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FBN1-Related Marfan Syndrome

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Summary

Clinical characteristics

FBN1-related Marfan syndrome (Marfan syndrome), a systemic disorder of connective tissue with a high degree of clinical variability, comprises a broad phenotypic continuum ranging from mild (features of Marfan syndrome in one or a few systems) to severe and rapidly progressive neonatal multiorgan disease. Cardinal manifestations involve the ocular, skeletal, and cardiovascular systems. Ocular findings include myopia (>50% of affected individuals); ectopia lentis (seen in approximately 60% of affected individuals); and an increased risk for retinal detachment, glaucoma, and early cataracts. Skeletal system manifestations include bone overgrowth and joint laxity; disproportionately long extremities for the size of the trunk (dolichostenomelia); overgrowth of the ribs that can push the sternum in (pectus excavatum) or out (pectus carinatum); and scoliosis that ranges from mild to severe and progressive. The major morbidity and early mortality in Marfan syndrome relate to the cardiovascular system and include dilatation of the aorta at the level of the sinuses of Valsalva (predisposing to aortic tear and rupture), mitral valve prolapse with or without regurgitation, tricuspid valve prolapse, and enlargement of the proximal pulmonary artery. Severe and prolonged regurgitation of the mitral and/or aortic valve can predispose to left ventricular dysfunction and occasionally heart failure. With proper management, the life expectancy of someone with Marfan syndrome approximates that of the general population.

Diagnosis/testing

The diagnosis of Marfan syndrome is established in a proband (by definition a person without a known family history of Marfan syndrome) who has an *FBN1* pathogenic variant known to be associated with Marfan syndrome and EITHER of the following:

- Aortic root enlargement (z score ≥2.0)
- Ectopia lentis

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Management

Treatment of manifestations: Comprehensive management by a multidisciplinary team including a clinical geneticist, cardiologist, ophthalmologist, orthopedist, and cardiothoracic surgeon is strongly recommended. Treatment typically includes spectacle correction for refractive errors and, sometimes, surgical removal of a dislocated lens with artificial lens implantation (preferably after growth is complete). Glaucoma, cataracts, and retinal detachment are treated in the standard fashion per an ophthalmologist. Scoliosis may require bracing or surgical stabilization; repair of pectus deformity is largely cosmetic. Functional deficits or pain associated with protusio acetabulae may respond to physical therapy, analgesics, or anti-inflammatory medications. Orthotics and arch supports can lessen leg fatigue, joint pain, and muscle cramps associated with pes planus. Dental crowding may be addressed through orthodontia and a palatal expander may be considered in some cases. Surgical repair of the aorta is indicated either when the maximal measurement of the aortic root approaches 5.0 cm in adults or older children, when the rate of increase of the aortic root diameter approaches 0.5-1.0 cm per year, or if there is progressive and severe aortic regurgitation. For younger children, aortic root surgery should be considered once: (1) the rate of increase of the aortic root diameter approaches 0.5-1.0 cm per year, or (2) there is progressive and severe aortic regurgitation. Severe and progressive mitral valve regurgitation with attendant ventricular dysfunction requires immediate attention of a cardiologist or cardiothoracic surgeon and is the leading indication for cardiovascular surgery in children with Marfan syndrome. Afterload-reducing agents can improve cardiovascular function when congestive heart failure is present. Standard treatment for hernias and pneumothorax is recommended. There are no known effective therapies for symptomatic dural ectasia.

Prevention of primary manifestations: Medications that reduce hemodynamic stress on the aortic wall, such as beta-blockers or angiotensin receptor blockers (ARBs), are routinely prescribed. This therapy should be managed by a cardiologist or clinical geneticist familiar with its use. Therapy is generally initiated at the time of diagnosis with Marfan syndrome at any age or upon appreciation of progressive aortic root dilatation even in the absence of a definitive diagnosis.

Surveillance: Measurement of length/height/weight at each visit. Ophthalmologic examination annually or as clinically indicated. Clinical assessment for chest wall deformities and scoliosis at each visit until skeletal maturity, although severe scoliosis may require ongoing surveillance in adulthood. At least annual dental evaluation, including orthodontia, as indicated. Echocardiography annually when aortic dimensions are small and the rate of aortic dilatation is slow; more frequent than annual examinations are indicated when the aortic root diameter exceeds approximately 4.5 cm in adults, rates of aortic dilatation exceed approximately 0.3 cm per year, or significant aortic regurgitation is present. Intermittent surveillance of the entire aorta with CT or MRA scans beginning in young adulthood or at least annually in anyone with a history of aortic root replacement or dissection.

Agents/circumstances to avoid: Contact sports, competitive sports, and isometric exercise; activities that cause joint injury or pain; agents that stimulate the cardiovascular system, including decongestants and excessive caffeine; agents that cause vasoconstriction, including triptans; LASIK correction of refractive errors; breathing against resistance or positive pressure ventilation in those with a documented predisposition for pneumothorax; fluoroquinolone antibiotics, which may exacerbate the predisposition for aneurysm and dissection; classes of antihypertensive agents (e.g., calcium channel blockers, ACE inhibitors) where there is an absence of direct evidence for their efficacy or safety in individuals with Marfan syndrome.

Evaluation of relatives at risk: It is recommended that the genetic status of at-risk relatives of any age be clarified so that affected individuals can undergo routine surveillance for early detection of medically significant complications, particularly potentially life-threatening cardiac manifestations. Genetic status of at-risk relatives can be established EITHER:

- By molecular genetic testing if the *FBN1* pathogenic variant in the family is known; OR

- In those with a rigorously defined family history of Marfan syndrome, by the presence of ONE OR MORE of the following:
  - Ectopia lentis
  - A systemic score ≥7
  - Aortic root dilatation (z score ≥2.0 for individuals age ≥20 years or z score ≥3.0 for those age <20 years)

Pregnancy management: An individual with Marfan syndrome should consider pregnancy only after appropriate counseling from a clinical geneticist or cardiologist familiar with this condition, a genetic counselor, and a high-risk obstetrician because of the risk of more rapid dilation of the aorta or aortic dissection during pregnancy, delivery, or in the immediate postpartum period. Cardiovascular imaging with echocardiography should be performed every two to three months during pregnancy to monitor aortic root size and growth. Monitoring should continue in the immediate postpartum period because of the increased risk for aortic dissection.

