

Dilated Cardiomyopathy/Left Ventricular Noncompaction Panel

Disorders also known as: Idiopathic Dilated Cardiomyopathy (IDC); Familial Dilated Cardiomyopathy (FDC); Left Ventricular Noncompaction Cardiomyopathy (LVNC)

Panel Gene List: *ABCC9, ACTC1, ACTN2, ALMS1, ANKRD1, BAG3, CHRM2, CRYAB, CSRP3, DES, DMD, DOLK, DSC2, DSG2, DSP, DTNA, EMD, FKTN, FLNC, GATAD1, HCN4, ILK, LAMA4, LAMP2, LDB3, LMNA, LRRC10, MIB1, MTND1, MTND5, MTND6, MTTD, MTTG, MTTT, MTTI, MTTK, MTTL1, MTTL2, MTTM, MTTQ, MTTT1, MTTT2, MYBPC3, MYH6, MYH7, MYPN, NEBL, NEXN, NKX2-5, PLN, PRDM16, RAF1, RBM20, RYR2, SCN5A, SGCD, TAZ, TBX20, TCAP, TMPO, TNNC1, TNNT2, TNNI3, TNNT2, TPM1, TTN, TTR, TXNRD2, VCL*

Additional genes from our cardiology test menu may be added to this panel by selecting test code J554C.

Clinical Features:

Dilated cardiomyopathy (DCM) is a disease of the heart muscle that is diagnosed based on the findings of both left ventricular enlargement and systolic dysfunction, resulting in a reduction in the myocardial force of contraction.^{1,2} This condition is primarily determined by echocardiogram to measure cardiac chamber dimensions, ventricular thickness, and ejection fraction.^{2,3} 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.² However, individuals with DCM may also be asymptomatic. The prevalence of idiopathic DCM is at least 1/2,700 in the general population.²

Left ventricular non-compaction (LVNC) is characterized by abnormal trabeculations in the left ventricle, most frequently at the apex. Prominent trabeculations and deep intertrabecular recesses give the myocardium a sponge-like appearance that can be detected using echocardiogram.^{1,3,4} LVNC 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.^{3,4,5} LVNC is a rare condition, which affects less than 0.3% of the population.³

While DCM/LVNC can be an isolated finding, it can also occur in association with neuromuscular disorders or mitochondrial myopathy.^{2,4,5} In addition, DCM/LVNC can be a presenting feature of various genetic syndromes, including Danon disease, Carvajal Syndrome, Barth syndrome, or Emery-Dreifuss muscular dystrophy.^{2,4,5}

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

Test Methods:

Using genomic DNA extracted from the submitted specimen, the coding regions and splice junctions of the 61 genes (except 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 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; 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 Cardiomyopathy Panel is available as a separate test if the DCM/LVNC 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. 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, Cantu syndrome
<i>ACTC1</i>	ACTIN, ALPHA, CARDIAC MUSCLE 1	AD	CHD, DCM, HCM, LVNC
<i>ACTN2</i>	ACTININ, ALPHA-2	AD	DCM, HCM
<i>ALMS1</i>	CENTROSOME AND BASAL BODY ASSOCIATED PROTEIN	AR	Alstrom syndrome, DCM
<i>ANKRD1</i>	ANKYRIN REPEAT DOMAIN-CONTAINING PROTEIN 1	AD	DCM
<i>BAG3</i>	BCL2-ASSOCIATED ATHANOGENE 3	AD	DCM, myofibrillar myopathy
<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, AR	ARVC, AV block, DCM, LGMD, myopathy
<i>DMD</i>	DYSTROPHIN	XL	DMD, BMD, DCM
<i>DOLK</i>	DOLICHOL KINASE	AR	DCM, CDG type 1M
<i>DSC2</i>	DESMOCOLLIN 2	AD, AR	ARVC, ARVC+skin and hair findings
<i>DSG2</i>	DESMOGLEIN 2	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	EDMD
<i>FKTN</i>	FUKUTIN	AR	DCM, LGMD, Fukuyama Congenital Muscular Dystrophy
<i>FLNC</i>	FILAMIN C	AD	RCM, HCM, ARVC, DCM, myopathy
<i>GATAD1</i>	GATA ZINC FINGER DOMAIN-CONTAINING PROTEIN 1	AR	DCM
<i>HCN4</i>	HYPERPOLARIZATION-ACTIVATED CYCLIC NUCLEOTIDE-GATED POTASSIUM CHANNEL 4	AD	LVNC, SSS, BrS
<i>ILK</i>	INTEGRIN-LINKED KINASE	AD	DCM

