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Marfan Syndrome

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Summary

Disease characteristics. Marfan syndrome is a systemic disorder of connective tissue with a high degree of clinical variability. Cardinal manifestations involve the ocular, skeletal, and cardiovascular systems. *FBN1* mutations associate with a broad phenotypic continuum, ranging from isolated features of Marfan syndrome to neonatal presentation of severe and rapidly progressive disease in multiple organ systems. Myopia is the most common ocular feature; displacement of the lens from the center of the pupil, seen in about 60% of affected individuals, is a hallmark feature. People with Marfan syndrome are at increased risk for retinal detachment, glaucoma, and early cataract formation. The skeletal system involvement is characterized by bone overgrowth and joint laxity. The extremities are disproportionately long for the size of the trunk (dolichostenomelia). Overgrowth of the ribs can push the sternum in (pectus excavatum) or out (pectus carinatum). Scoliosis is common and can be mild or severe and progressive. The major sources of morbidity and early mortality in the Marfan syndrome relate to the cardiovascular system. Cardiovascular manifestations include dilatation of the aorta at the level of the sinuses of Valsalva, a predisposition for aortic tear and rupture, mitral valve prolapse with or without regurgitation, triscuspid valve prolapse, and enlargement of the proximal pulmonary artery. With proper management, the life expectancy of someone with Marfan syndrome approximates that of the general population.

Diagnosis/testing. Marfan syndrome is a clinical diagnosis based upon family history and the observation of characteristic findings in multiple organ systems. The four major diagnostic findings include dilatation or dissection of the aorta at the level of the sinuses of Valsalva, ectopia lentis, dural ectasia, and four of eight specific skeletal features. Molecular genetic testing of the *FBN1* gene, the only gene known to be associated with Marfan syndrome, detects 70-93% of mutations and is available in clinical laboratories.

Management. Management of Marfan syndrome uses a team approach by a geneticist, cardiologist, ophthalmologist, orthopedist, and cardiothoracic surgeon. Most eye problems are controlled with eyeglasses; lens dislocation requires surgical aphakia; an artificial lens can be implanted when growth is complete. Scoliosis may require surgical stabilization of the spine; surgical intervention may be needed to treat pectus excavatum. Orthotics and arch supports lessen leg fatigue and muscle cramps associated with pes planus. Medications that reduce hemodynamic stress on the aortic wall, such as beta blockers, are initiated at diagnosis or for progressive aortic dilatation even in the absence of a definitive diagnosis; verapamil is used if beta blockers are not tolerated. Surgical repair of the aorta is indicated when the maximal measurement exceeds 5.0 cm in adults or older children, the rate of increase of the aortic diameter approaches 1.0 cm per year, or progressive aortic regurgitation occurs. Afterload-reducing agents can improve cardiovascular function when congestive heart failure is present.

Surveillance includes echocardiography to monitor the status of the ascending aorta at yearly intervals with small aortic dimensions and slow rates of aortic dilation; more frequent examinations are indicated when the aortic root diameter exceeds about 4.5 centimeters in adults, with rates of aortic dilation that exceed about 0.5 cm per year, and with the onset of significant aortic regurgitation. Echocardiography of relatives is indicated if they have any suspicious signs of Marfan syndrome and in apparently unaffected individuals if findings are subtle in the index case. Individuals should avoid contact sports, competitive sports, and isometric exercise and perform aerobic activities in moderation. They should avoid agents that stimulate the cardiovascular system, including use of decongestants and caffeine, and avoid breathing against resistance or positive pressure ventilation if they are at risk for recurrent pneumothorax. Individuals should use subacute bacterial endocarditis prophylaxis for dental work.

Genetic counseling. Marfan syndrome is inherited in an autosomal dominant manner. About 75% of individuals diagnosed with Marfan syndrome have an affected parent. About 25% of probands with Marfan syndrome have the disorder as the result of a *de novo* gene mutation. The risk to the sibs of the proband depends upon the status of the parents. If a parent is affected, the risk is 50%. If an affected child is born to clinically unaffected parents, it is likely that the child has a *de novo* mutation, and the risk to sibs is far less than 50% but above the population risk because of reported (but rare) cases of somatic and germline mosaicism. The children of an affected parent are at 50% risk of inheriting the mutant allele and the disorder. Prenatal testing for Marfan syndrome is possible using both linkage analysis and mutation analysis in at-risk pregnancies when the disease-causing mutation has been identified in affected family member(s) or linkage has been established prior to prenatal testing. Requests for prenatal testing for typically adult-onset diseases (such as Marfan syndrome) that do not affect intellect or life span are uncommon.