Individuals with Marfan syndrome who anticipate pregnancy or become pregnant should continue use of beta-blockers; however, some other classes of medications such as ARBs should be discontinued because of the increased risk for fetal loss, oligohydramnios, and abnormal development, often related to second- and third-trimester exposure.

Genetic counseling

Marfan syndrome is inherited in an autosomal dominant manner. Approximately 75% of individuals with Marfan syndrome have an affected parent; approximately 25% have a *de novo FBN1* pathogenic variant. Each child of an individual with Marfan syndrome has a 50% chance of inheriting the pathogenic variant and the disorder. Once the *FBN1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Consensus clinical diagnostic criteria for *FBN1*-related Marfan syndrome (Marfan syndrome) have been published [Loeys et al 2010].

Suggestive Findings

Marfan syndrome **should be suspected** in individuals with the following clinical findings and family history.

Clinical findings

- Aortic root enlargement (z score ≥2.0). Note: Aortic size must be standardized to age and body size for accurate interpretation. A z score ≥2.0 indicates a value at or above the 95th percentile, while a z score ≥3.0 indicates a value at or above the 99th percentile. References and calculators for this determination are available at the Marfan Foundation website.
- Ectopia lentis; most reliably diagnosed by slit-lamp examination after maximal pupillary dilation
- A systemic score ≥7 (Table 1)

Table 1. Calculation of the Systemic Score

Feature	Value	Enter Value if Feature Is Present
Wrist AND thumb sign	3	
Wrist OR thumb sign	1	
Pectus carinatum deformity	2	
Pectus excavatum or chest asymmetry	1	

Table 1. continued from previous page.

Feature	Value	Enter Value if Feature Is Present
Hindfoot deformity	2	
Plain flat foot (pes planus)	1	
Pneumothorax	2	
Dural ectasia	2	
Protrusio acetabulae	2	
Reduced upper segment to lower segment AND increased arm span to height ratios	1	
Scoliosis or thoracolumbar kyphosis	1	
Reduced elbow extension	1	
3 of 5 facial features	1	
Skin striae	1	
Myopia	1	
Mitral valve prolapse	1	
Total		

A systemic score calculator and a complete description of each component evaluation can be found at the Marfan Foundation website. Click here for a printable copy (pdf) of this table.

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history of Marfan syndrome does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *FBN1*-related Marfan syndrome **is established** in a proband (by definition a person without a known family history of Marfan syndrome) who has an *FBN1* pathogenic variant known to be associated with Marfan syndrome and EITHER of the following [Loeys et al 2010]:

- Aortic root enlargement (z score ≥2.0)
- Ectopia lentis

Note: Given that many manifestations of Marfan syndrome emerge with age, the author suggests the use of tentative diagnostic designations in individuals younger than age 20 years with suggestive findings who do not quite reach diagnostic thresholds:

- **Nonspecific connective tissue disorder.** If the systemic score is <7 and/or aortic root measurements are borderline (z score <3) (without an *FBN1* pathogenic variant), use of this term is suggested until follow-up echocardiographic evaluation shows aortic root dilatation (z score ≥3).
- **Potential Marfan syndrome.** If an *FBN1* pathogenic variant that has not previously been associated with aortic enlargement is identified in a person who represents a simplex case (i.e., a single occurrence in a family) and the aortic root z score is <3.0, this term should be used until the aorta reaches this threshold.

Molecular genetic testing approaches (see Table 2) can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings of Marfan syndrome described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those who do not have sufficiently

discriminating features to consider the diagnosis of Marfan syndrome are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the clinical findings suggest the diagnosis of Marfan syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *FBN1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A Marfan syndrome / Loeys-Dietz syndrome / familial thoracic aortic aneurysms and dissections multigene panel** that includes *FBN1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from other inherited disorders with features observed in Marfan syndrome, **comprehensive genomic testing** (exome sequencing and genome sequencing) may be considered. Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 2. Molecular Genetic Testing Used in *FBN1*-Related Marfan Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
FBN1	Sequence analysis [3]	~90%-93% [4]
	Gene-targeted deletion/duplication analysis [5]	~5% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. In individuals with classic Marfan syndrome an *FBN1* pathogenic variant was identified by sequence analysis in 86 (93%) of 93 [Loeys et al 2004] and 76 (91%) of 87 individuals [Baetens et al 2011]. Subsequently, a number of these individuals were found to have *FBN1* deletions that had not been detected by sequencing [Bart Loeys, personal communication].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Deletions and duplications ranging in size from one to multiple exons as well as full-gene deletions have been described (www.hgmd.cf.ac.uk). In one systematic study, four of 86 individuals with classic Marfan syndrome had a large deletion or duplication [Baetens et al 2011].

Clinical Characteristics

Clinical Description

FBN1-related Marfan syndrome (Marfan syndrome), a systemic disorder of connective tissue, is part of a broad phenotypic continuum associated with heterozygous *FBN1* pathogenic variants that ranges from mild (features of Marfan syndrome in one or a few systems) to severe (rapidly progressive multiorgan disease in neonates). Cardinal manifestations of Marfan syndrome involving the ocular, skeletal, and cardiovascular systems have a high degree of clinical variability.

Table 3. *FBN1*-Related Marfan Syndrome: Frequency of Cardinal Manifestations in Adults by System

System	Feature [1]	% of Persons w/Feature	Comment
Ocular	Myopia	>50%	
	Ectopia lentis	~60%	
	Retinal detachment	<25%	
	Glaucoma	~30%	
	Early cataracts	<25%	
Skeletal [2]	Joint laxity	>50%	
	Disproportionately long extremities for size of trunk (dolichostenomelia)	>50%	Typically due to bone overgrowth
	Pectus anomaly [3]	~50%	Excavatum & carinatum have both been described.
	Scoliosis	~60%	Ranges from mild to severe & progressive

Table 3. continued from previous page.

System	Feature [1]	% of Persons w/Feature	Comment
Cardiovascular [4]	Dilatation of aorta at level of sinuses of Valsalva	>80%	
	Aortic tear & rupture	<25%	Risk is greatly ↓ w/proper medical & surgical mgmt.
	Mitral valve prolapse	>50%	W/or w/o regurgitation
	Tricuspid valve prolapse	<25%	Enriched in those w/infantile presentations of severe MFS
	Enlargement of the proximal pulmonary artery	~50%	Dissection or rupture is exceedingly rare in this population.

