVNC, myopathy
<i>LMNA</i>	LAMIN A/C	AD, AR	DCM, , congenital muscular dystrophy, EMD, ARVC
<i>MAP2K1</i>	MITOGEN-ACTIVATED PROTEIN KINASE KINASE 1	AD	Noonan/CFC/Costello
<i>MAP2K2</i>	MITOGEN-ACTIVATED PROTEIN KINASE KINASE 2	AD	Noonan/CFC/Costello
<i>MIB1</i>	MINDBOMB E3 UBIQUITIN PROTEIN LIGASE 1	AD	LVNC
<i>MTND1</i>	mtDNA ENCODED COMPLEX I, SUBUNIT ND1	MITO	Cardiomyopathy, myopathy
<i>MTND5</i>	mtDNA ENCODED COMPLEX I, SUBUNIT ND5	MITO	Cardiomyopathy, myopathy
<i>MTND6</i>	mtDNA ENCODED COMPLEX I, SUBUNIT ND6	MITO	Cardiomyopathy, myopathy
<i>MTTD</i>	MITOCHONDRIAL tRNA FOR ASPARTIC ACID	MITO	Cardiomyopathy, myopathy
<i>MTTG</i>	MITOCHONDRIAL tRNA FOR GLYCINE	MITO	Cardiomyopathy, myopathy
<i>MTTH</i>	MITOCHONDRIAL tRNA FOR HISTIDINE	MITO	Cardiomyopathy, myopathy
<i>MTTI</i>	MITOCHONDRIAL tRNA FOR ISOLEUCINE	MITO	Cardiomyopathy, myopathy
<i>MTTK</i>	MITOCHONDRIAL tRNA FOR LYSINE	MITO	Cardiomyopathy, myopathy
<i>MTTL1</i>	MITOCHONDRIAL tRNA FOR LEUCINE 1	MITO	Cardiomyopathy, myopathy

Gene (cont.)	Protein	Inheritance	Disease Association(s)
<i>MTTL2</i>	MITOCHONDRIAL tRNA FOR LEUCINE 2	MITO	Cardiomyopathy, myopathy
<i>MTTM</i>	MITOCHONDRIAL tRNA FOR METHIONINE	MITO	Cardiomyopathy, myopathy
<i>MTTQ</i>	MITOCHONDRIAL tRNA FOR GLUTAMINE	MITO	Cardiomyopathy, myopathy
<i>MTTS1</i>	MITOCHONDRIAL tRNA FOR SERINE 1	MITO	Cardiomyopathy, myopathy
<i>MTTS2</i>	MITOCHONDRIAL tRNA FOR SERINE 2	MITO	Cardiomyopathy, myopathy
<i>MURC</i>	MUSCLE-RELATED COILED-COIL PROTEIN	AD	DCM
<i>MYBPC3</i>	MYOSIN-BINDING PROTEIN C, CARDIAC	AD	HCM, DCM
<i>MYH6</i>	MYOSIN, HEAVY CHAIN 6, CARDIAC MUSCLE, ALPHA	AD	CHD, DCM, HCM, SSS
<i>MYH7</i>	MYOSIN, HEAVY CHAIN 7, CARDIAC MUSCLE, BETA	AD	DCM, HCM, myopathy
<i>MYL2</i>	MYOSIN, LIGHT CHAIN 2, REGULATORY, CARDIAC, SLOW	AD	HCM
<i>MYL3</i>	MYOSIN, LIGHT CHAIN 3, ALKALI, VENTRICULAR, SKELETAL, SLOW	AD, AR	HCM
<i>MYLK2</i>	MYOSIN LIGHT CHAIN KINASE 2	AD	HCM
<i>MYOZ2</i>	MYOZENIN 2	AD	HCM
<i>MYPN</i>	MYOPALLADIN	AD	DCM, RCM, HCM
<i>NEBL</i>	NEBULETTE	AD	DCM, endocardial fibroelastosis
<i>NEXN</i>	NEXILIN	AD	DCM, HCM
<i>NKX2-5</i>	NK2 HOMEODOMAIN 5	AD	CHD, CCD
<i>NRAS</i>	NEUROBLASTOMA RAS VIRAL ONCOGENE HOMOLOG	AD	Noonan/CFC/Costello
<i>PDLIM3</i>	PDZ AND LIM DOMAIN PROTEIN 3	AD	HCM, DCM
<i>PKP2</i>	PLAKOPHILIN 2	AD	ARVC, DCM, BrS
<i>PLN</i>	PHOSPHOLAMBAN	AD	DCM, HCM, ARVC
<i>PRDM16</i>	PR DOMAIN CONTAINING 16	AD	DCM, LVNC
<i>PRKAG2</i>	PROTEIN KINASE, AMP-ACTIVATED, NONCATALYTIC, GAMMA2	AD	HCM, Wolff-Parkinson-White syndrome
<i>PTPN11</i>	PROTEIN-TYROSINE PHOSPHATASE, NONRECEPTOR-TYPE 11	AD	Noonan/CFC/Costello
<i>RAF1</i>	V-RAF-1 MURINE LEUKEMIA VIRAL ONCOGENE HOMOLOG 1	AD	Noonan/CFC/Costello
<i>RBM20</i>	RNA-BINDING MOTIF PROTEIN 20	AD	DCM
<i>RIT1</i>	RAS-LIKE WITHOUT CAAX 1	AD	Noonan
<i>RANGRF</i>	RAN GUANINE NUCLEOTIDE RELEASE FACTOR	AD	BrS
<i>RYR2</i>	RYANODINE RECEPTOR 2	AD	ARVC, CPVT, LQTS
<i>SCN10A</i>	SODIUM CHANNEL, VOLTAGE-GATED, TYPE X, ALPHA SUBUNIT	AD	BrS
<i>SCN1B</i>	SODIUM CHANNEL, VOLTAGE-GATED, TYPE I, BETA SUBUNIT	AD, AR	BrS, Cardiac conduction disease
<i>SCN2B</i>	SODIUM CHANNEL, VOLTAGE-GATED, TYPE II, BETA SUBUNIT	AD	BrS, AF
<i>SCN3B</i>	SODIUM CHANNEL, VOLTAGE-GATED, TYPE III, BETA SUBUNIT	AD	BrS, AF, VF, SIDS
<i>SCN4B</i>	SODIUM CHANNEL, VOLTAGE-GATED, TYPE IV, BETA SUBUNIT	AD	LQTS
<i>SCN5A</i>	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT	AD, AR	BrS, DCM, Heart block, LQTS, SSS, SIDS
<i>SGCD</i>	SARCOGLYCAN, DELTA	AD, AR	DCM, LGMD
<i>SNTA1</i>	ALPHA SYNTROPHIN	AD	LQTS
<i>SOS1</i>	SON OF SEVENLESS, DROSOPHILA, HOMOLOG 1	AD	Noonan/CFC/Costello
<i>TAZ</i>	TAFAZZIN	XL	DCM, LVNC, Barth syndrome
<i>TCAP</i>	TITIN-CAP (TELETHONIN)	AD, AR	HCM, DCM, LGMD
<i>TGFB3</i>	TRANSFORMING GROWTH FACTOR BETA 3	AD	ARVC, Loeys-Dietz syndrome
<i>TMEM43</i>	TRANSMEMBRANE PROTEIN 43	AD	ARVC, EMD
<i>TMPO</i>	THYMOPOIETIN	AD	DCM

