

# Marfan Syndrome (*FBN1*) Sequencing and Deletion/ Duplication

## *TO CONFIRM A CLINICAL SUSPICION/DIAGNOSIS OF MARFAN SYNDROME*

### Disease Overview

- Marfan syndrome (MFS) is a systemic connective tissue disorder characterized by a variety of clinical manifestations, including ocular, skeletal, and cardiovascular findings.
- According to a 2010 revised Ghent nosology for Marfan syndrome (MFS), to confirm a clinical diagnosis of MFS in an individual without family history of MFS one must meet any of the following criteria:
  - Aortic root dilatation or dissection and ectopia lentis.
  - Aortic root dilatation or dissection and a pathogenic *FBN1* mutation.
  - Aortic root dilatation or dissection and at least seven points scored for the following systemic findings:
    - Wrist and thumb sign (three points)
    - Wrist or thumb sign (one point)
    - Pectus carinatum (two points) or excavatum (one point)
    - Hindfoot deformity (two points)
    - Pneumothorax (two points)
    - Dural ectasia (two points)
    - Acetabular protrusion (two points)
    - Scoliosis or thoracolumbar kyphosis (one point)
    - Reduced upper/lower segment ratio and increased arm/height ratio in persons with no severe scoliosis (one point)
    - Reduced elbow extension (one point)
    - Skin striae (one point)
    - Myopia (one point)
    - Mitral valve prolapse (one point)
    - Characteristic facial features (one point)
  - Ectopia lentis and an *FBN1* mutation previously reported to be associated with cardiovascular disease.
  - Diagnosis of Shprintzen-Goldberg syndrome (SGS), Loays-Dietz syndrome (LDS), and Ehlers-Danlos syndrome IV vascular type (vEDS) has been excluded.
- A clinical diagnosis of MFS in an individual with a family history of MFS and with an excluded diagnosis of SGS, LDS, and vEDS, is based on the presence of any of the following:
  - Ectopia lentis.
  - Systemic findings scoring seven points or higher.
  - Aortic root dilatation or dissection.
- MFS is characterized by high clinical variability and age-dependent penetrance.
- The size of an affected individual's aortic root should determine echocardiogram surveillance frequency and the timing of possible prophylactic surgery. Assessment of the aortic root in children should be performed at least annually.

- Annual ophthalmology exams are essential to detect ectopia lentis, cataract, glaucoma, and retinal detachment. Skeletal manifestations such as scoliosis and pectus deformity should be followed by orthopedic specialists.
- Individuals with MFS should avoid contact sports, exercise to exhaustion, and isometric activities.
- Pregnancy increases risk for aortic root dilatation and dissection, especially when initial aortic root diameter is greater than 4.0 cm at the onset of pregnancy.
- The average life expectancy of properly managed individuals with MFS is similar to the general population.
- *FBN1* mutations are also associated with type I fibrillinopathy, conditions with an increased risk of aortic dilatation/dissection related to MFS, ranging from early lethal disease in neonatal MFS to isolated features of MFS and near-normal phenotype. These conditions include:
  - Mitral valve prolapse syndrome (MVPS) (mitral valve prolapse, pectus excavatum, scoliosis, and mild arachnodactyly).
  - Autosomal dominant familial ectopia lentis (bilateral ectopia lentis and sometimes scoliosis).
  - MASS syndrome (myopia, mitral valve prolapse, borderline aortic enlargement, and skin and skeletal features of MFS).
  - Weill-Marchesani syndrome 2 (ectopia lentis, brachydactyly, joint stiffness, and short stature).
  - Shprintzen-Goldberg syndrome (craniosynostosis, arachnodactyly, brachycephaly, pectus deformities, scoliosis, mental retardation, and, more rarely, aortic root dilatation).
- *FBN1* mutations have also been detected in patients with MFS phenotype and a severe congenital lipodystrophy with a neonatal progeroid-like appearance.
- Neonatal MFS is typically diagnosed within 3 months of life with symptoms of atrioventricular valve dysfunction, pulmonary emphysema, joint contractures, crumpled ears and loose skin, and death within the first 2 years of life.
- Regular cardiologic follow-up is advised for all patients diagnosed with ectopia lentis syndrome, MASS syndrome, and MVPS, as the incidence of aortic dilatation increases with age.

### Epidemiology

Prevalence of MFS is one in 5,000 to one in 10,000.