MFS = *FBN1*-related Marfan syndrome
1. Many of the features of Marfan syndrome are not recognized in infancy/childhood or develop later in life. However, in severe cases, some of these features may be present in infancy and/or childhood.
2. All skeletal findings can develop in young children and tend to progress during periods of rapid growth.
3. Due to overgrowth of the ribs that then push on the sternum
4. The major morbidity and early mortality in Marfan syndrome relate to the cardiovascular system.

As a general rule, clinical manifestations run true within families, suggesting that the *FBN1* pathogenic variant is the predominant determinant of phenotype.

Eye

- Myopia is a common ocular feature (>50% of affected individuals), often progressing rapidly during childhood.
- Displacement of the lens from the center of the pupil (ectopia lentis) is a hallmark feature of Marfan syndrome, and is seen in approximately 60% of affected individuals.

  While generally evident in early childhood, ectopia lentis can evolve later in life.
- The globe is often elongated and the cornea may be flat.
- Individuals with Marfan syndrome are at increased risk for retinal detachment, glaucoma, and early cataract formation.

Skeletal. The skeletal system is characterized by excessive linear growth of the long bones and joint laxity. All skeletal findings can develop in young children and tend to progress during periods of rapid growth. It is important to note that individuals with Marfan syndrome are not necessarily tall by population standards; they are taller than predicted for their family background [Erkula et al 2002].

- Paradoxically, some individuals can show reduced joint mobility, especially of the elbow and digits, and can have an exaggerated arch to the foot (pes cavus).
- The extremities are disproportionately long for the size of the trunk (dolichostenomelia), leading to an increase in the arm span to height ratio (>1.05 in adults) and a decrease in the upper to lower segment ratio <0.85 in adults).
- Overgrowth of the ribs can push the sternum in (pectus excavatum) or out (pectus carinatum).
- Scoliosis is also common and can be mild or severe and progressive (see Management).
- The combination of bone overgrowth and joint laxity leads to the characteristic thumb and wrist signs.
- Flat feet (pes planus) is common in Marfan syndrome and may be associated with inward rotation at the ankle (also known as hindfoot deformity), contributing to difficulty with ambulation, leg fatigue, and muscle cramps.

- The acetabulum can be abnormally deep and show accelerated erosion (protrusio acetabuli). This can lead to associated pain and functional limitations (see Management).

Craniofacial features include the following:

- A long and narrow face with deeply set eyes (enophthalmos)
- Downward slanting of the palpebral fissures
- Flat cheek bones (malar hypoplasia)
- Small and receding chin (micrognathia, retrognathia)
- Highly arched and narrow palate, often associated with tooth crowding

Cardiovascular. The major sources of morbidity and early mortality relate to the cardiovascular system. Cardiovascular manifestations include the following:

- Dilatation of the aorta at the level of the sinuses of Valsalva with a predisposition for aortic tear and rupture
    - Aortic dilatation tends to progress over time; however, the onset and rate of progression of aortic dilatation is highly variable.
    - Aortic dissection is exceedingly rare in early childhood.
    - In adults, a significant risk for aortic dissection or rupture occurs when the maximal dimension reaches approximately 5.0 cm. Histologic examination reveals fragmentation of elastic fibers, loss of elastin content, and accumulation of amorphous matrix components in the aortic media.

      These histologic findings do not distinguish Marfan syndrome from other causes of aortic aneurysm.
    - As an aneurysm enlarges, the aortic annulus can become stretched, leading to secondary aortic regurgitation.
- Mitral valve prolapse (MVP) with or without regurgitation
- Tricuspid valve prolapse with or without regurgitation
- Enlargement of the proximal pulmonary artery

Valvular dysfunction can lead to volume overload with secondary left ventricular dilatation and failure. Indeed, MVP with congestive heart failure is the leading cause of cardiovascular morbidity and mortality – and the leading indication for cardiovascular surgery – in young children with severe features of Marfan syndrome. The majority of individuals with Marfan syndrome and MVP have a tolerable degree of mitral regurgitation that shows slow, if any, progression with age. A study of 87 individuals with Marfan syndrome identified enlarged pulmonary artery root in 54% [Lundby et al 2012].

Other

- **Dura.** Stretching of the dural sac in the lumbosacral region (dural ectasia) can lead to bone erosion and nerve entrapment.
    - Symptoms include low back pain, proximal leg pain, weakness and numbness above and below the knees, and genital/rectal pain.
    - Leaking of cerebrospinal fluid (CSF) from a dural sac can cause postural drop in CSF pressure and headache.
- **Skin and integument** manifestations include hernias and skin stretch marks (striae distensae). Individuals can show a paucity of muscularity and fat stores despite adequate exercise and caloric intake.

- **Lung bullae** can develop, especially of the upper lobes, and can predispose to spontaneous pneumothorax. Increased total and residual lung volume and reduced peak oxygen uptake have been demonstrated, with reduced aerobic capacity.
- **Pregnancy** can be dangerous for women with Marfan syndrome, especially if the aortic root exceeds 4.0 cm (see Pregnancy Management). Complications include rapid progression of aortic root enlargement and aortic dissection or rupture during pregnancy, delivery, and the postpartum period. Pregnancy-associated dissection can occur in the ascending or descending segments of the aorta.
- **Self-image.** The vast majority of affected individuals older than age 13 years report a positive general self-image.
- **Learning disability** and/or hyperactivity has been suggested as a rare manifestation of Marfan syndrome, but may simply occur in this context at a frequency observed in the general population.

Prognosis. With proper management of the cardiovascular manifestations, the life expectancy of someone with Marfan syndrome approximates that of the general population [Silverman et al 1995].

Genotype-Phenotype Correlations

Few genotype-phenotype correlations exist in *FBN1*-related Marfan syndrome; none is definitive [Dietz & Pyeritz 2001].

- As a general rule, a variant that causes the in-frame loss or gain of central coding sequence through deletions, insertions, or splicing errors is associated with more severe disease.
- Pathogenic variants that create a premature termination codon (PTC) have been associated with clinical presentations that range from mild (not meeting clinical diagnostic criteria for Marfan syndrome) to classic Marfan syndrome. Ectopia lentis is less common in individuals with haploinsufficiency of FBN1.
- Some, but not all, studies have suggested that pathogenic variants that create a PTC can be associated with more frequent aortic events including dissection, surgery, and death in adults with Marfan syndrome [Arnaud et al 2021] or an improved response to treatment with angiotensin receptor blockers [Franken et al 2015].
- Other studies have emphasized a significant enrichment of in-frame pathogenic variants in a central region of *FBN1* among young children with severe, early-onset, and rapidly progressive Marfan syndrome and worse clinical outcomes.