Diagnosis

Clinical Diagnosis

Marfan syndrome is a clinical diagnosis based upon family history and the observation of characteristic findings in multiple organ systems. Criteria have been established for the clinical diagnosis of Marfan syndrome (Table 1) [DePaepe et al 1996].

- **Family history.** In the absence of a family history of documented Marfan syndrome one must observe major involvement of two body systems with minor involvement of a third (see Table 1).
- Once the diagnosis of Marfan syndrome has been established in a proband, the requirements for diagnosis of a first-degree family member include major involvement of one organ system with minor involvement of a second. These criteria also apply if an individual has an *FBN1* mutation that has previously been associated with Marfan syndrome or an *FBN1* haplotype, inherited by descent, that segregates with disease within the extended family. Thus, even in the presence of a documented genetic predisposition for disease, one must document significant clinical findings for the positive diagnosis of Marfan syndrome.

Major and minor criteria. The four findings with major diagnostic significance include dilatation or dissection of the aorta at the level of the sinuses of Valsalva, ectopia lentis, dural ectasia, and four of eight specific skeletal features. Accurate diagnosis requires a specialized examination including anthropometric measurements.

Table 1. Marfan Syndrome: Diagnostic Criteria

System	Criteria	
	Major	**Minor**
Skeletal	Presence of at least four of the following components: • Pectus carinatum, OR pectus excavatum requiring surgery • Reduced upper-to-lower segment ratio for age (<0.85 for older children or adults) or arm span-to-height ratio (>1.05) [1] • Wrist (Walker-Murdoch) and thumb (Steinberg) signs [2] • Scoliosis of >20° or spondylolisthesis • Reduced extension at the elbow (<170°) • Medial rotation of the medial malleolus causing pes planus • Protrusio acetabulae (abnormally deep acetabulum with accelerated erosion) of any degree (ascertained on radiographs)	Two major components or one major component and at least two of the following: • Pectus excavatum of moderate severity • Joint hypermobility • Highly arched palate with tooth crowding • Facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)
Ocular	• Ectopia lentis	At least two of the following: • Abnormally flat cornea (as measured by keratometry) • Increased axial length of the globe (as measured by ultrasound) • Hypoplastic iris or hypoplastic ciliary muscle causing decreased pupillary miosis
Cardiovascular	At least one of the following: • Dilatation of the ascending aorta involving the sinuses of Valsalva • Dissection of the ascending aorta	At least one of the following: • Mitral valve prolapse with or without mitral regurgitation • Dilatation of the main pulmonary artery, in the absence of obvious cause, before the age of 40 years • Calcification of the mitral annulus before the age of 40 years • Dilatation or dissection of the descending thoracic or abdominal aorta before the age of 50 years
Pulmonary		At least one of the following: • Spontaneous pneumothorax • Apical blebs (ascertained by chest radiography)
Skin and Integument		At least one of the following: • Striae atrophicae without obvious cause • Recurrent or incisional herniae
Dura	• Lumbosacral dural ectasia (ascertained by CT or MRI)	

Family/ Genetic History	At least one of the following: • Having a parent, child, or sib who meets these diagnostic criteria independently • Presence of a mutation in *FBN1* known to cause Marfan syndrome • Presence of a haplotype around *FBN1*, inherited by descent, known to be associated with Marfan syndrome in the family (ascertained by linkage analysis)	

1. The lower segment (LS) is measured from the top of the symphysis pubis to the floor; the LS is subtracted from the height to obtain the upper segment (US). The arm span is measured between the tips of the middle fingers with the arms outstretched.
2. Walker-Murdoch wrist sign is the overlapping of the complete distal phalanx of the thumb and fifth finger when wrapped around the opposite wrist. The "thumb sign" (Steinberg) is extension of the entire distal phalanx of the thumb beyond the ulnar border of the hand when apposed across the palm.

Testing

Protein-based methods for the molecular diagnosis of Marfan syndrome are being explored [Aoyama et al 1995, Brenn et al 1996, Robinson & Godfrey 2000]. Immunohistochemical or pulse-chase analysis of the fibrillin-1 protein expressed from cultured dermal fibroblasts can detect abnormalities in most samples from individuals with Marfan syndrome. Both methods require specialized laboratories with expertise in test execution and interpretation. Further research experience is needed before the precise clinical utility of these methods is known.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *FBN1* is the only gene known to be associated with Marfan syndrome.

