Hypertrophic Cardiomyopathy Panel

Panel Gene List: *ACTC1, ACTN2, ALPK3, CAV3, CSRP3, FHL1, FLNC, GAA, GLA, JPH2, LAMP2, MTND1, MTND5, MTND6, MTTD, MTTG, MTTH, MTTI, MTTK, MTTL1, MTTL2, MTTM, MTTQ, MTTS1, MTTS2, 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.[1] HCM is also the most common cause of sudden cardiac death in the young (<30 years of age) and in athletes.[2]

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.[1]

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.[3] Danon disease is characterized by cardiomyopathy in addition to myopathy and varying intellectual disability.[4] 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.[5,6] 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.[7] Noonan syndrome may be suspected in individuals with characteristic facies, short stature, variable development delay, and congenital heart disease.[8] Mitochondrial cardiomyopathies may result in isolated cardiomyopathy or present with various organ system involvement.[9]

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

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel 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. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. 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 HCM Panel is negative.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in the HCM Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined HCM and a family history of disease. 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)
ACTC1	ACTIN, ALPHA, CARDIAC MUSCLE 1	AD	CHD, DCM, HCM, LVNC
ACTN2	ACTININ, ALPHA-2	AD	DCM, HCM
ALPK3	ALPHA KINASE 3	AR	HCM
CAV3	CAVEOLIN 3	AD	HCM, LQTS, LGMD, Tateyama-type distal myopathy, SIDS, rippling muscle disease
CSRP3	CYSTEINE- AND GLYCINE-RICH PROTEIN 3	AD	HCM, DCM
FHL1	FOUR-AND-A-HALF LIM DOMAINS 1	XL	HCM, EDMD, myofibrillar myopathy
FLNC	FILAMIN C	AD	RCM, HCM, ARVC, DCM, myopathy
GAA	GLUCOSIDASE, ALPHA, ACID	AR	Pompe Disease (Glycogen storage disease II)
GLA	GALACTOSIDASE, ALPHA	XL	Fabry disease
JPH2	JUNCTOPHILIN 2	AD	HCM
LAMP2	LYSOSOME-ASSOCIATED MEMBRANE PROTEIN 2	XL	Danon disease
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

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