In general, identification of the precise *FBN1* pathogenic variant in a proband has limited prognostic value and has not been proven to reliably guide individual management.

Penetrance

Although intrafamilial clinical variability can be extensive, *FBN1*-related Marfan syndrome shows high clinical penetrance.

Nomenclature

Outdated terms used in the description of Marfan syndrome include the following:

- **Neonatal Marfan syndrome.** Although many have used the term "neonatal Marfan syndrome" to describe the earliest and most severe presentation of Marfan syndrome, in reality, this term does not adequately represent a discrete subset of individuals with truly distinguishing characteristics and its use should be abandoned. The terms "early onset" and "rapidly progressive" are adequate to describe the clinical course in these children.

- **Marfan syndrome type 2.** This term is no longer in use. It was used by Mizuguchi et al [2004] in a report of individuals with a phenotype that resembled Marfan syndrome but is now known to be Loeys-Dietz syndrome (see Differential Diagnosis).

Prevalence

The estimated prevalence of *FBN1*-related Marfan syndrome is 1:5,000-1:10,000.

There is no apparent enrichment in any ethnic or racial group. Males and females are affected with equal frequency.

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *FBN1* are summarized in in Tables 4a and 4b. Disorders included in Table 4a have features that overlap with Marfan syndrome and should be considered in the differential diagnosis.

Table 4a. *FBN1* Allelic Disorders in the Differential Diagnosis of Marfan Syndrome

Disorder	OMIM Entry
Familial ectopia lentis	OMIM 129600
MASS phenotype	OMIM 604308
Marfan lipodystrophy syndrome	OMIM 616914

Familial ectopia lentis caused by pathogenic variants in *FBN1* generally associates with subtle skeletal manifestations of Marfan syndrome and is alternatively referred to as ectopia lentis syndrome.

MASS phenotype is characterized by *m*itral valve prolapse, *m*yopia, borderline and non-progressive *a*ortic enlargement, and nonspecific *s*kin and *s*keletal findings that overlap with those seen in Marfan syndrome. One is most confident in this diagnosis when concordant manifestations are seen in multiple generations in a given family. However, some individuals in such a family could be predisposed to more severe vascular involvement, and thus a regimen of intermittent cardiovascular imaging should be maintained. It is difficult to distinguish MASS phenotype from "emerging" Marfan syndrome when assessing a simplex case (i.e., single occurrence in a family), especially during childhood.

Predominant mitral valve or aortic disease. There are rare reports of individuals with predominant mitral valve or aortic disease with minimal if any apparent systemic manifestations of Marfan syndrome. There are no established phenotype-genotype correlations. It remains unclear whether these exceptional cases reflect the influence of modifier alleles, ascertainment bias, or other determinants of variable clinical expressivity.

Table 4b. Other *FBN1* Allelic Disorders (not in the Differential Diagnosis of Marfan Syndrome)

Disorder	OMIM Entry
Geleophysic dysplasia & acromicric dysplasia	OMIM 614185 & 102370
Stiff skin syndrome	OMIM 184900
Weill-Marchesani syndrome	OMIM 608328

Differential Diagnosis

Loeys-Dietz syndrome (LDS) is an autosomal dominant condition that includes many features of Marfan syndrome (long face, downslanted palpebral fissures, highly arched palate, malar hypoplasia, micrognathia, retrognathia, pectus deformity, scoliosis, arachnodactyly, joint laxity, dural ectasia, and aortic root aneurysm

with dissection). Some features of Marfan syndrome are either less common or prominent (dolichostenomelia) or absent (ectopia lentis). Unique features can include widely spaced eyes, broad or bifid uvula, cleft palate, hydrocephalus (rare), Chiari I malformation, blue sclerae, exotropia, craniosynostosis, cervical spine instability, talipes equinovarus, soft and velvety skin, translucent skin, easy bruising, milia, generalized arterial tortuosity, and frequent aneurysms and dissection throughout the arterial tree. Individuals with LDS are at risk for cervical spine malformation and/or instability, food and environmental allergies, asthma, eczema, eosinophilic esophagitis, and inflammatory bowel disease (rare).

Aortic aneurysms in LDS behave very differently from those in Marfan syndrome, with frequent dissection and rupture at small dimensions and in early childhood.

LDS results from a heterozygous pathogenic variant in *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2*.

Shprintzen-Goldberg syndrome (SGS). The phenotype of SGS is distinctive but shows significant overlap with LDS and Marfan syndrome (Table 5). Major distinctions include the unique and highly penetrant developmental delay in SGS, with less frequent and milder cardiovascular manifestations than in either Marfan syndrome or LDS.

Table 5. Comparison of Clinical Features in Marfan Syndrome, Loeys-Dietz Syndrome, and Shprintzen-Goldberg Syndrome

Clinical Feature	Marfan Syndrome	Loeys-Dietz Syndrome					Shprintzen-Goldberg Syndrome
	FBN1	*TGFBR1/ TGFBR2*	*SMAD3*	*TGFB2*	*TGFB3*	SMAD2	*SKI*
Developmental delay	–	–	–	–	–	–	++
Ectopia lentis	+++	–	–	–	–	–	–
Cleft palate / bifid uvula	–	++	+	+	+	+	+
Widely spaced eyes	–	++	+	+	+	+	++
Craniosynostosis	–	++	+	–	–	–	+++
Tall stature	+++	+	+	++	+	+	+
Arachnodactyly	+++	++	+	+	+	+	++
Pectus deformity	++	++	++	++	+	+	++
Clubfoot	–	++	+	++	+	–	+
Osteoarthritis	+	+	+++	+	+	+	–
Aortic root aneurysm	+++	++	++	++	+	+	+
Arterial aneurysm	–	++	+	+	+	+	+
Arterial tortuosity	–	++	++	+	+	+	+
Early dissection	+	+++	++	+	+	+	–
Bicuspid aortic valve	–	++	+	+	+	+	+
Mitral valve insufficiency	++	+	+	++	+	+	+
Striae	++	+	+	+	+	+	+
Dural ectasia	+	+	+	+	–	–	+

+ = feature is present; the presence of more than one "+" indicates that a feature is more common, with "+++" indicating most common.
– = feature is absent.

