Hypertrophic Cardiomyopathy Panel

Panel Gene List: *ACTC1, ACTN2, CAV3, CSRP3, FHL1, GLA, JPH2, LAMP2, MTTG, MTTI, MTTK, MTTQ, MYBPC3, MYH7, MYL2, MYL3, PLN, PRKAG2, 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 and is characterized by left ventricular hypertrophy (LVH), myocyte disarray, and fibrosis. Symptoms may include dyspnea, chest pain, palpitations, fatigue, syncope, and heart failure. HCM is also the most common cause of sudden cardiac death in the young (<30 years of age) and in athletes.[1,2] Nonetheless, many 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. The clinical diagnosis is often established by the observation of LVH on cardiac imaging such as echocardiogram or cardiac MRI 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 and the condition occurs in approximately 1 in 500 individuals.[1]

Less commonly, ventricular hypertrophy is a presenting feature of a genetic systemic disorder and should be distinguished from sarcomeric HCM. TTR-related cardiac amyloidosis is characterized by progressive left ventricular hypertrophy 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 affects the peripheral nervous system, kidneys, and heart, and also causes angiokeratomas, corneal and lens opacities, and retinal abnormalities.[5] Mitochondrial cardiomyopathies may result in isolated cardiomyopathy or present with various organ system involvement.[6]

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

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.

Gene	Protein	Inheritance	Disease Association(s)
ACTC1	ACTIN, ALPHA, CARDIAC MUSCLE	AD	CHD, DCM, HCM, LVNC
ACTN2	ACTININ, ALPHA-2	AD	Pediatric HCM/DCM
CAV3	CAVEOLIN 3	AD, AR	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, EMD, myofibrillar myopathy, reducing body myopathy
GLA	GALACTOSIDASE, ALPHA	XL	Fabry disease
JPH2	JUNCTOPHILIN 2	AD	HCM
LAMP2	LYSOSOME-ASSOCIATED MEMBRANE PROTEIN 2	XL	Danon disease
MTTG	MITOCHONDRIAL tRNA FOR GLYCINE	MITO	Cardiomyopathy, myopathy
MTTI	MITOCHONDRIAL tRNA FOR ISOLEUCINE	MITO	Cardiomyopathy, myopathy
MTTK	MITOCHONDRIAL tRNA FOR LYSINE	MITO	Cardiomyopathy, myopathy
MTTQ	MITOCHONDRIAL tRNA FOR GLUTAMINE	MITO	Cardiomyopathy, myopathy
MYBPC3	MYOSIN-BINDING PROTEIN C, CARDIAC	AD	HCM, DCM
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
PLN	PHOSPHOLAMBAN	AD	DCM, HCM
PRKAG2	PROTEIN KINASE, AMP-ACTIVATED, NONCATALYTIC, GAMMA2	AD	HCM, Wolff-Parkinson-White syndrome
TCAP	TITIN-CAP (TELETHONIN)	AD, AR	HCM, DCM, LGMD
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
TTR	TRANSTHYRETIN	AD	TTR-related amyloidosis
VCL	VINCULIN	AD	HCM, DCM, LVNC

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

References:

1. Cirino AL, Ho C. Hypertrophic Cardiomyopathy Overview. 2008 Aug 5 [Updated 2014 Jan 16]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1768/
2. Maron et al. (2003) J. Am. Coll. Cardiol. 41 (6):974-80 (PMID: 12651044)
3. Sekijima Y, Yoshida K, Tokuda T, et al. Familial Transthyretin Amyloidosis. 2001 Nov 5 [Updated 2012 Jan 26]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1194/
4. 4.D'souza et al. (2014) Circulation. Heart Failure 7 (5):843-9 (PMID: 25228319)
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7. Friedrich et al. (2012) Human Molecular Genetics 21 (14):3237-54 (PMID: 22523091)