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, MTTH, MTTI, MTTK, MTTL1, MTTL2, MTTM, MTTQ, MTTS1, MTTS2, 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, Autosomale 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)
ABCC9	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 9	AD	DCM, Cantu syndrome
ACTC1	ACTIN, ALPHA, CARDIAC MUSCLE	AD	CHD, DCM, HCM, LVNC
ACTN2	ACTININ, ALPHA-2	AD	Pediatric HCM/DCM
ALMS1	CENTROSOME AND BASAL BODY ASSOCIATED PROTEIN	AR	Alstrom syndrome, mitogenic cardiomyopathy
ALPK3	ALPHA KINASE 3	AR	HCM, DCM
ANKRD1	ANKYRIN REPEAT DOMAIN-CONTAINING PROTEIN 1	AD	HCM, DCM
BAG3	BCL2-ASSOCIATED ATHANOGENE 3	AD	DCM, myofibrillar myopathy
BRAF	V-RAF MURINE SARCOMA VIRAL ONCOGENE HOMOLOG B1	AD	Noonan/CFC/Costello syndromes
CAV3	CAVEOLIN 3	AD, AR	HCM, LQTS, LGMD, Tateyama-type distal myopathy, SIDS, rippling muscle disease
CHRM2	M2-MUSCARINIC ACETYLCHOLINE RECEPTOR	AD	DCM
CRYAB	CRYSTALLIN, ALPHA-B	AD, AR	DCM, myofibrillar myopathy
CSRP3	CYSTEINE- AND GLYCINE-RICH PROTEIN 3	AD	HCM, DCM
DES	DESMIN	AD	DCM, ARVC, myopathy, AV block
DMD	DYSTROPHIN	XL	DMD, BMD, DCM
DOLK	DOLICHOL KINASE	AR	DCM, congenital disorder of glycosylation type Im
DSC2	DESMOCOLLIN	AD, AR	ARVC, ARVC+skin and hair findings
DSG2	DESMOGLEIN	AD	ARVC, DCM
DSP	DESMOPLAKIN	AD, AR	ARVC, DCM, Carvajal syndrome
DTNA	DYSTROBREVIN, ALPHA	AD	LVNC, CHD

Gene (cont.)	Protein	Inheritance	Disease Association(s)
EMD	EMERIN	XL	EMD
FHL1	FOUR-AND-A-HALF LIM DOMAINS 1	XL	HCM, EMD, myofibrillar myopathy, reducing body myopathy
FKRP	FUKUTIN RELATED PROTEIN	AR	muscular dystrophy, dystroglycanopathies
FKTN	FUKUTIN	AR	DCM, LGMD, Fukuyama Congenital Muscular Dystrophy
GATAD1	GATA ZINC FINGER DOMAIN-CONTAINING PROTEIN 1	AR	DCM
GLA	GALACTOSIDASE, ALPHA	XL	Fabry disease
HCN4	HYPERPOLARIZATION-ACTIVATED CYCLIC NUCLEOTIDE-GATED POTASSIUM CHANNEL 4	AD	LVNC, AF, AV block, bradycardia, BrS, sinus node dysfunction, tachycardia
HRAS	V-HA-RAS HARVEY RAT SARCOMA VIRAL ONCOGENE HOMOLOG	AD	Costello syndrome
ILK	INTEGRIN-LINKED KINASE	AD	DCM
JPH2	JUNCTOPHILIN 2	AD	HCM
JUP	JUNCTION PLAKOGLOBIN	AD, AR	ARVC, Naxos Disease
KRAS	V-KI-RAS2 KIRSTEN RAT SARCOMA VIRAL ONCOGENE HOMOLOG	AD	Noonan/CFC/Costello syndromes
LAMA4	LAMININ, ALPHA-4	AD	DCM
LAMP2	LYSOSOME-ASSOCIATED MEMBRANE PROTEIN 2	XL	Danon disease
LDB3	LIM DOMAIN-BINDING 3	AD	DCM, LVNC, myopathy
LMNA	LAMIN A/C	AD, AR	DCM, HCM, congenital muscular dystrophy, EMD
MAP2K1	MITOGEN-ACTIVATED PROTEIN KINASE KINASE 1	AD	Noonan/CFC/Costello syndromes
MAP2K2	MITOGEN-ACTIVATED PROTEIN KINASE KINASE 2	AD	Noonan/CFC/Costello syndromes
MIB1	MINDBOMB E3 UBIQUITIN PROTEIN LIGASE 1	AD	LVNC
MTND1	mtDNA ENCODED COMPLEX I, SUBUNIT ND1	MITO	Cardiomyopathy, myopathy
MTND5	mtDNA ENCODED COMPLEX I, SUBUNIT ND5	MITO	Cardiomyopathy, myopathy
MTND6	mtDNA ENCODED COMPLEX I, SUBUNIT ND6	MITO	Cardiomyopathy, myopathy