Other connective tissue disorders. Many of the skeletal features of Marfan syndrome are common in the general population. When severe and found in combination, such findings usually indicate a disorder of connective tissue, including those summarized in Table 6.

Table 6. Other Connective Tissue Disorders of Interest in the Differential Diagnosis of *FBN1*-Related Marfan Syndrome

Gene(s)	Disorder	MOI	Clinical Features / Comments
ACTA2 *FOXE3* *LOX* *MAT2A* *MFAP5* *MYH11* *MYLK* *PRKG1* *TGFB3* (selected HTAD-related genes [1])	Other causes of heritable thoracic aortic disease (HTAD)	Primarily AD	HTAD refers to TAAD caused by mutation of a gene that confers a high risk for TAAD. ≤20% of individuals w/TAAD who do not have features of MFS, vascular EDS, or LDS have a family history of TAAD. ~30% of families w/HTAD who do not have a clinical diagnosis of MFS or another syndrome have a causative pathogenic variant in one of the known HTAD-related genes. [1]
BGN	Meester-Loeys syndrome (OMIM 300989)	XL	Early-onset TAAD, hypertelorism, pectus deformity, joint hypermobility, contractures, & mild skeletal dysplasia
CBS	Homocystinuria caused by cystathionine β-synthase (CBS) deficiency	AR	Variable ID, ectopia lentis &/or severe myopia, skeletal abnormalities (incl excessive height & limb length), & a tendency for intravascular thrombosis & thromboembolic events. ~50% of those affected are responsive to pharmacologic doses of vitamin B_6, highlighting need to consider this diagnosis. Overlap w/MFS can be extensive & incl an asthenic (long & lean) body habitus, pectus deformity, scoliosis, mitral valve prolapse, highly arched palate, hernia, & ectopia lentis. Thromboembolic events can be life threatening.
COL2A1 *COL9A1* *COL9A2* *COL9A3* *COL11A1* *COL11A2*	Stickler syndrome	AD AR [2]	May incl ocular findings (myopia, cataract, & retinal detachment); hearing loss that is both conductive & sensorineural; midfacial hypoplasia & cleft palate (either alone or as part of Pierre Robin sequence); & mild spondyloepiphyseal dysplasia &/or precocious arthritis. The diagnosis is clinically based.
COL3A1	Vascular EDS (vEDS)	AD [3]	Joint laxity (often limited to small joints in hands), translucent skin w/easily visible underlying veins, easy bruising, wide & dystrophic scars, characteristic facies (prominent eyes & a tight or "pinched" appearance), organ rupture (spleen, bowel, gravid uterus), & a tendency for aneurysm &/or dissection of any medium-to-large muscular artery throughout the body. Unlike in MFS or LDS, there is no particular tendency for involvement of aortic root, although this location is not spared from risk. The tissues can be extremely friable, often contributing to surgical catastrophe. Arteries often tear or rupture w/o prior dilatation.
COL5A1 *COL5A2* (*COL1A1*)	Classic EDS (cEDS)	AD	Skin hyperextensibility, abnormal wound healing, smooth velvety skin, & joint hypermobility; aortic root dilatation reported, apparently more common in young persons & rarely progressing
FBN1	MASS syndrome (OMIM 604308)	AD	See Genetically Related Disorders.

Table 6. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features / Comments
FBN2	Classic congenital contractural arachnodactyly (CCA)	AD	Marfan-like appearance & long, slender fingers & toes. Most affected persons have "crumpled" ears w/folded upper helix, & most have contractures of knees & ankles at birth that usually improve w/time. Proximal interphalangeal joints also have flexion contractures, as do toes. Hip contractures, adducted thumbs, & clubfoot may occur. Kyphosis/scoliosis, present in ~50%, begins as early as infancy & is progressive. Majority of affected persons have muscular hypoplasia. Mild dilatation of aorta is rarely present.
FMR1	Fragile X syndrome	XL	Moderate ID in affected males & mild ID in affected females. Males have large testes (postpubertally), and may have characteristic appearance (large head, long face, prominent forehead & chin, protruding ears) & connective tissue findings (joint laxity) that suggest MFS phenotype. Behavior abnormalities, sometimes incl ASD, are common.
PLOD1	*PLOD1*-related kyphoscoliotic EDS (kEDS)	AD	Friable, hyperextensible skin, thin scars, & easy bruising; generalized joint laxity; severe muscular hypotonia at birth; progressive scoliosis, present at birth or w/in 1st yr of life; & scleral fragility w/↑ risk of rupture of globe. Intelligence is normal; life span may be normal, but affected persons are at risk for rupture of medium-sized arteries & respiratory compromise if kyphoscoliosis is severe.

AD = autosomal dominant; AR = autosomal recessive; ASD = autism spectrum disorder; EDS = Ehlers-Danlos syndrome; ID = intellectual disability; LDS = Loeys-Dietz syndrome; MFS = Marfan syndrome; MOI = mode of inheritance; TAAD = thoracic aortic aneurysms and aortic dissections; XL = X-linked

1. To date, 16 genes are known to predispose to TAAD (see Table 1 in Heritable Thoracic Aortic Disease Overview). Note that many families with a family history of TAAD do not have a pathogenic variant in one of these 16 genes: additional HTAD-related genes are yet to be identified.

2. Stickler syndrome caused by pathogenic variants in *COL2A1*, *COL11A1*, or *COL11A2* is inherited in an autosomal dominant manner; Stickler syndrome caused by pathogenic variants in *COL9A1*, *COL9A2*, or *COL9A3* is inherited in an autosomal recessive manner.

3. Vascular EDS is almost always inherited in an autosomal dominant manner, but rare examples of biallelic inheritance have been reported.

Management

No comprehensive or widely adopted clinical practice guidelines for *FBN1*-related Marfan syndrome (Marfan syndrome) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *FBN1*-related Marfan syndrome, the evaluations summarized in Table 7 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 7. Recommended Evaluations Following Initial Diagnosis in Individuals with *FBN1*-Related Marfan Syndrome

System/Concern	Evaluation	Comment
Constitutional	Measurement of length/height	To assess for tall stature & growth [1]

Table 7. continued from previous page.