Gene (cont.)	Protein	Inheritance	Disease Association(s)
<i>TNNC1</i>	TROPONIN C, SLOW	AD	DCM, HCM
<i>TNNI3</i>	TROPONIN I, CARDIAC	AD, AR	DCM, HCM, RCM
<i>TNNT2</i>	TROPONIN T2, CARDIAC	AD	DCM, HCM, RCM, LVNC
<i>TPM1</i>	TROPOMYOSIN 1	AD	DCM, HCM
<i>TRDN</i>	TRIADIN	AR	CPVT, LQTS
<i>TRPM4</i>	TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL, SUBFAMILY M, MEMBER 4	AD	HB, BrS
<i>TTN</i>	TITIN	AD	DCM, ARVC, TTN-related myopathies and muscular dystrophies
<i>TTR</i>	TRANSTHYRETIN	AD	TTR-related amyloidosis
<i>TXNRD2</i>	THIOREDOXIN REDUCTASE 2	AD, AR	DCM
<i>VCL</i>	VINCULIN	AD	HCM, DCM, LVNC

Abbreviations: AD- Autosomal dominant; AF- Atrial Fibrillation; AR- Autosomal recessive; ARVC – Arrhythmogenic Right Ventricular Cardiomyopathy; BMD – Becker Muscular Dystrophy; BrS – Brugada Syndrome; CHD – Congenital Heart Defects; CPVT – Catecholaminergic Polymorphic Ventricular Tachycardia; DCM – Dilated Cardiomyopathy; DMD- Duchenne Muscular Dystrophy; EMD – Emery Dreifuss Muscular Dystrophy; ERS-Early repolarization syndrome; HB- Heart Block; HCM – Hypertrophic Cardiomyopathy; JLNS – Jervell and Lange-Nielsen Syndrome; LGMD – Limb Girdle Muscular Dystrophy; LQTS – Long QT Syndrome; LVNC – Left Ventricular Non-Compaction; RCM – Restrictive Cardiomyopathy; SIDS – Sudden Infant Death Syndrome; SSS – Sick Sinus Syndrome; VF-Ventricular fibrillation; XL- X-linked

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