Other loci. There are no examples of locus heterogeneity in Marfan syndrome. Although Mizuguchi et al (2004) reported identification of mutations in *TGFBR2* in individuals with Marfan syndrome (designated Marfan syndrome type II), a number of characteristic findings, including ectopia lentis and prominent dolichostenomelia, were not observed. Loeys and colleagues (2005) subsequently reported heterozygous mutations in either *TGFBR1* or *TGFBR2* in a novel aortic aneurysm syndrome that included some features of Marfan syndrome (arachnodactyly, aortic root aneurysms, pectus deformity, scoliosis and dural ectasia) but also many distinguishing features (see Differential Diagnosis). Genotyping of 93 individuals presenting with classic Marfan syndrome identified *FBN1* mutations in 86 (93%); none of the remainder had mutations in either *TGFBR1* or *TGFBR2* [Loeys et al 2004, Loeys et al 2005].

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Predictive testing (if a familial mutation is known or if the family size is sufficiently large to allow for valid conclusions by linkage analysis)
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Sequence analysis and mutation scanning.** The mutation detection rate of *FBN1* mutation scanning and cDNA sequence analysis ranges from approximately 70% to 93% and is influenced by: (1) the accuracy of the clinical diagnosis of Marfan syndrome (i.e., individuals fulfilling the established clinical diagnostic criteria with positive family histories are much more likely to have detectable *FBN1* mutations); (2) mutation type (certain genetic alterations may preclude detection by various testing techniques); and (3) the ability of the testing methodology to detect mutations [Korkko et al 2002].
  - **Sequence analysis of cDNA.** Screening of cDNA (DNA reverse transcribed from RNA), rather than genomic DNA (gDNA), allows time-efficient screening of the full *FBN1* coding region and permits identification of certain splice mutations undetectable by sequence analysis of gDNA. Mutation detection rates may be as high as 90% [V Schaefer, personal communication, 2003] in individuals meeting Marfan syndrome diagnostic criteria.
  - **Mutation scanning using gDNA.** CSGE, DHPLC, or direct sequencing (of all 65 *FNB1* exons) can detect mutations resulting in rapid RNA degradation which are undetectable by cDNA sequence analysis. Mutation detection rates range from 70% to 93% in individuals meeting Marfan syndrome clinical diagnostic criteria [Halliday et al 2002, Korkko et al 2002].
- **Linkage analysis.** Linkage analysis may be used to determine if an individual has inherited an *FBN1* allele that is associated with Marfan syndrome in multiple family members. The markers used for Marfan syndrome linkage are highly informative and are within the *FBN1* gene; they can be used in nearly 100% of families.

  Note: (1) Linkage testing is not available to families in which only a single member is affected. (2) Linkage analysis should be used with great caution particularly in families exhibiting atypical phenotypes because multiple phenotypes with some clinical overlap with Marfan syndrome are not caused by mutations in *FBN1* and locus heterogeneity for Marfan syndrome has not been definitely excluded. (3) Linkage analysis has the greatest predictive value when a particular allele is shown to consistently cosegregate with disease in a large family.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in Marfan Syndrome

Test method	Mutations Detected	Mutation Detection Rate [1]	Test Availability
Mutation scanning	*FBN1* mutations	~70-93%	Clinical Testing
cDNA sequence analysis			

1. Halliday et al 2002; Korkko et al 2002; Loeys et al 2004, Loeys et al 2005

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related Disorders

Other phenotypes associated with mutations in *FBN1*:

- Mitral valve prolapse syndrome — with or without skeletal features
- MASS phenotype — Myopia, **m**itral valve prolapse, borderline and non-progressive **a**ortic enlargement,and nonspecific **s**kin and **s**keletal features
- Predominant aortic aneurysm with other subdiagnostic features of Marfan syndrome

- Predominant or isolated skeletal features of Marfan syndrome
- Familial ectopia lentis — associates the eye and skeletal features of Marfan syndrome and can only be differentiated from "emerging" Marfan syndrome with prolonged clinical follow-up including frequent echocardiograms
- Shprintzen-Goldberg syndrome — associates the skeletal and heart findings of Marfan syndrome with craniosynostosis and other skeletal and neurodevelopmental abnormalities. Multiple distinct presentations are included in this diagnostic category. Genetic heterogeneity is likely; to date, only one atypical case has been associated with a mutation in *FBN1* [Sood et al 1996].
- Autosomal dominant Weill-Marchesani syndrome [Faivre et al 2003]