System/Concern	Evaluation	Comment
Eyes	Ophthalmologic eval, ideally by ophthalmologist w/ expertise in MFS	To incl: • Slit lamp exam through maximally dilated pupil for evidence of lens subluxation • Refraction, esp in young children at risk for amblyopia • Assessment for glaucoma & cataract
Musculoskeletal	Clinical assessment for skeletal manifestations that may require immediate attn of an orthopedist (e.g., severe scoliosis)	
Dental	Assessment by dentist	For dental crowding & palatal issues
Cardiovascular	Echocardiography [2]	Esp aortic root measurements, which must be based on consideration of normal values for age & body size; click here for a calculator.
Neurologic	Consider spinal MRI to assess for dural ectasia.	In those w/low back pain, proximal leg pain, weakness & numbness above knee & genital/rectal pain
Skin	Clinical assessment for hernias	
Respiratory	Consider chest radiograph to assess for pneumothorax.	In those w/pain in chest, dyspnea, chest tightness, &/or cyanosis
Genetic counseling	By genetics professionals [3]	To inform affected persons & their families re nature, MOI, & implications of MFS to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

MFS = *FBN1*-related Marfan syndrome
1. Marfan syndrome-specific growth curves allow accurate prediction of adult height.
2. Surveillance of the entire aorta with computerized tomography angiography (CTA) or magnetic resonance angiography (MRA) begins in early adulthood or after aortic root surgery (see Surveillance, Table 9).
3. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Management is most effectively accomplished through the coordinated input of a multidisciplinary team of specialists including a clinical geneticist, cardiologist, ophthalmologist, orthopedist, and cardiothoracic surgeon.

Table 8. Treatment of Manifestations in Individuals with *FBN1*-Related Marfan Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Tall stature	Use of hormone supplementation to limit adult height is rarely requested or considered. [1]	This treatment should only be considered when an extreme height is anticipated.

Table 8. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Refractive errors	Standard treatment per ophthalmologist	• Spectacle correction is often adequate. • Prompt & aggressive assessment & correction of refractive error is mandatory in young children at risk for amblyopia.
Lens dislocation	May require surgical aphakia (removal of lens) if lens is freely mobile or margin of lens obstructs vision	• An intraocular lens can be implanted after puberty (i.e., once growth is complete). • While intraocular lens implants are currently considered quite safe when performed in specialized centers, major complications incl retinal detachment can occur.
Glaucoma / Cataracts / Retinal detachment	Standard treatment per ophthalmologist	
Severe &/or progressive scoliosis	Bracing or surgical stabilization of spine may be required.	
Pectus deformity	Standard treatment per orthopedist or general surgeon	In very rare circumstances, surgical intervention is indicated for medical (rather than cosmetic) reasons.
Protusio acetabulae	Functional deficits or pain may respond to PT, analgesics, or anti-inflammatory medications.	Surgical intervention is rarely indicated.
Pes planus	Arch supports may be considered, although some find them irritating.	Orthotics for severe cases; surgical intervention is rarely indicated or fully successful.
Dental crowding	Orthodontia	Palatal expander may be considered in some cases.
Aortic root dilatation [2]	Consider surgical repair of aorta **during infancy** [3] when: • Rate of ↑ of aortic root diameter approaches 0.5-1.0 cm/yr; OR • There is progressive & severe aortic regurgitation.	• While there is no agreed-upon absolute size threshold for aortic root surgery in childhood, many centers use adult guideline of 5.0 cm given extreme rarity of aortic dissection in young children. • Every effort is made to allow aortic annulus to reach size of ≥2.0-2.2 cm, allowing placement of aortic graft of sufficient size to accommodate body growth.
	Surgical repair of aorta is indicated **after infancy & in adults** when: • Max measurement approaches 5.0 cm; OR • Rate of ↑ of aortic root diameter approaches 1.0 cm/yr; OR • There is progressive & severe aortic regurgitation.	• More aggressive therapy may be indicated in persons w/family history of early aortic dissection. • Many persons can receive a valve-sparing procedure that precludes need for chronic anticoagulation.
Severe valve dysfunction / Congestive heart failure / Arrhythmia [2]	Requires immediate attention of cardiologist or cardiothoracic surgeon [4]	Severe & progressive mitral valve regurgitation w/ attendant ventricular dysfunction is leading indication for cardiovascular surgery in children w/ MFS. [5]
Dural ectasia	No effective therapies for symptomatic dural ectasia currently exist.	

Table 8. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Hernia	Standard treatment per general surgeon	• Hernias tend to recur after surgical intervention. • A supporting mesh can be used during surgical repair to minimize recurrence risk.
Pneumothorax	Standard treatment per pulmonologist	• Pneumothorax can be a recurrent problem. • Optimal mgmt may require chemical or surgical pleurodesis or surgical removal of pulmonary blebs.

MFS = *FBN1*-related Marfan syndrome; PT = physical therapy

1. Complications can include the psychosocial burden of accelerated puberty, an accelerated rate of growth prior to final closure of the growth plate, and perhaps the undesirable consequences of the increased blood pressure associated with puberty on progression of aortic dilatation.

2. Cardiovascular manifestations should be managed by a cardiologist familiar with *FBN1*-related Marfan syndrome.

3. Guidelines are based on far less clinical experience than for adults and older children, and need to be tailored to the clinical situation at hand.

4. When congestive heart failure is present, afterload-reducing agents (in combination with a beta-blocker) can improve cardiovascular function, but surgical intervention may be indicated in refractory cases. Most often the mitral valve can be repaired rather than replaced.

5. In this circumstance, caution is warranted when considering concomitant aortic root surgery, as the increased length and complexity of the procedure can put extra strain on the myocardium and delay or compromise postoperative recovery.

Prevention of Primary Manifestations

Medications that reduce hemodynamic stress on the aortic wall, such as beta-blockers or angiotensin receptor blockers (ARBs), are routinely prescribed. This therapy should be managed by a cardiologist or clinical geneticist familiar with its use. Therapy is generally initiated at the time of diagnosis of Marfan syndrome at any age or upon appreciation of progressive aortic root dilatation even in the absence of a definitive diagnosis.

