FBN1 Sequencing and Deletion/Duplication Analysis

DISORDER ALSO KNOWN AS
Marfan syndrome, Ectopia lentis syndrome, MASS syndrome

PANEL GENE LIST
FBN1

CLINICAL REATURES
Marfan syndrome is a connective tissue disorder that can affect multiple organ systems including the skeletal, ocular, and cardiovascular systems and is caused by pathogenic variants in the FBN1gene. A diagnosis is based on the presence of major and minor clinical criteria, as established by the Ghent nosology.[1,2] Skeletal features can include chest malformations (pectus carinatum/excavatum), tall stature, increased joint mobility, and scoliosis. Eye findings most commonly include lens dislocation (ectopia lentis) and myopia. The cardiovascular features are typically mitral valve prolapse and/or aortic root dilatation, which can progress to aortic dissection. Patient management and treatment is mainly focused on slowing the progression of aortic root dilation, the most common cause of morbidity and early mortality. Therefore, genetic testing is important for identifying presymptomatic family members who carry a *FBN1* pathogenic variant, and at risk for developing features of Marfan syndrome, who will benefit from appropriate monitoring for aortic root dilatation.

Pathogenic variants in the *FBN1* gene have also been observed in families with isolated ectopia lentis and MASS syndrome (myopia, *m*itral valve prolapse, borderline/non-progressive aortic root dilation, skeletal and skin findings). MASS is a connective tissue disorder related to Marfan syndrome but with milder cardiovascular findings.

INHERITANCE PATTERN/GENETICS
Autosomal Dominant

TEST METHODS
Using genomic DNA extracted from the submitted specimen, the coding regions and splice junctions of exons 2 to 66are 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 SENSTIVITY
Sequence analysis of all exons in the FBN1gene is expected to identify a pathogenic variant in 72-93% of individuals with a clinical suspicion of Marfan syndrome, with the pathogenic detection rate approaching 93% in individuals fulfilling a clinical diagnosis of Marfan syndrome based on the Ghent nosology.[4,5,8,9] The test sensitivity significantly decreases for individuals who do not meet Ghent criteria for Marfan syndrome.8Large deletions have been detected in approximately 2% of individuals who did not have a pathogenic variant identified by sequencing.[6] 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.

Sequence and deletion/duplication analysis of 25other genes associated with related disorders is also available. Please see the Marfan syndrome / Thoracic Aortic Aneurysm and Dissection (TAAD) and Related Disorders panel at www.genedx.com.

Gene	Protein	Inheritance	Disease Association(s)
FBN1	Fibrillin 1	Autosomal Dominant	Marfan syndrome, Ectopia lentis syndrome, MASS syndrome, Aortic aneurysm

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