Clinical Description

Natural History

Marfan syndrome is a systemic disorder of connective tissue with a high degree of clinical variability [reviewed in Judge & Dietz, in press]. Cardinal manifestations involve the ocular, skeletal, and cardiovascular systems. *FBN1* mutations associate with a broad phenotypic continuum, ranging from isolated features of Marfan syndrome to neonatal presentation of severe and rapidly progressive disease in multiple organ systems. The diagnosis of Marfan syndrome is clinically defined and does not include this whole spectrum, especially the milder overlap phenotypes. As a general rule, conditions run true within families, suggesting that the *FBN1* genotype is the predominant determinant of phenotype.

Eye. Myopia is the most common ocular feature and often progresses rapidly during childhood. Displacement of the lens from the center of the pupil (ectopia lentis) is a hallmark feature of Marfan syndrome, but is only seen in about 60% of affected individuals. This finding is most reliably diagnosed by slit-lamp examination after maximal pupillary dilatation. 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. Most often the eye problems of Marfan syndrome can be managed with the use of eyeglasses. Other problems can be mitigated using surgical techniques, including the implantation of artificial lenses.

Skeletal. The skeletal system is characterized by excessive linear growth of the long bones and joint laxity. The extremities are disproportionately long for the size of the trunk (dolichostenomelia) leading to an increase in the arm span-to-height and upper-to-lower segment ratios. 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 (see Table 1 footnote). Inward rotation of the medial aspect of the ankle can result in flat feet (pes planus). 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 acetabulum can be abnormally deep and show accelerated erosion (protrusio acetabuli). All skeletal findings can develop in young children and tend to progress during periods of rapid growth.

The facial features of Marfan syndrome include a long and narrow face with deeply set eyes (enophthalmos), downward slanting of the palpebral fissues, flat cheek bones (malar hypoplasia), and a small and receding chin (micrognathia, retrognathia). The palate can be highly arched and narrow, often associated with tooth crowding.

It is important to note that individuals with Marfan syndrome are not necessarily tall by population standards; they are taller than predicted by their genetic background (excluding the *FBN1* mutation) [Erkula et al 2002].

Cardiovascular. The major sources of morbidity and early mortality in the Marfan syndrome relate to the cardiovascular system.

Cardiovascular manifestations include dilatation of the aorta at the level of the sinuses of Valsalva, a predisposition for aortic tear and rupture, mitral valve prolapse (MVP) with or without regurgitation, tricuspid valve prolapse, and enlargement of the proximal pulmonary artery.

Aortic dilatation in the Marfan syndrome tends to progress over time. Histologic examination reveals fragmentation of elastic fibers, loss of elastin content, and accumulation of amorphous matrix components in the aortic media. This picture of 'cystic medial necrosis' does not distinguish Marfan syndrome from other causes of aortic aneurysm. In adults, a significant risk of aortic dissection or rupture occurs when the maximal dimension reaches about 5.0 centimeters. The onset and rate of progression of aortic dilatation is highly variable. Aortic dissection is exceedingly rare in early childhood. As an aneurysm enlarges, the aortic annulus can become stretched, leading to secondary aortic regurgitation. 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 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 recent study of 50 individuals with Marfan syndrome identified enlarged pulmonary artery root in 74% [Nollen & Mulder 2004].

With proper managementof the cardiovascular manifestations, the life expectancy of someone with Marfan syndrome approximates that of the general population.

Other. Individuals with Marfan syndrome often develop stretching of the dural sac in the lumbosacral region (dural ectasia) that 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 CSF from a dural sac can cause postural hypotension and headache [Foran et al 2005]. Manifestations in the skin and integument include hernias and skin stretch marks (striae distensae). Individuals can show a paucity of muscularity and fat stores despite adequate 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 [Giske et al 2003]. 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.

Pregnancy. Pregnancy can be dangerous for women with the Marfan syndrome, especially if the aortic root exceeds 4.0 cm [Rossiter et al 1995]. Complications include rapid progression of aortic root enlargement and aortic dissection or rupture during pregnancy, delivery, and in the postpartum period.

Self-image. The vast majority of affected individuals over age 13 years report a positive general self-image [De Bie et al 2004].