The confluence of data from clinical trials of beta-blockers or ARBs suggests that both classes of medication can be effective at reducing aortic root growth rate and are safe and well tolerated. A meta-analysis of seven studies and more than 1,500 individuals with Marfan syndrome documented that ARBs significantly reduce normalized aortic root and ascending aortic growth rate when compared to placebo [Al-Abcha et al 2020] or when added to pre-existing therapy with a beta-blocker [Al-Abcha et al 2020, Wang et al 2022].

General principles applied by the author include:

- Initiation of therapy at the time of diagnosis with Marfan syndrome. This would include children without aortic enlargement if there is a family history of Marfan syndrome with aortic involvement or the identified pathogenic variant has previously been associated with significant aortic involvement in unrelated individuals.
- Targeting of high dosing (as tolerated) irrespective of blood pressure in recognition that benefit likely relates to desirable biochemical effects in the aortic wall that do not strictly correlate with hemodynamic parameters
- Dose optimization of one agent (e.g., an ARB) before consideration of adding another (e.g., a beta-blocker)
- Avoidance of ARBs in pregnant individuals or if pregnancy is imminently anticipated
- Avoidance of other classes of antihypertensive agents (e.g., calcium channel blockers, ACE inhibitors) in the absence of direct evidence for their efficacy or safety in individuals with Marfan syndrome

Surveillance

Table 9. Recommended Surveillance for Individuals with *FNB1*-Related Marfan Syndrome

System/Concern	Evaluation	Frequency
Constitutional	Measurement of length/height/weight [1]	At each visit
Eyes	Ophthalmologic exam incl specific assessment for glaucoma & cataracts	At least annually, or as clinically indicated
Musculoskeletal	Clinical assessment for chest wall deformities & scoliosis [2]	At each visit until skeletal maturity; severe scoliosis may require ongoing surveillance in adulthood.
Dental	Dental eval (incl orthodontia, as indicated)	At least annually after eruption of teeth
Cardiovascular [3]	Echocardiography	• Annually when aortic dimension is relatively small & rate of aortic dilatation is relatively slow • More often than annually when aortic root diameter > ~4.5 cm in adults, rate of aortic dilatation > ~0.3 cm/yr, or if there is significant aortic regurgitation • Other indications for more frequent echocardiographic imaging incl significant or progressive valve dysfunction or left ventricular enlargement or dysfunction.
	CT or MRA scans of entire aorta	Intermittently starting in young adulthood & at least annually in anyone w/history of aortic root replacement or dissection

1. A subset of children with severe Marfan syndrome can show evidence of severe malnutrition that may require intervention by a nutritionist or gastroenterologist.
2. Radiographs and referral to an orthopedist may be indicated in those with moderate-to-severe features.
3. More frequent evaluations by a cardiologist are indicated with severe or progressive valve or ventricular dysfunction or with documented or suspected arrhythmia.

Agents/Circumstances to Avoid

The following should be avoided:

- Contact sports, competitive sports, and isometric exercise. Note: Individuals can and should remain active with aerobic activities performed in moderation.
- Activities that cause joint injury or pain
- Agents that stimulate the cardiovascular system including routine use of decongestants. Caffeine can aggravate a tendency for arrhythmia.
- Agents that cause vasoconstriction, including triptans
- LASIK eye surgery to correct refractive errors
- For individuals at risk for recurrent pneumothorax, breathing against resistance (e.g., playing a brass instrument) or positive pressure ventilation (e.g., SCUBA diving)
- Fluoroquinolone antibiotics due to the considerable evidence suggesting exacerbation of predisposition for aneurysm and dissection
- Avoidance of classes of antihypertensive agents (e.g., calcium channel blockers, ACE inhibitors) where there is an absence of direct evidence for their efficacy or safety in individuals with Marfan syndrome

Evaluation of Relatives at Risk

It is recommended that the genetic status of relatives of any age at risk for Marfan syndrome be clarified either by molecular genetic testing or by clinical examination so that affected individuals can undergo routine surveillance for early detection of medically significant complications, particularly potentially life-threatening cardiac manifestations. Approaches include the following:

- If the *FBN1* pathogenic variant has been identified in an affected relative, molecular genetic testing can be used.
- In the presence of a rigorously defined family history of Marfan syndrome, clinical examination can establish the clinical diagnosis of Marfan syndrome in a first-degree relative of an affected individual who has any one of the following three findings [Loeys et al 2010]:
  - Ectopia lentis
  - Systemic score ≥7 (See Suggestive Findings.)
  - Aortic root enlargement (z score ≥2.0 in those age ≥20 years or ≥3.0 in those age <20 years) (see Suggestive Findings). Note: (1) Echocardiography of relatives is indicated upon appreciation of any suspicious signs of Marfan syndrome, and even in apparently unaffected individuals if findings are subtle in the index case. (2) It is generally appropriate to delay echocardiography for infants and toddlers until they can cooperate with the examination without needing sedation. Exceptions include those with evidence of valve dysfunction and/or congestive heart failure. (3) All first-degree relatives of an individual with apparent isolated aortic enlargement should be evaluated by echocardiography when they are old enough to cooperate with the exam. Earlier evaluation may be indicated based on a particularly aggressive family history or a worrisome clinical finding such as a murmur, dyspnea, or poor weight gain.

See Genetic Counseling for issues related to evaluation of at-risk relatives for genetic counseling purposes.

Pregnancy Management

It is recommended that an individual with Marfan syndrome consider pregnancy only after appropriate counseling from a clinical geneticist or cardiologist familiar with this condition, a genetic counselor, and a high-risk obstetrician because of the risk of more rapid dilation of the aorta or aortic dissection during pregnancy, delivery, or in the immediate postpartum period. This is especially relevant to individuals who begin pregnancy with a maximal aortic dimension that exceeds 4.0 cm. Note: Some individuals with Marfan syndrome and aortic root dilatation opt for elective aortic repair with a valve-sparing procedure prior to reaching a conventional threshold for surgical intervention (i.e., at a root dimension <5.0 cm) before becoming pregnant. While this is thought to decrease the risk for ascending aortic dissection in association with pregnancy, it will not lessen risk for descending aortic dissection or other potential cardiovascular manifestations of Marfan syndrome.

Pregnant individuals with Marfan syndrome should be followed by a high-risk obstetrician both during pregnancy and through the immediate postpartum period.

Individuals with Marfan syndrome who anticipate pregnancy or become pregnant should continue use of beta-blockers; however, some other classes of medications such as ARBs should be discontinued because of the increased risk for fetal loss, oligohydramnios, and abnormal development, often related to second- and third-trimester exposure.

