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

Panel Gene List: *ACTA2, BGN, CBS, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, LOX, MAT2A, MED12, MFAP5, MYH11, MYLK, NOTCH1, PRKG1, SKI, SLC2A10, SMAD2, 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, genetic testing aids in diagnosis, management and establishing recurrence risk for family members.

Syndromic TAAD includes Marfan syndrome, Loeys-Dietz syndrome, Meester-Loeys syndrome, and Shprintzen-Goldberg syndrome. Marfan syndrome is a heritable connective tissue disorder caused by variants in the *FBN1* gene, and clinical diagnosis is based on the presence of major and minor criteria, as established by the Ghent nosology.[3] Features of Loeys-Dietz syndrome (LDS) overlap with those of Marfan syndrome, and may also include extensive arteriopathy and craniofacial features such as hypertelorism, craniosynostosis, cleft palate/bifid uvula.[4] LDS is due to a pathogenic variant in one of several genes, including *TGFBR1*[4], *TGFBR2*[4], *SMAD2*[5], *SMAD3*[6], *TGFB2*[7,8] or *TGFB3*[9,10]. Shprintzen-Goldberg syndrome[11], Meester-Loeys syndrome[12], vascular Ehlers-Danlos syndrome[13], arterial tortuosity syndrome[14], congenital contractural arachnodactyly[15], and Lujan syndrome[16] may also present with some features overlapping those of Marfan syndrome and Loeys-Dietz syndrome.

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*[17], *LOX*[18,19], *MAT2A*[20], *MFAP5*[21], *MYH11*[22], *MYLK*[23], *PRKG1*[24]. Pathogenic variants in other genes included on this panel, such as *NOTCH1*[25] and *SMAD4*[26], 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 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) (only exons 2-66 for FBN1). 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.

Sequencing and deletion/duplication analysis of the remaining genes on the Heritable Disorders of Connective Tissue Panel is available as a separate test if the Marfan/TAAD Panel is negative.

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)
ACTA2	ACTIN, ALPHA-2, SMOOTH MUSCLE, AORTA	AD	fTAAD
BGN	PROTEOGLYCAN I	XL	Meester-Loeys syndrome, SEMDX
CBS	CYSTATHIONINE BETA-SYNTHASE	AR	Homocystinuria
COL3A1	COLLAGEN TYPE III ALPHA 1	AD	Vascular EDS
COL5A1	COLLAGEN TYPE V ALPHA 1	AD	Classical EDS
COL5A2	COLLAGEN TYPE V ALPHA 2	AD	Classical EDS
FBN1	FIBRILLIN 1	AD	Marfan syndrome, Acromicric dysplasia, Geleophysic dysplasia, Weill-Marschani syndrome, Stiff Skin syndrome
FBN2	FIBRILLIN 2	AD	Congenital contractural arachnodactyly
FLNA	FILAMIN A	XL	EDS variant with PVH
LOX	LYSYL OXIDASE	AD	fTAAD
MAT2A	METHIONINE ADENOSYLTRANSFERASE II, ALPHA	AD	fTAAD
MED12	MEDIATOR COMPLEX SUBUNIT 12	XL	Lujan syndrome, Ohdo syndrome, FG 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	Aortic valve disease
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
SMAD2	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 2	AD	fTAAD, LDS
SMAD3	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 3	AD	fTAAD, LDS
SMAD4	MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 4	AD	JP/HHT
TGFB2	TRANSFORMING GROWTH FACTOR, BETA-2	AD	fTAAD, LDS

Gene	Protein	Inheritance	Disease Association(s)
TGFB3	TRANSFORMING GROWTH FACTOR, BETA-3	AD	fTAAD, LDS
TGFBR1	TRANSFORMING GROWTH FACTOR-BETA RECEPTOR, TYPE I	AD	fTAAD, LDS
TGFBR2	TRANSFORMING GROWTH FACTOR-BETA RECEPTOR, TYPE II	AD	fTAAD, 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; PVH – periventricular heterotopia; XL – X-linked; SEMDX- spondyloepimetaphyseal dysplasia

References:

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