Genotype-Phenotype Correlations

Few genotype-phenotype correlations exist in the Marfan syndrome; none is definitive [reviewed in Dietz & Pyeritz 2001]. In the absence of definitive phenotype-to-genotype correlations, identification of a mutation in a proband has little prognostic value and has not been proven to reliably guide individual management. The following are some generalizations:

- In those with identified mutations, all individuals with the most severe and rapidly progressive form of Marfan syndrome, sometimes termed "neonatal Marfan syndrome," have alterations in a center portion of the gene between exons 24 and 32. It must be stressed that some individuals with this severe presentation have not had identifiable mutations in this region, and that many other individuals with mutations in this region have classic or even mild variants of Marfan syndrome.
- As a general rule, mutations causing the in-frame loss or gain of central coding sequence through deletions, insertions, or splicing errors are associated with more severe disease.
- Mutations that create a premature termination codon and result in rapid degradation of mutant transcripts can be associated with mild conditions that may fail to meet diagnostic criteria for Marfan syndrome [Dietz et al 1993, Tynan et al 1993, Hayward et al 1994, Nijbroek et al 1995].
- Individuals harboring a mutation preventing C-terminal propeptide processing have shown predominantly skeletal manifestations [Milewicz et al 1995].
- Substitution of amino acids with intuitive functional significance, such as cysteines that participate in intramolecular linkages and residues that dictate the calcium binding affinity of epidermal growth factor-like domains, tend to cause Marfan syndrome of variable severity.
- Substitution of residues without obvious functional importance can be phenotypically neutral or can cause mild disease variants such as mitral valve prolapse syndrome.

Penetrance

While intrafamilial clinical variability can be extensive, no examples of non-penetrance in classic Marfan syndrome have been published.

Anticipation

Anticipation has not been observed in Marfan syndrome.

Nomenclature

Although many have adopted the use of 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.

Prevalence

The estimated prevalence of Marfan syndrome is one in 5-10,000. There is no apparent enrichment in any ethnic or racial group and no gender preference.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Many of the skeletal features of Marfan syndrome are common in the general population. When severe and found it combination, such findings usually indicate a disorder of connective tissue.

Genetically related disorders caused by *FBN1* mutations:

- **MASS phenotype** is an autosomal dominant condition that can be caused by heterozygous mutations in *FBN1*. The acronym MASS stands for **m**itral valve prolapse, myopia, 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. Still, it remains unclear whether some individuals in such a family might be predisposed to more severe vascular involvement, and a regimen of intermittent cardiovascular imaging should be maintained. It is difficult to distinguish MASS phenotype from "emerging" Marfan syndrome when assessing an isolated individual, especially during childhood.
- **Mitral valve prolapse syndrome** is an autosomal dominant condition that associates mitral valve prolapse and skeletal features (often subtle) that are reminiscent of the Marfan syndrome. This condition can be caused by mutations in *FBN1*.
- **Familial ectopia lentis** is an autosomal dominant condition that associates ectopia lentis and variable skeletal manifestations that are reminiscent of the Marfan syndrome. The condition is caused by heterozygous mutations in *FBN1*. It remains unclear whether some individuals in affected families are destined to show later onset of progressive aortic enlargement. A regimen of intermittent cardiovascular imaging should be maintained.
- **Shprintzen-Goldberg syndrome** (SGS) is a condition with an unclear inheritance pattern that associates many features of Marfan syndrome [dolichostenomelia, arachnodactyly, pectus deformity, scoliosis, aortic root enlargement (rare), highly arched palate] with other discriminating features (craniosynostosis, developmental delay, Chiari malformation, hypertelorism, proptosis, rib anomalies, equinovarus deformity). While one case with many of these unique features had an *FBN1* mutation, the presentation was atypical (ectopia lentis was present). It is clear that the majority of cases are not caused by mutations in *FBN1*.

Loeys-Dietz syndrome (LDS) is an autosomal dominant condition that includes many features of Marfan syndrome (long face, downward slant of the palpebral fissues, 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 hypertelorism, broad or bifid uvula, cleft palate, learning disability, hydrocephalus, Chiari I malformation, blue sclerae, exotropia, craniosynostosis, talipes equinovarus, soft and velvety skin, translucent skin, easy bruising, generalized arterial tortuosity and aneurysms, and dissection throughout the arterial tree. Aortic aneurysms behave very differently from those in Marfan syndrome, with frequent dissection and rupture at small dimensions and in early childhood. Surgical repair has not been complicated by the tissue friability observed in vascular Ehlers-Danlos syndrome. The condition is caused by mutations in either the *TGFBR1* or *TGFBR2* gene [Loeys et al 2005].

