FBN1 Sequencing and Deletion/Duplication Analysis

Disorder also known as: Marfan syndrome, Ectopia lentis syndrome, MASS syndrome

Panel Gene List: *FBN1*

Clinical Features:

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 *FBN1* gene. 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, mitral 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 from the submitted specimen, the coding regions and splice junctions of exons 1 to 65 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 this gene 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:

Sequence analysis of all exons in the *FBN1* gene 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.[8] Large deletions have been detected in approximately 2% of individuals who did not have a pathogenic variant identified by sequencing.[6] The technical sensitivity of the sequencing test is estimated to be 98%. Sequencing 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.

Sequence and deletion/duplication analysis of 15 other 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

References:

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5. Arbustini E et al. Identification of sixty-two novel and twelve known FBN1 mutations in eighty-one unrelated probands with Marfan syndrome and other fibrillinopathies. Hum Mut. 26:494-509, 2005.
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