### Genetics

- Autosomal dominant inheritance; 25 percent of cases are de novo.

- Rarely, somatic or germline mosaicism has been reported.
- Fibrillin 1 gene, *FBNI*, located on chromosome 15q21.1, is the only gene known to be associated with MFS.
- Fibrillin 1 glycoprotein and other extracellular proteins form microfibrils that contribute to elastic fibers; support the eye lens, nerves, and muscles; and play a role in transforming growth factor-beta (TGF- $\beta$ ) regulation.
- Reduced or abnormal *FBNI* leads to disturbed microfibril structure, increased TGF- $\beta$  signaling, and MFS pathogenesis.
- The pathogenicity of *FBNI* mutations is complex and involves dominant negative effects as well as haploinsufficiency.
- The revised Ghent nosology has defined causal *FBNI* mutations as follows:
  - Mutations previously shown to segregate with disease in MFS families.
  - De novo mutations that are nonsense, in- or out-of frame deletions/insertions, splice-site mutations, missense mutations involving cysteine residues or affecting epidermal growth factor-like (EGF) consensus sequence, and missense mutations absent in 400 ethnically matched controls.
- Few phenotype-genotype correlations have been found.
- Patients diagnosed with neonatal MFS carry *FBNI* mutations located predominantly within exons 24–32; mutations identified in this region in patients of all ages are generally associated with severe prognosis.
- Exon 64 frameshift *FBNI* mutations have been reported in three patients with Marfan phenotype, generalized lipodystrophy, and progeroid facial appearance.
- Large genomic deletions of regulatory elements have been reported in individuals with MFS or MFS spectrum disorders, including MASS phenotype.

### Indication for Ordering

- To confirm a diagnosis of MFS.
- To determine the specific *FBNI* mutation in a known affected individual.
- To determine disease status in children or other at-risk family members of affected relatives.

### Contraindication

- Testing for individuals with a previously identified familial *FBNI* mutation. To test individuals for a specific *FBNI* mutation, it is more cost-effective to order Familial Mutation, Targeted Sequencing (ARUP test code 2001961) and provide a copy of the laboratory report detailing the familial mutation.
- Prenatal testing for an unknown *FBNI* mutation. Pathogenic *FBNI* mutation of an affected family member must be identified before prenatal testing can be performed.

### Interpretation

- Identification of a known pathogenic *FBNI* mutation in a symptomatic individual predicts the presence of MFS or an *FBNI*-related disorder. Clinical phenotypes may vary.
- Lack of an identifiable *FBNI* mutation in a clinically affected individual decreases, but does not exclude, a diagnosis of MFS. Medical management should rely on clinical findings and family history.
- *FBNI* sequence variants of unknown clinical significance may be detected by sequencing.

### Methodology

- PCR and bidirectional sequencing of the *FBNI* coding regions and intron-exon boundaries.
- Multiplex ligation-dependent probe amplification (MLPA) for large deletions/duplication analysis of the *FBNI* gene.
- Analytical sensitivity and specificity of sequencing and MLPA are 99 percent. Clinical sensitivity is dependent on the accuracy of the clinical diagnosis and ranges between 70 and 93 percent for sequencing and is unknown for MLPA.

### Limitations

- Deep intronic mutations and some regulatory region mutations are not detected.
- Large deletions/duplications of exons 11, 12, 21, 23, 28, 33, 38, 40, 49, 52, 60, and 62 will not be detected.
- Breakpoints of large *FBNI* locus and intragenic deletions/duplications will not be determined.
- Rare diagnostic errors may occur due to primer- or probe-site mutations.
- Mutations in genes other than *FBNI* are not evaluated.

### Related Tests

- Marfan Syndrome, *FBNI* Sequencing (2005589)
- Marfan Syndrome, *FBNI* Deletion/Duplication (2005580)
- Familial Mutation, Targeted Sequencing (2001961)

### References

1. Canadas V, et al. Marfan syndrome. Part 1: pathophysiology and diagnosis. *Nat Rev Cardiol* 2010;7:256–65.
2. Gene Tests: Marfan Syndrome. <http://www.genetests.org> (accessed on September 27, 2011).
3. Loeys BL, et al. The revised Ghent nosology for the Marfan syndrome. *J Med Genet* 2010;47:476–85.

## Test Information

2005584

**Marfan Syndrome, *FBNI* Sequencing and Deletion/Duplication**

For specific collection, transport, and testing information, refer to the ARUP website at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).

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