Other connective tissue disorders. Marfan syndrome shows limited overlap with other connective tissue disorders including the following:

- **Congenital contractural arachnodactyly** (CCA) is an autosomal dominant disorder characterized by a Marfan-like appearance and long, slender fingers and toes. The condition is caused by heterozygous mutations in the *FBN2* gene (encoding

fibrillin-2). Most affected individuals have "crumpled" ears, with a folded upper helix, and most have contractures of knees and ankles at birth, which usually improve with time. The proximal interphalangeal joints also have flexion contractures (i.e., camptodactyly), as do the toes. Hip contractures, adducted thumbs, and club foot may occur. Kyphosis/scoliosis, present in about half of all affected individuals, begins as early as infancy and is progressive. The majority of affected individuals have muscular hypoplasia. In individuals with classic CCA, serious ocular and cardiovascular problems are absent.

- **Familial thoracic aortic aneurysms and aortic dissection (TAAD).** Familial TAAD is an autosomal dominant cardiovascular disorder without other phenotypic manifestations. The aortic disease observed is similar to that observed in the Marfan syndrome and includes dilatation of the aorta and dissections either at the level of the sinuses of Valsalva or the ascending thoracic aorta. *TGFBR2*, the gene encoding transforming growth factor beta receptor type II, and two loci, FAA1 and TAAD1, are known to be associated with TAAD. Further locus heterogeneity is evident.
- **Ehlers-Danlos syndrome** (EDS) is a group of disorders that have joint hypermobility as a common feature.
  - **EDS, classic form** is autosomal dominant and is also characterized by skin hyperextensibility, abnormal wound healing and smooth, velvety skin. Approximately 50% of individuals with classic EDS have an identifiable mutation in the *COL5A1* or *COL5A2* gene.
  - **EDS, kyphoscoliotic form** (previously known as EDS VI) is an autosomal recessive disorder characterized by kyphoscoliosis, joint laxity, muscle hypotonia, and, in some individuals, ocular problems. Affected individuals are at risk for rupture of medium-sized arteries and respiratory compromise if kyphoscoliosis is severe. The kyphoscoliotic form is caused by deficient activity of the enzyme procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 (PLOD1: lysyl hydroxylase 1). The diagnosis of EDS, kyphoscoliotic form relies upon the demonstration of an increased ratio of deoxypyridinoline to pyridinoline crosslinks in urine measured by HPLC, a highly sensitive and specific test. Assay of lysyl hydroxylase enzyme activity in skin fibroblasts is also available. Molecular genetic testing of the *PLOD* gene that encodes the enzyme lysyl hydroxylase 1 is available on a research basis.
  - **EDS, vascular form** (previously known as EDS IV) is an autosomal dominant disorder characterized by joint laxity (often limited to small joints), translucent skin with easily visible underlying veins, easy bruising, wide and dystrophic scars, characteristic facies (prominent eyes and a tight or "pinched" appearance), organ rupture (spleen, bowel, gravid uterus), and a tendency for aneurysm and/or dissection of any medium to large muscular artery throughout the body. Unlike in Marfan syndrome, there is no particular tendency for involvement of the aortic root, although this location is not spared from risk. The tissues can be extremely friable, often contributing to surgical catastrophe. The condition is caused by mutations in *COL3A1*; the diagnosis can be confirmed by observation of abnormal type III collagen biosynthesis by cultured dermal fibroblasts.
- **Homocystinuria** is an autosomal recessive disorder caused by cystathionine-synthase deficiency resulting from mutations in the *CBS* gene. The disorder is characterized by variable mental retardation, ectopia lentis and/or severe myopia, skeletal abnormalities (including excessive height and limb length) and a tendency for intravascular thrombosis and thromboembolic events. Overlap with Marfan syndrome

can be extensive and includes an aesthenic (long and lean) body habitus, pectus deformity, scoliosis, mitral valve prolapse, highly arched palate, hernia, and ectopia lentis. Thromboembolic events can be life threatening. About half of affected individuals are responsive to pharmacologic doses of vitamin B6, highlighting the need to consider this diagnosis.