MTTD	MITOCHONDRIAL tRNA FOR ASPARTIC ACID	MITO	Cardiomyopathy, myopathy
MTTG	MITOCHONDRIAL tRNA FOR GLYCINE	MITO	Cardiomyopathy, myopathy
MTTH	MITOCHONDRIAL tRNA FOR HISTIDINE	MITO	Cardiomyopathy, myopathy
MTTI	MITOCHONDRIAL tRNA FOR ISOLEUCINE	MITO	Cardiomyopathy, myopathy
MTTK	MITOCHONDRIAL tRNA FOR LYSINE	MITO	Cardiomyopathy, myopathy
MTTL1	MITOCHONDRIAL tRNA FOR LEUCINE 1	MITO	Cardiomyopathy, myopathy
MTTL2	MITOCHONDRIAL tRNA FOR LEUCINE 2	MITO	Cardiomyopathy, myopathy
MTTM	MITOCHONDRIAL tRNA FOR METHIONINE	MITO	Cardiomyopathy, myopathy
MTTQ	MITOCHONDRIAL tRNA FOR GLUTAMINE	MITO	Cardiomyopathy, myopathy
MTTS1	MITOCHONDRIAL tRNA FOR SERINE 1	MITO	Cardiomyopathy, myopathy
MTTS2	MITOCHONDRIAL tRNA FOR SERINE 2	MITO	Cardiomyopathy, myopathy
MURC	MUSCLE-RELATED COILED-COIL PROTEIN	AD	DCM
MYBPC3	MYOSIN-BINDING PROTEIN C, CARDIAC	AD	HCM, DCM
MYH6	MYOSIN, HEAVY CHAIN 6, CARDIAC MUSCLE, ALPHA	AD	CHD, DCM, HCM, SSS
MYH7	MYOSIN, HEAVY CHAIN 7, CARDIAC MUSCLE, BETA	AD	DCM, HCM, myopathy
MYL2	MYOSIN, LIGHT CHAIN 2, REGULATORY, CARDIAC, SLOW	AD	HCM
MYL3	MYOSIN, LIGHT CHAIN 3, ALKALI, VENTRICULAR, SKELETAL, SLOW	AD, AR	HCM
MYLK2	MYOSIN LIGHT CHAIN KINASE 2	AD, AR	HCM
MYOZ2	MYOZENIN 2	AD	HCM
MYPN	MYOPALLADIN	AD	DCM, RCM, HCM
NEBL	NEBULETTE	AD	DCM, endocardial fibroelastosis
NEXN	NEXILIN	AD	DCM, HCM
NKX2-5	NK2 HOMEOBOX 5	AD	CHD, CCD
NRAS	NEUROBLASTOMA RAS VIRAL ONCOGENE	AD	Noonan/CFC/Costello syndromes

	HOMOLOG		
Gene (cont.)	**Protein**	**Inheritance**	**Disease Association(s)**
PDLIM3	PDZ AND LIM DOMAIN PROTEIN 3	AD	HCM, DCM
PKP2	PLAKOPHILIN 2	AD	ARVC
PLN	PHOSPHOLAMBAN	AD	DCM, HCM
PRDM16	PR DOMAIN CONTAINING 16	AD	DCM, LVNC
PRKAG2	PROTEIN KINASE, AMP-ACTIVATED, NONCATALYTIC, GAMMA2	AD	HCM, Wolff-Parkinson-White syndrome
PTPN11	PROTEIN-TYROSINE PHOSPHATASE, NONRECEPTOR-TYPE 11	AD	Noonan/CFC/Costello syndromes
RAF1	V-RAF-1 MURINE LEUKEMIA VIRAL ONCOGENE HOMOLOG 1	AD	Noonan/CFC/Costello syndromes
RBM20	RNA-BINDING MOTIF PROTEIN 20	AD	DCM
RIT1	RAS-LIKE WITHOUT CAAX 1	AD	Noonan syndrome
RYR2	RYANODINE RECEPTOR 2	AD	ARVC, CPVT, LQTS
SCN5A	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT	AD	BrS, DCM, Heart block, LQTS, SSS, SIDS
SGCD	SARCOGLYCAN, DELTA	AD, AR	DCM, LGMD
SOS1	SON OF SEVENLESS, DROSOPHILA, HOMOLOG 1	AD	Noonan/CFC/Costello syndromes
TAZ	TAFAZZIN	XL	DCM, LVNC, Barth syndrome
TCAP	TITIN-CAP (TELETHONIN)	AD, AR	HCM, DCM, LGMD
TGFB3	TRANSFORMING GROWTH FACTOR BETA 3	AD	ARVC, Loeys-Dietz syndrome-5, TAAD
TMEM43	TRANSMEMBRANE PROTEIN 43	AD	ARVC, EMD
TMPO	THYMOPOIETIN	AD	DCM
TNNC1	TROPONIN C, SLOW	AD	DCM, HCM
TNNI3	TROPONIN I, CARDIAC	AD, AR	DCM, HCM, RCM
TNNT2	TROPONIN T2, CARDIAC	AD	DCM, HCM, RCM, LVNC
TPM1	TROPOMYOSIN 1	AD	DCM, HCM
TTN	TITIN	AD	DCM, myopathy
TTR	TRANSTHYRETIN	AD	TTR-related amyloidosis
TXNRD2	THIOREDOXIN REDUCTASE 2	AD, AR	DCM
VCL	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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