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 from the submitted specimen, the coding regions and splice junctions of the 25 genes are enriched using a proprietary targeted capture system developed by GeneDx. These targeted regions are sequenced simultaneously by massively parallel (NextGen) sequencing on an Illumina platform with paired-end reads. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing is used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 15 reads are achieved by NextGen sequencing. Concurrent deletion/duplication testing is performed for the genes in the panel using exon-level oligo array CGH (ExonArrayDx), except for the *MTTG*, *MTTI*, *MTTK* and *MTTQ* genes. Data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. The array is designed to detect most intragenic

deletions and duplications. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat array CGH analysis. Sequence and array CGH alterations are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Benign and likely benign variants, if present, are not included in this report but are available upon request.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the 25 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 the sequencing test is estimated to be 98%. The sequencing panel will not reliably detect deletions, insertions, or rearrangements greater than or equal to five base pairs (bp). Deletions or duplications of less than 500 bp are not reliably detected by array CGH.

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)
5. Mehta A, Hughes DA. Fabry Disease. 2002 Aug 5 [Updated 2013 Oct 17]. 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/NBK1292/
6. Dominic et al. (2014) Heart (British Cardiac Society) 100 (8):611-8 (PMID: 24449718)
7. Friedrich et al. (2012) Human Molecular Genetics 21 (14):3237-54 (PMID: 22523091)