- **Stickler syndrome** is an autosomal dominant connective tissue disorder that can include ocular findings of myopia, cataract, and retinal detachment; hearing loss that is both conductive and sensorineural; midfacial hypoplasia and cleft palate (either alone or as part of the Robin sequence); and mild spondyloepiphyseal dysplasia and/or precocious arthritis. The diagnosis of Stickler syndrome is clinically based. Mutations affecting one of three genes *(COL2A1*, *COL11A1*, and *COL11A2*) have been associated with Stickler syndrome.
- **Fragile-X syndrome** is an X-linked disorder characterized by moderate mental retardation in affected males and mild mental retardation in affected females. Males may have a characteristic appearance (large head, long face, prominent forehead and chin, protuding ears) and connective tissue findings (joint laxity) that suggest the Marfan syndrome phenotype. They also have large testes (postpubertally). Behavioral abnormalities, sometimes including autism spectrum disorder, are common. More than 99% of individuals with fragile X syndrome have a full mutation in the *FMR1* gene caused by an increased number of CGG trinucleotide repeats (>200 typically) accompanied by aberrant methylation of the *FMR1* gene.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Evaluation by an ophthalmologist with expertise in Marfan syndrome, including: slit lamp examination through a maximally dilated pupil to see lens subluxation; careful refraction and visual correction, especially in young children at risk for amblyopia; specific assessment for glaucoma and cataracts
- Evaluation for skeletal manifestations that may require immediate attention by an orthopedist (e.g., severe scoliosis)
- Echocardiography. Aortic root measurements must be interpreted based upon consideration of normal values for age and body size [Roman et al 1989]. Click here to see nomograms. Selected findings may require the immediate attention of a cardiologist or cardiothoracic surgeon (e.g., severe valve dysfunction, severe aortic dilatation, congestive heart failure, history or evidence suggestive of arrhythmia).

Treatment of Manifestations

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

Eye

- The ocular manifestations of Marfan syndrome should be managed by an ophthalmologist with expertise in this condition.
- Most often, eye problems can be adequately controlled with eyeglasses alone.
- Lens dislocation can require surgical aphakia if the lens is freely mobile or the margin of the lens obstructs vision. An artificial lens can be implanted once growth is

complete. While this procedure is currently considered quite safe when performed in specialized centers, major complications, including retinal detachment, can occur.

- Careful and aggressive refraction and visual correction is mandatory in young children at risk for amblyopia.

Skeletal

- Bone overgrowth and ligamentous laxity can lead to severe problems (including progressive scoliosis) and should be managed by an orthopedist; surgical stabilization of the spine may be required.
- Pectus excavatum can be severe; in rare circumstances, surgical intervention is medically (rather than cosmetically) indicated.
- Protusio acetabulae can be associated with pain or functional limitations. Surgical intervention is rarely indicated.
- Pes planus is often associated with inward rotation at the ankle, contributing to difficulty with ambulation, leg fatigue, and muscle cramps. Orthotics are only indicated in severe cases. Some individuals prefer use of arch supports, while others find them irritating; the choice should be left to personal preference. Surgical intervention is rarely indicated or fully successful.
- Dental crowding may require orthodonture or use of a palatal expander.
- Use of hormone supplementation to limit adult height is rarely requested or considered. Complications can include the psychosocial burden of accelerated puberty or 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. This treatment should only be considered when an extreme height is anticipated. Marfan syndrome-specific growth curves now allow accurate prediction of adult height.

Cardiovascular

- All individuals with Marfan syndrome should be managed by a cardiologist who is familiar with this condition.
- Medications that reduce hemodynamic stress on the aortic wall, such as beta blockers, are routinely prescribed [Shores et al 1994]. This therapy should be managed by a cardiologist or 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. The dose needs to be titrated to effect, keeping heart rate after submaximal exercise or agitation less than 110 in young children or less than 100 in older children or adults.
  - Verapamil is commonly used if beta blockers cannot be used (e.g., in individuals with asthma) or are not tolerated (e.g., prolonged lethargy, depression).
  - Yetman and colleagues (2005) suggested that use of ACE inhibitors may be more beneficial than beta blockers. Of note, the treatments were not randomized and the dose of beta-blocker was not titrated to effect. ACE inhibitors have been used for decades in Marfan syndrome to manage volume overload resulting from valve dysfunction, and (unlike beta-blockers) have not previously been reported to provide notable protection from progressive aortic enlargement.

  - There is at least some theoretical concern that reducing afterload without a concomitant reduction in inotropy (as provided by a beta blocker) could increase hemodynamic stress in the ascending aorta. Currently, afterload-reducing agents are only commonly used in conjunction with a beta-blocker to manage volume overload in the setting of valve dysfunction. Their isolated use does not seem warranted in the absence of additional study.

