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, MTTH, MTTI, MTTK, MTTL1, MTTL2, MTTM, MTTQ, MTTS1, MTTS2, MYBPC3, MYH6, MYH7, MYPN, NEBL, NEXN, NKX2-5, PLN, PRDM16, RAF1, RBM20, RYR2, SCN5A, SGCD, TAZ, TBX20, TCAP, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, TXNRD2, VCL

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.

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 genes 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.

207 Perry Parkway, Gaithersburg, MD 20877 • T: (888) 729-1206, (301) 519-2100 • F: (201) 421-2010 • support@genedx.com • GeneDx.com

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. Sequence variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Copy number variants are reported based on the probe coordinates, the coordinates of the exons involved, or precise breakpoints when known. The entire mitochondrial genome from the submitted sample is amplified and sequenced using Next Generation sequencing. DNA sequence is assembled and analyzed in comparison with the revised Cambridge Reference Sequence (rCRS GeneBank number NC_012920) and the reported variants listed in the MITOMAP database (http://www.mitomap.org). Alternative sequencing or other detection methods may be used to analyze or confirm mtDNA variants. 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. For *TTN*, sequencing of exons 1-171 and 199-363 only. 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: mitochondrial gene(s), no copy number testing; *ALMS1, EMD, HCN4, and TBX20* genes only whole gene deletions or duplications may be detected. *SCN5A* gene, exon level coverage for exons 2-12 and 21-28 only. For mitochondrial genome testing, sequencing analysis is performed on the following genes: *MTND1, MTND5, MTND6, MTTD, MTTG, MTTH, MTTI, MTTK, MTTL1, MTTL2, MTTM, MTTQ, MTTS1*, and *MTTS2*. Next-generation sequencing may not detect mtDNA point variants present at 10 % heteroplasmy or lower.

Gene	Protein	Inheritance	Disease Association(s)
ABCC9	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 9	AD	DCM, BrS, Cantu syndrome
ACTC1	ACTIN, ALPHA, CARDIAC MUSCLE 1	AD	CHD, DCM, HCM, LVNC
ACTN2	ACTININ, ALPHA-2	AD	DCM, HCM
ALMS1	CENTROSOME AND BASAL BODY ASSOCIATED PROTEIN	AR	Alstrom syndrome, DCM
ANKRD1	ANKYRIN REPEAT DOMAIN-CONTAINING PROTEIN 1	AD	DCM
BAG3	BCL2-ASSOCIATED ATHANOGENE 3	AD	DCM, myofibrillar myopathy
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, AR	ARVC, AV block, DCM, LGMD, myopathy
DMD	DYSTROPHIN	XL	DMD, BMD, DCM
DOLK	DOLICHOL KINASE	AR	DCM, CDG type 1M

DSC2	DESMOCOLLIN 2	AD, AR	ARVC, ARVC+skin and hair findings
DSG2	DESMOGLEIN 2	AD	ARVC, DCM
DSP	DESMOPLAKIN	AD, AR	ARVC, DCM, Carvajal syndrome and related disorders
DTNA	DYSTROBREVIN, ALPHA	AD	LVNC, CHD
EMD	EMERIN	XL	EDMD
FKTN	FUKUTIN	AR	DCM, LGMD, Fukuyama Congenital Muscular Dystrophy
FLNC	FILAMIN C	AD	RCM, HCM, ARVC, DCM, myopathy
GATAD1	GATA ZINC FINGER DOMAIN-CONTAINING PROTEIN 1	AR	DCM
HCN4	HYPERPOLARIZATION-ACTIVATED CYCLIC NUCLEOTIDE-GATED POTASSIUM CHANNEL 4	AD	LVNC, SSS, BrS
ILK	INTEGRIN-LINKED KINASE	AD	DCM
LAMA4	LAMININ, ALPHA-4	AD	DCM
LAMP2	LYSOSOME-ASSOCIATED MEMBRANE PROTEIN 2	XL	Danon disease
LDB3	LIM DOMAIN-BINDING 3	AD	ARVC, DCM, LVNC, LDB3-related myopathies
LMNA	LAMIN A/C	AD, AR	ARVC/ARVC-like disease, DCM, LMNA-related neuromuscular, lipodystrophy, and premature aging disorders
LRRC10	LEUCINE-RICH REPEAT-CONTAINING PROTEIN 10	AD, AR	DCM
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
MYBPC3	MYOSIN-BINDING PROTEIN C, CARDIAC	AD	HCM, DCM, LVNC
MYH6	MYOSIN, HEAVY CHAIN 6, CARDIAC MUSCLE, ALPHA	AD	CHD, DCM, HCM
MYH7	MYOSIN, HEAVY CHAIN 7, CARDIAC MUSCLE, BETA	AD	DCM, HCM, LVNC, myopathy
MYPN	MYOPALLADIN	AD	DCM, RCM, HCM
NEBL	NEBULETTE	AD	DCM, endocardial fibroelastosis
NEXN	NEXILIN	AD	DCM, HCM
NKX2-5	NK2 HOMEOBOX 5	AD	CHD, DCM, LVNC

207 Perry Parkway, Gaithersburg, MD 20877 • T: (888) 729-1206, (301) 519-2100 • F: (201) 421-2010 • support@genedx.com • GeneDx.com

PLN	PHOSPHOLAMBAN	AD	ARVC, DCM, HCM
PRDM16	PR DOMAIN CONTAINING 16	AD	DCM, LVNC
RAF1	V-RAF-1 MURINE LEUKEMIA VIRAL ONCOGENE HOMOLOG 1	AD	DCM, HCM, Noonan spectrum
RBM20	RNA-BINDING MOTIF PROTEIN 20	AD	DCM
RYR2	RYANODINE RECEPTOR 2	AD	ARVC, CPVT, DCM, LVNC
SCN5A	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT	AD	ARVC/ARVC-like disease, BrS, DCM, Heart block, LQTS, SIDS, SSS
SGCD	SARCOGLYCAN, DELTA	AD, AR	DCM, LGMD
TAZ	TAFAZZIN	XL	DCM, LVNC, Barth syndrome
TBX20	T-BOX 20	AD	CHD, DCM, LVNC
TCAP	TITIN-CAP (TELETHONIN)	AD, AR	HCM, DCM, LGMD
TMPO	THYMOPOIETIN	AD	DCM
TNNC1	TROPONIN C, SLOW	AD	DCM, HCM
TNNI3	TROPONIN I, CARDIAC	AD	DCM, HCM, RCM
TNNT2	TROPONIN T2, CARDIAC	AD	DCM, HCM, RCM, LVNC
TPM1	TROPOMYOSIN 1	AD	DCM, HCM, LVNC
TTN	TITIN	AD, AR	ARVC, DCM, TTN-related myopathies and muscular dystrophies
TTR	TRANSTHYRETIN	AD	TTR-related amyloidosis
TXNRD2	THIOREDOXIN REDUCTASE 2	AD, AR	DCM, familial glucocorticoid deficiency
VCL	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 NonCompaction; 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)