Gene	Protein	Inheritance	Disease Association(s)
<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	ARVC, DCM, LVNC, LDB3-related myopathies
<i>LMNA</i>	LAMIN A/C	AD, AR	ARVC/ARVC-like disease, DCM, LMNA-related neuromuscular, lipodystrophy, and premature aging disorders
<i>LRRC10</i>	LEUCINE-RICH REPEAT-CONTAINING PROTEIN 10	AD, AR	DCM
<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>MYBPC3</i>	MYOSIN-BINDING PROTEIN C, CARDIAC	AD	HCM, DCM, LVNC
<i>MYH6</i>	MYOSIN, HEAVY CHAIN 6, CARDIAC MUSCLE, ALPHA	AD	CHD, DCM, HCM
<i>MYH7</i>	MYOSIN, HEAVY CHAIN 7, CARDIAC MUSCLE, BETA	AD	DCM, HCM, LVNC, myopathy
<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, DCM, LVNC
<i>PLN</i>	PHOSPHOLAMBAN	AD	ARVC, DCM, HCM
<i>PRDM16</i>	PR DOMAIN CONTAINING 16	AD	DCM, LVNC
<i>RAF1</i>	V-RAF-1 MURINE LEUKEMIA VIRAL ONCOGENE HOMOLOG 1	AD	DCM, HCM, Noonan spectrum
<i>RBM20</i>	RNA-BINDING MOTIF PROTEIN 20	AD	DCM
<i>RYR2</i>	RYANODINE RECEPTOR 2	AD	ARVC, CPVT, DCM, LVNC
<i>SCN5A</i>	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT	AD	ARVC/ARVC-like disease, BrS, DCM, Heart block, LQTS, SIDS, SSS
<i>SGCD</i>	SARCOGLYCAN, DELTA	AD, AR	DCM, LGMD
<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>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>TPM1</i>	TROPOMYOSIN 1	AD	DCM, HCM, LVNC
<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, familial glucocorticoid deficiency
<i>VCL</i>	VINCULIN	AD	DCM, HCM, 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; CDG- Congenital Disorder of Glycosylation; CHD – Congenital Heart Defects; CPVT – Catecholaminergic Polymorphic Ventricular

Tachycardia; DCM – Dilated Cardiomyopathy; DMD- Duchenne Muscular Dystrophy; EDMD – Emery Dreifuss Muscular Dystrophy; HCM – Hypertrophic Cardiomyopathy; 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; XL – X-linked

References:

1. Online Mendelian Inheritance in Man, OMIM. Johns Hopkins University, Baltimore, MD. MIM Number: {115200; 604169}; {04/21/2015; 09/04/2013}; World Wide Web URL: <http://omim.org/>
2. Hershberger RE, Morales A. Dilated Cardiomyopathy Overview. 2007 Jul 27 [Updated 2015 Sep 24]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1309>
3. Callis et al. (2010) Expert review of molecular diagnostics 10(3):329-351 (PMID: 20370590)
4. Bennett et al. (2016) Cardiology Research and Practice 2016:5172308 (PMID: 26881173)
5. Rooms et al. (2015) Acta Cardiol 70 (6):625-31 (PMID: 26717209)