

Cardiomyopathy Panel

Panel Gene List: *ABCC9, ACTC1, ACTN2, ALMS1, ALPK3, ANKRD1, BAG3, BRAF, CAV3, CHRM2, CRYAB, CSRP3, DES, DMD, DOLK, DSC2, DSG2, DSP, DTNA, EMD, FHL1, FKRP, FKTN, GATAD1, GLA, HCN4, HRAS, ILK, JPH2, JUP, KRAS, LAMA4, LAMP2, LDB3, LMNA, MAP2K1, MAP2K2, MIB1, MTND1, MTND5, MTND6, MTTD, MTTG, MTTT, MTTI, MTTK, MTTL1, MTTL2, MTTM, MTTQ, MTTT1, MTTT2, MURC, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOZ2, MYPN, NEBL, NEXN, NKX2-5, NRAS, PDLIM3, PKP2, PLN, PRDM16, PRKAG2, PTPN11, RAF1, RBM20, RIT1, RYR2, SCN5A, SGCD, SOS1, TAZ, TCAP, TGFB3, TMEM43, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, TXNRD2, VCL*

Additional genes from our cardiology test menu may be added to this panel by selecting test code 694C.

Clinical Features:

Cardiomyopathy is defined as disease of the heart muscle and has many different presentations. **Hypertrophic cardiomyopathy (HCM)** is characterized by myocardial hypertrophy and myocyte disarray in the absence of other cardiac or systemic causes.¹⁻³ **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.^{4,5} **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.^{4,6} **Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC)** is a disorder that 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.^{7,8} **Noonan syndrome (NS)** is a relatively common multi-system disorder with features including HCM, facial dysmorphism, congenital heart defects, short stature, skeletal malformations, motor delay, learning disabilities, and impaired blood clotting ability.⁹ Cardiomyopathy can also be a presenting feature of other inherited disorders, such as Danon disease, Fabry disease, mitochondrial myopathy, or muscular dystrophy.¹⁻⁵

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 91 genes (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 the *HRAS* gene, the *FKRP* gene, and the 14 mitochondrial genes. The *EMD* and *TAZ* genes 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 91 genes included in the Cardiomyopathy 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 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, Cantu syndrome
<i>ACTC1</i>	ACTIN, ALPHA, CARDIAC MUSCLE	AD	CHD, DCM, HCM, LVNC
<i>ACTN2</i>	ACTININ, ALPHA-2	AD	Pediatric HCM/DCM
<i>ALMS1</i>	CENTROSOME AND BASAL BODY ASSOCIATED PROTEIN	AR	Alstrom syndrome, mitogenic cardiomyopathy
<i>ALPK3</i>	ALPHA KINASE 3	AR	HCM, DCM
<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 syndromes
<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
<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
<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

<i>EMD</i>	EMERIN	XL	EMD
Gene (cont.)	Protein	Inheritance	Disease Association(s)
<i>FHL1</i>	FOUR-AND-A-HALF LIM DOMAINS 1	XL	HCM, EMD, myofibrillar myopathy, reducing body myopathy
<i>FKRP</i>	FUKUTIN RELATED PROTEIN	AR	muscular dystrophy, dystroglycanopathies
<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>HCN4</i>	HYPERPOLARIZATION-ACTIVATED CYCLIC NUCLEOTIDE-GATED POTASSIUM CHANNEL 4	AD	LVNC, AF, AV block, bradycardia, BrS, sinus node dysfunction, tachycardia
<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>KRAS</i>	V-KI-RAS2 KIRSTEN RAT SARCOMA VIRAL ONCOGENE HOMOLOG	AD	Noonan/CFC/Costello syndromes
<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, HCM, congenital muscular dystrophy, EMD
<i>MAP2K1</i>	MITOGEN-ACTIVATED PROTEIN KINASE KINASE 1	AD	Noonan/CFC/Costello syndromes
<i>MAP2K2</i>	MITOGEN-ACTIVATED PROTEIN KINASE KINASE 2	AD	Noonan/CFC/Costello syndromes
<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
<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, AR	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 HOMEBOX 5	AD	CHD, CCD
<i>NRAS</i>	NEUROBLASTOMA RAS VIRAL ONCOGENE	AD	Noonan/CFC/Costello syndromes

Gene (cont.)	HOMOLOG Protein	Inheritance	Disease Association(s)
<i>PDLIM3</i>	PDZ AND LIM DOMAIN PROTEIN 3	AD	HCM, DCM
<i>PKP2</i>	PLAKOPHILIN 2	AD	ARVC
<i>PLN</i>	PHOSPHOLAMBAN	AD	DCM, HCM
<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 syndromes
<i>RAF1</i>	V-RAF-1 MURINE LEUKEMIA VIRAL ONCOGENE HOMOLOG 1	AD	Noonan/CFC/Costello syndromes
<i>RBM20</i>	RNA-BINDING MOTIF PROTEIN 20	AD	DCM
<i>RIT1</i>	RAS-LIKE WITHOUT CAAX 1	AD	Noonan syndrome
<i>RYR2</i>	RYANODINE RECEPTOR 2	AD	ARVC, CPVT, LQTS
<i>SCN5A</i>	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT	AD	BrS, DCM, Heart block, LQTS, SSS, SIDS
<i>SGCD</i>	SARCOGLYCAN, DELTA	AD, AR	DCM, LGMD
<i>SOS1</i>	SON OF SEVENLESS, DROSOPHILA, HOMOLOG 1	AD	Noonan/CFC/Costello syndromes
<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-5, TAAD
<i>TMEM43</i>	TRANSMEMBRANE PROTEIN 43	AD	ARVC, EMD
<i>TMPO</i>	THYMOPOIETIN	AD	DCM
<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>TTN</i>	TITIN	AD	DCM, myopathy
<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; AV block- Atrioventricular Block; BMD – Becker Muscular Dystrophy; BrS – Brugada Syndrome; CCD- Cardiac Conduction Disease; CHD – Congenital Heart Defects; CPVT – Catecholaminergic Polymorphic Ventricular Tachycardia; DCM – Dilated Cardiomyopathy; DMD – Duchenne Muscular Dystrophy; EMD – Emery Dreifuss Muscular Dystrophy; 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; TAAD- Thoracic Aortic Aneurysm and Dissection; XL – X-linked

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