

## Hypertrophic Cardiomyopathy Panel

**Panel Gene List:** *ACTC1, ACTN2, ALPK3, CAV3, CSRP3, FHL1, FLNC, GAA, GLA, JPH2, LAMP2, MTND1, MTND5, MTND6, MTTD, MTTG, MTTT, MTTI, MTTK, MTTL1, MTTL2, MTTM, MTTQ, MTTT1, MTTT2, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYOZ2, PLN, PRKAG2, RAF1, RIT1, TCAP, TNNC1, TNNI3, TNNT2, TPM1, TTR, VCL*

*Additional genes from our cardiology test menu may be added to this panel by selecting test code J553C.*

### Clinical Features:

Hypertrophic cardiomyopathy (HCM) is a disease of the cardiac muscle characterized by left ventricular hypertrophy (LVH), myocyte disarray, and fibrosis. Symptoms may include shortness of breath, chest pain, palpitations, fatigue, fainting (syncope), and heart failure. Nonetheless, some affected individuals have no symptoms or remain clinically stable. Age of onset spans childhood to adulthood, and the clinical phenotype is variable, even within the same family.<sup>1</sup> HCM is also the most common cause of sudden cardiac death in the young (<30 years of age) and in athletes.<sup>2</sup>

The clinical diagnosis is often established by the observation of LVH on cardiac imaging such as echocardiogram in the absence of a predisposing cardiac or cardiovascular condition (e.g. hypertension or aortic stenosis). HCM is caused by pathogenic variants in genes that result in sarcomere dysfunction. The condition occurs in approximately 1 in 500 individuals.<sup>1</sup>

Ventricular hypertrophy may also be a presenting feature of a systemic genetic disorder and should be distinguished from sarcomeric HCM. TTR-related cardiac amyloidosis is characterized by progressive LVH and restrictive cardiomyopathy with or without peripheral neuropathy; the age of onset is typically in the sixth decade of life.<sup>3</sup> Danon disease is characterized by cardiomyopathy in addition to myopathy and varying intellectual disability.<sup>4</sup> Fabry disease is a lysosomal storage disease that presents variably depending on residual enzyme activity, though may be the underlying diagnosis in unexplained LVH in adults.<sup>5,6</sup> Pompe disease is a glycogen storage disorder associated with cardiomyopathy; the severity of disease is variable, and additional features can include proximal muscular weakness and respiratory insufficiency.<sup>7</sup> Noonan syndrome may be suspected in individuals with characteristic facies, short stature, variable development delay, and congenital heart disease.<sup>8</sup> Mitochondrial cardiomyopathies may result in isolated cardiomyopathy or present with various organ system involvement.<sup>9</sup>

**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). 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.

## 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 the mitochondrial genes sequencing but not deletion/duplication analysis, is performed.

Gene	Protein	Inheritance	Disease Association(s)
<i>ACTC1</i>	ACTIN, ALPHA, CARDIAC MUSCLE 1	AD	CHD, DCM, HCM, LVNC
<i>ACTN2</i>	ACTININ, ALPHA-2	AD	DCM, HCM
<i>ALPK3</i>	ALPHA KINASE 3	AR	HCM
<i>CAV3</i>	CAVEOLIN 3	AD	HCM, LQTS, LGMD, Tateyama-type distal myopathy, SIDS, rippling muscle disease
<i>CSRP3</i>	CYSTEINE- AND GLYCINE-RICH PROTEIN 3	AD	HCM, DCM
<i>FHL1</i>	FOUR-AND-A-HALF LIM DOMAINS 1	XL	HCM, EDMD, myofibrillar myopathy
<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>GLA</i>	GALACTOSIDASE, ALPHA	XL	Fabry disease
<i>JPH2</i>	JUNCTOPHILIN 2	AD	HCM
<i>LAMP2</i>	LYSOSOME-ASSOCIATED MEMBRANE PROTEIN 2	XL	Danon disease
<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

Gene	Protein	Inheritance	Disease Association(s)
<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>MYL2</i>	MYOSIN, LIGHT CHAIN 2, REGULATORY, CARDIAC, SLOW	AD, AR	HCM, Infantile type 1 muscle fiber disease
<i>MYL3</i>	MYOSIN, LIGHT CHAIN 3, ALKALI, VENTRICULAR, SKELETAL, SLOW	AD, AR	HCM
<i>MYOZ2</i>	MYOZENIN 2	AD	HCM
<i>PLN</i>	PHOSPHOLAMBAN	AD	ARVC, DCM, HCM
<i>PRKAG2</i>	PROTEIN KINASE, AMP-ACTIVATED, NONCATALYTIC, GAMMA2	AD	HCM, Wolff-Parkinson-White syndrome
<i>RAF1</i>	V-RAF-1 MURINE LEUKEMIA VIRAL ONCOGENE HOMOLOG 1	AD	DCM, HCM, Noonan spectrum
<i>RIT1</i>	RIC-LIKE PROTEIN WITHOUT CAAX MOTIF 1	AD	Noonan syndrome
<i>TCAP</i>	TITIN-CAP (TELETHONIN)	AD, AR	HCM, DCM, LGMD
<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>TTR</i>	TRANSTHYRETIN	AD	TTR-related amyloidosis
<i>VCL</i>	VINCULIN	AD	DCM, HCM, LVNC

Abbreviations: AD – Autosomal dominant; AR – Autosomal recessive; ARVC- Arrhythmogenic Right Ventricular Cardiomyopathy; CHD – Congenital Heart Defects; DCM – Dilated Cardiomyopathy; EDMD – Emery Dreifuss Muscular Dystrophy; HCM – Hypertrophic Cardiomyopathy; ; LVNC – Left Ventricular Non-Compaction; LGMD – Limb Girdle Muscular Dystrophy; LQTS – Long QT Syndrome, RCM- Restrictive Cardiomyopathy; SIDS – Sudden Infant Death Syndrome; XL – X-linked

## References:

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