See MotherToBaby for further information on medication use during pregnancy.

Efforts should be made to minimize cardiovascular stress through pregnancy and delivery.

Cardiovascular imaging with echocardiography should be performed every two to three months during pregnancy to monitor aortic root size and growth. Monitoring should continue in the immediate postpartum period because of the increased risk for aortic dissection.

The choice between a controlled vaginal delivery and cesarean section remains controversial and should be tailored to the specific clinical context.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

FBN1-related Marfan syndrome (Marfan syndrome) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 75% of individuals diagnosed with Marfan syndrome have an affected parent.
- Approximately 25% of individuals diagnosed with Marfan syndrome have the disorder as the result of a *de novo* pathogenic variant.
- If the proband appears to represent a simplex case (i.e., the only family member known to have Marfan syndrome), it is appropriate to evaluate both parents of the proband for manifestations of Marfan syndrome by performing a comprehensive clinical examination and echocardiogram. Molecular genetic testing for the *FBN1* pathogenic variant identified in the proband is recommended for the parents to confirm their genetic status and to facilitate reliable recurrence risk counseling.
- If the *FBN1* pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant.
    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. *

      Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

      * A parent with somatic and germline mosaicism for an *FBN1* pathogenic variant may be mildly/minimally affected.
- The family history of some individuals diagnosed with Marfan syndrome may appear to be negative because of failure to recognize the disorder in family members or early death of the parent before the onset of symptoms. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%. Sibs who inherit an *FBN1* pathogenic variant from a parent will have Marfan syndrome, although the severity cannot be predicted.
- If the *FBN1* pathogenic variant identified in the proband cannot be detected in parental leukocyte DNA and both parents are clinically unaffected, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental mosaicism.

Offspring of a proband

- Each child of an individual with *FBN1*-related Marfan syndrome has a 50% chance of inheriting the pathogenic variant and the disorder.
- The penetrance of *FBN1* pathogenic variants is reported to be 100%; thus, offspring who inherit an *FBN1* pathogenic variant from a parent will have Marfan syndrome, although the severity cannot be predicted.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Predictive testing for at-risk asymptomatic family members requires prior identification of the *FBN1* pathogenic variant in the family.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

Prenatal Testing and Preimplantation Genetic Testing

Once the *FBN1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Genetic Aortic Disorders Association (GADA) Canada**
  Centre Plaza Postal Outlet
  128 Queen Street South
  PO Box 42257
  Mississauga Ontario L5M 4Z0
  Canada

Phone: 866-722-1722 (toll free); 905-826-3223
Email: info@gadacanada.ca
www.gadacanada.ca

- **MedlinePlus**
  Marfan Syndrome
- **NCBI Genes and Disease**
  Marfan syndrome
- **The Marfan Foundation**
  22 Manhasset Avenue
  Port Washington, 11050
  Phone: 800 8 MARFAN; 516-883-8712
  www.marfan.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. FBN1-Related Marfan Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FBN1	15q21.1	Fibrillin-1	FBN1 @ LOVD	FBN1	FBN1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for FBN1-Related Marfan Syndrome (View All in OMIM)

134797	FIBRILLIN 1; FBN1
154700	MARFAN SYNDROME; MFS

Molecular Pathogenesis

Fibrillin-1 is an extracellular matrix protein that contributes to large structures called microfibrils that are found in both elastic and non-elastic tissues. They participate in the formation and homeostasis of the elastic matrix, in matrix-cell attachments, and in the regulation of selected growth factors.

The pathogenesis of Marfan syndrome is complex. Abnormal forms of fibrillin-1 are believed to have dominant-negative activity. In affected individuals, the residual level of protein is generally far below the 50% level predicted by the presence of a wild type copy of *FBN1*. A hallmark feature of Marfan syndrome is a severe reduction of microfibrils in explanted tissues and in the matrix deposited by cultured dermal fibroblasts.

Studies in animal models of Marfan syndrome have demonstrated that microfibrils regulate the matrix sequestration and activation of the growth factor TGFβ. Excess TGFβ signaling has been observed in the developing lung, the mitral valve, the skeletal muscle, the dura, and the ascending aorta [Neptune et al 2003, Ng et al 2004, Jones et al 2005, Loeys et al 2005, Habashi et al 2006, Cohn et al 2007]. TGFβ antagonism in vivo has been shown to attenuate or prevent pulmonary emphysema, myxomatous changes of the mitral valve, skeletal muscle myopathy, and progressive aortic enlargement seen in fibrillin-1-deficient mice. Further evidence suggests the particular relevance of specific cellular signaling events including activation of the extracellular signal-regulated kinase cascade [Habashi et al 2011, Holm et al 2011]. The relevance of this mechanism to other manifestations of Marfan syndrome is currently being explored. Other studies have highlighted the potential role

of matrix-degrading enzymes in the pathogenesis of aortic disease in Marfan syndrome [Bunton et al 2001, Booms et al 2005].

Mechanism of disease causation. Both dominant-negative effects and haploinsufficiency have been implicated in the pathogenesis of Marfan syndrome.

Missense changes associated with disease include:

- Missense variant that creates or destroys a cysteine residue;
- Missense variant affecting conserved residues in the EGF-like domain consensus sequence (D/N)X(D/N)(E/Q)Xm(D/N)Xn(Y/F) (m and n represent variable numbers of residues).

***FBN1*-specific laboratory technical considerations.** Three exons at the extreme 5' end of the gene are alternatively utilized and do not appear to contribute to the coding sequence. For a detailed summary of gene and protein information, see Table A, **Gene**. Additionally, high evolutionary conservation of intronic sequence at the 5' end of the gene suggests the presence of intronic regulatory elements, but these have not been implicated in the etiology of Marfan syndrome.

Chapter Notes

Author Notes

Harry (Hal) Dietz is the Victor A McKusick Professor of Medicine and Genetics in the Institute of Genetic Medicine at the Johns Hopkins University School of Medicine and an Investigator in the Howard Hughes Medical Institute. He serves on the Professional Advisory Board of the Marfan Foundation. His research focuses on the development of rational therapeutic strategies for Marfan syndrome and related conditions through elucidation of disease pathogenesis using animal models of disease. He directs a multidisciplinary clinic for the diagnosis and management of Marfan syndrome and other connective tissue disorders affecting the cardiovascular system.

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