

Cardiomyopathy Panel

Panel Gene List: ABCC9, ACTC1, ACTN2, AKAP9, ALMS1, ALPK3, ANKRD1, BAG3, BRAF, CAV3, CHRM2, CRYAB, CSRP3, CTNNA3, DES, DMD, DOLK, DSC2, DSG2, DSP, DTNA, EMD, EYA4, FHL1, FKRP, FKTN, FLNC, GAA, GATA4, GATAD1, GLA, HCN4, HFE, HRAS, ILK, JPH2, JUP, KRAS, LAMA4, LAMP2, LDB3, LMNA, LRRC10, 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, SHOC2, SOS1, TAZ, TBX20, TCAP, TGFB3, TMEM43, TMPO, TNNC1, TNNT1, TNNT2, TOR1AIP1, 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, Pompe disease, mitochondrial myopathy, or muscular dystrophy.^{1-5,10}

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

Test Methods:

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV) (excluding exon 6 of the *PKP2* gene, only the KCNQ1-binding domains including Ser1570 residue for AKAP9

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; 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. 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 Cardiomyopathy 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. For *FKRP*, *HRAS* and the mitochondrial genes, sequencing but not deletion/duplication analysis, is performed. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: *TAZ* and *TBX20* genes only whole gene deletions or duplications may be detected.

Gene	Protein	Inheritance	Disease Association(s)
<i>ABCC9</i>	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 9	AD	DCM, Brs, ERS, Cantu syndrome and related disorders
<i>ACTC1</i>	ACTIN, ALPHA, CARDIAC MUSCLE	AD	CHD, DCM, HCM, LVNC
<i>ACTN2</i>	ACTININ, ALPHA-2	AD	HCM, DCM
<i>AKAP9</i>	A-KINASE ANCHOR PROTEIN 9	AD	LQTS, cardiomyopathy
<i>ALMS1</i>	CENTROSOME AND BASAL BODY ASSOCIATED PROTEIN	AR	Alstrom syndrome, mitogenic cardiomyopathy, infantile DCM
<i>ALPK3</i>	ALPHA KINASE 3	AR	HCM, DCM
<i>ANKRD1</i>	ANKYRIN REPEAT DOMAIN-CONTAINING PROTEIN 1	AD	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	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>CTNNA3</i>	CATENIN ALPHA 3	AD	ARVC, Autism

Gene	Protein	Inheritance	Disease Association(s)
<i>DES</i>	DESMIN	AD, AR	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 1m
<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 and related disorders
<i>DTNA</i>	DYSTROBREVIN, ALPHA	AD	LVNC, CHD
<i>EMD</i>	EMERIN	XL	EMD
<i>EYA4</i>	EYES ABSENT, DROSOPHILA, HOMOLOG OF, 4	AD	DCM, Hearing loss
<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>FLNC</i>	FILAMIN C	AD	RCM, HCM, ARVC, DCM, myopathy
<i>GAA</i>	GLUCOSIDASE, ALPHA, ACID	AR	Pompe Disease (Glycogen storage disease II)
<i>GATA4</i>	GATA-BINDING PROTEIN 4	AD	AF, CHD, cardiomyopathy, SUDS
<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, SSS, tachycardia
<i>HFE</i>	HUMAN HEMOCHROMATOSIS PROTEIN (HFE)	AR	Hereditary hemochromatosis, cardiomyopathy
<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 and related disorders
<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, ARVC, LDB3-related myopathies
<i>LMNA</i>	LAMIN A/C	AD, AR	DCM, LMNA-related neuromuscular disorder, ARVC/ARVC-like disease, lipodystrophy, and premature aging disorders
<i>LRRC10</i>	LEUCINE-RICH REPEAT-CONTAINING PROTEIN 10	AD, AR	DCM
<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

Gene	Protein	Inheritance	Disease Association(s)
<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, muscle fiber disease
<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 syndromes
<i>PDLIM3</i>	PDZ AND LIM DOMAIN PROTEIN 3	AD	HCM, DCM
<i>PKP2</i>	PLAKOPHILIN 2	AD	ARVC, 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 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, DCM
<i>SCN5A</i>	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT	AD	DCM, ARVC/ARVC-like disease, BrS, Heart block, LQTS, SIDS, SSS
<i>SGCD</i>	SARCOGLYCAN, DELTA	AD, AR	DCM, LGMD
<i>SHOC2</i>	SOC-2 HOMOLOG	AD	Noonan-like syndrome with loose anagen hair
<i>SOS1</i>	SON OF SEVENLESS, DROSOPHILA, HOMOLOG 1	AD	Noonan/CFC/Costello syndromes
<i>TAZ</i>	TAFAZZIN	XL	DCM, LVNC, Barth syndrome
<i>TBX20</i>	T-BOX 20	AD	CHD, DCM, LVNC
<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	DCM, HCM, RCM
<i>TNNT2</i>	TROPONIN T2, CARDIAC	AD	DCM, HCM, RCM, LVNC
<i>TOR1AIP1</i>	TORSIN-1A-INTERACTING PROTEIN 1	AR	LGMD, Contractures, DCM
<i>TPM1</i>	TROPOMYOSIN 1	AD	DCM, HCM
<i>TTN</i>	TITIN	AD, AR	ARVC, DCM, TTN-related myopathies and muscular dystrophies
<i>TTR</i>	TRANSTHYRETIN	AD	TTR-related amyloidosis
<i>TXNRD2</i>	THIOREDOXIN REDUCTASE 2	AD, AR	DCM, glucocorticoid deficiency
<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; ERS- Early repolarization syndrome; 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

References:

1. Marian et al. (1995) Annual Review Of Medicine 46 :213-22 (PMID: 7598458)
2. Maron et al. (2002) JAMA : the journal of the American Medical Association 287 (10):1308-20 (PMID: 11886323)
3. Cirino AL, Ho C. Hypertrophic Cardiomyopathy Overview. 2008 Aug 5 [Updated 2014 Jan 16]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1768/>
4. Callis et al. (2010) Expert Review Of Molecular Diagnostics 10 (3):329-51 (PMID: 20370590)
5. Hershberger RE, Morales A. Dilated Cardiomyopathy Overview. 2007 Jul 27 [Updated 2015 Sep 24]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1309/>
6. Towbin et al. (2015) Lancet : (PMID: 25865865)
7. McNally E, MacLeod H, Dellefave-Castillo L. Arrhythmogenic Right Ventricular Cardiomyopathy. 2005 Apr 18 [Updated 2017 May 25]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1131/>
8. Nava et al. (2000) Journal Of The American College Of Cardiology 36 (7):2226-33 (PMID: 11127465)
9. Allanson JE, Roberts AE. Noonan Syndrome. 2001 Nov 15 [Updated 2016 Feb 25]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1124/#_NBK1124
10. Leslie N, Bailey L. Pompe Disease. 2007 Aug 31 [Updated 2017 May 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1261/>