Marfan Syndrome/Thoracic Aortic Aneurysm and Dissection and Related Disorders Panel

Panel Gene List: *ACTA2, CBS, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, MAT2A, MED12, MFAP5, MYH11, MYLK, NOTCH1, PRKG1, SKI, SLC2A10, SMAD3, SMAD4, TGFB2, TGFB3, TGFBR1, TGFBR2*

Additional genes from our cardiology test menu may be added to this panel by selecting test code 883C.

Clinical Features:

Familial thoracic aortic aneurysm and dissection (TAAD) is a genetically heterogeneous disorder that accounts for approximately 20% of all cases of thoracic aortic aneurysms and dissections.[1] Increased risk for aortopathy can occur in conjunction with other syndromic features or as a primarily isolated feature.[2] When syndromic features are absent or non-specific, molecular diagnosis with genetic testing aids in diagnosis, management and establishing recurrence risk for family members.

Syndromic TAAD includes Marfan syndrome, Loeys-Dietz syndrome, and Shprintzen-Goldberg syndrome. Marfan syndrome is a connective tissue disorder caused by variants in the FBN1 gene that can affect multiple organ systems, including the skeletal, ocular, and cardiovascular systems. Diagnosis is based on the presence of major and minor clinical criteria, as established by the Ghent nosology.[3,4] In addition to TAAD, affected individuals may develop mitral valve prolapse. Skeletal features can include pectus carinatum/excavatum, tall stature and scoliosis. Eye findings include ectopia lentis, myopia and retinal detachment. Features of Loeys-Dietz syndrome (LDS) overlap with those of Marfan syndrome with the exception of ectopia lentis; in addition, persons with LDS may have more extensive arteriopathy (aneurysms, dissections, tortuosity) and craniofacial features such as hypertelorism, craniosynostosis, cleft palate/bifid uvula.[5] LDS is due to a pathogenic variant in one of several genes, including *TGFBR1*, *TGFBR2*, *SMAD3*[6], *TGFB2*[7,8] or *TGFB3*[9,10]. Shprintzen-Goldberg syndrome shares overlapping physical features with Marfan syndrome and LDS but affected individuals are at higher risk for neurodevelopmental issues and intellectual disability.[11] Vascular Ehlers-Danlos syndrome, arterial tortuosity syndrome, congenital contractural arachnodactyly and Lujan syndrome may also present with some features overlapping those of Marfan syndrome and Loeys-Dietz syndrome.[12-15]

Familial non-syndromic TAAD may be due to a pathogenic variant in one of the same genes that cause Marfan syndrome and LDS, or in one of a number of other genes, including *ACTA2*[16], *MAT2A*[17], *MFAP5*[18], *MYH11*[19], *MYLK*[20], *PRKG1*[21]. Pathogenic variants in other genes included on this panel, such as *NOTCH1*[22] and *SMAD4*[23], may have a distinct clinical presentation but are also associated with increased risk of aortopathy.

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 23 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). 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 23 genes included in the Marfan/TAAD Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined Marfan/TAAD-related disorder 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)
ACTA2	ACTIN, ALPHA-2, SMOOTH MUSCLE, AORTA	AD	fTAAD
CBS	CYSTATHIONINE BETA-SYNTHASE	AR	Homocystinuria
COL3A1	COLLAGEN TYPE III ALPHA 1	AD	EDS, vascular type (type IV)
COL5A1	COLLAGEN TYPE V ALPHA 1	AD	EDS, classical type (type I/II)
COL5A2	COLLAGEN TYPE V ALPHA 2	AD	EDS, classical type (type I/II)
FBN1	FIBRILLIN 1	AD	Marfan syndrome
FBN2	FIBRILLIN 2	AD	Congenital contractural arachnodactyly
FLNA	FILAMIN A	XL	EDS with periventricular heterotopia
MAT2A	METHIONINE ADENOSYLTRANSFERASE II, ALPHA	AD	fTAAD
MED12	MEDIATOR COMPLEX SUBUNIT 12	XL	Lujan syndrome
MFAP5	MICROFIBRILLAR-ASSOCIATED PROTEIN 5	AD	fTAAD
MYH11	MYOSIN, HEAVY CHAIN 11, SMOOTH MUSCLE	AD	fTAAD
MYLK	MYOSIN LIGHT CHAIN KINASE	AD	fTAAD
NOTCH1	NOTCH, DROSOPHILA, HOMOLOG OF, 1	AD	fTAAD
PRKG1	PROTEIN KINASE, cGMP-DEPENDENT, REGULATORY, TYPE I	AD	fTAAD
SKI	V-SKI AVIAN SARCOMA VIRAL ONCOGENE HOMOLOG	AD	Shprintzen-Goldberg syndrome
SLC2A10	SOLUTE CARRIER FAMILY 2 (FACILITATED GLUCOSE TRANSPORTER), MEMBER 10	AR	Arterial tortuosity syndrome
SMAD3	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 3	AD	LDS
SMAD4	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 4	AD	JP/HHT
TGFB2	TRANSFORMING GROWTH FACTOR, BETA-2	AD	LDS
TGFB3	TRANSFORMING GROWTH FACTOR, BETA-3	AD	LDS

Gene (cont.)	Protein	Inheritance	Disease Association(s)
TGFBR1	TRANSFORMING GROWTH FACTOR-BETA RECEPTOR, TYPE I	AD	LDS
TGFBR2	TRANSFORMING GROWTH FACTOR-BETA RECEPTOR, TYPE II	AD	LDS

Abbreviations: AD – autosomal dominant; AR – autosomal recessive; EDS Ehlers-Danlos syndrome; fTAAD – familial thoracic aortic aneurysm and dissection; JP/HHT – juvenile polyposis/hereditary hemorrhagic telangiectasia; LDS – Loeys-Dietz syndrome; XL – X-linked

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