- Surgical repair of the aorta is indicated once: (1) the maximal measurement exceeds 5.0 cm in adults or older children, (2) the rate of increase of the aortic diameter approaches 1.0 cm per year, or (3) there is progressive aortic regurgitation. More aggressive therapy may be indicated in individuals with a family history of early aortic dissection. Many individuals can receive a valve-sparing procedure that precludes the need for chronic anticoagulation.
- 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.
- Judicious use of subacute bacterial endocarditis (SBE) prophylaxis is indicated for dental work or other procedures expected to contaminate the bloodstream with bacteria.

Other

- Dural ectasia is usually asymptomatic. No effective therapies for symptomatic dural ectasia currently exist.
- Hernias tend to recur after surgical intervention. A supporting mesh can be used during surgical repair to minimize this risk.
- Pneumothorax can be a recurrent problem. Optimal management may require chemical or surgical pleurodesis or surgical removal of pulmonary blebs.

Surveillance

All individuals with Marfan syndrome, with or without lens dislocation, should be seen by an ophthalmologist on a yearly basis; evaluations should include a specific assessment for glaucoma and cataracts.

Individuals with severe or progressive scoliosis should be followed by an orthopedist.

All individuals with Marfan syndrome require echocardiography at frequent intervals to monitor the status of the ascending aorta. Yearly examinations are sufficient with relatively small aortic dimensions and slow rates of aortic dilation. More frequent examinations are indicated when the aortic root diameter exceeds about 4.5 centimeters in adults, with rates of aortic dilation that exceed about 0.5 cm per year, and with the onset of significant aortic regurgitation. More frequent evaluations by a cardiologist are indicated with severe or progressive valve or ventricular dysfunction or with documented or suspected arrhythmia.

All individuals with Marfan syndrome should begin intermittent surveillance of the entire aorta with CT or MRA scans in young adulthood. Such imaging should be performed 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. 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.
- Lasik correction of visual deficits is contraindicated.
- For individuals at risk for recurrent pneumothorax, breathing against a resistance (e.g., playing a brass instrument) or positive pressure ventilation (e.g., SCUBA diving) should be avoided.

Testing of Relatives at Risk

Relatives of an individual with Marfan syndrome should be evaluated for signs of the disorder.

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. 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.

Note: All first-degree relatives of an individual with apparent isolated aortic enlargement should be evaluated by echocardiography.

Therapies Under Investigation

Experimental evidence suggests that many manifestations of Marfan syndrome relate to excess activation and signaling by the growth factor TGFbeta. Animal trials are underway to determine whether TGFbeta antagonists can slow or prevent manifestations of Marfan syndrome. The safety and efficacy of such interventions has not been addressed for people with Marfan syndrome.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Pregnancy should only be considered after appropriate counseling from a geneticist or cardiologist familiar with this condition, a genetic counselor, and a high-risk obstetrician. Pregnancy can be associated with the risk of more rapid dilation of the aorta or aortic dissection, either during pregnancy or in the immediate postpartum period This appears to be especially relevant to individuals who begin preganancy with a maximal aortic dimension that exceeds 4.0cm [Rossiter et al 1995].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Marfan syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About 75% of individuals diagnosed with Marfan syndrome have an affected parent.
- About 25% of probands with Marfan syndrome have the disorder as the result of a *de novo* gene mutation.
- It is appropriate to evaluate both parents for manifestations of Marfan syndrome by performing a comprehensive clinical examination and an echocardiogram.

Note: Although 75% of individuals diagnosed with Marfan syndrome have an affected parent, the family history 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.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low but above the population risk because of reported (but rare) cases of somatic and germline mosaicism.

Offspring of a proband

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

Other family members of a proband. The risk to other family members depends upon the genetic status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations, including alternate paternity or undisclosed adoption, could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk for Marfan syndrome is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation is analyzed. The disease-causing allele of an affected family member must be identified or linkage established in the family before prenatal testing can be performed. Linkage analysis should be used with caution unless *FBN1* marker alleles can be shown to cosegregate with disease in a large family.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Ultrasound examination. Ultrasound examination in the first two trimesters is insensitive in detecting manifestations of Marfan syndrome [Burke & Pyeritz 1998].

Requests for prenatal testing for Marfan syndrome are uncommon. [Loeys et al 2002]. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Marfan Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
FBN1	15q21.1	Fibrillin 1

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Marfan Syndrome

134797	FIBRILLIN 1; FBN1
154700	MARFAN SYNDROME; MFS

Table C. Genomic Databases for Marfan Syndrome

Gene Symbol	Entrez Gene	HGMD
FBN1	2200 (MIM No. 134797)	FBN1

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

Normal allelic variants: The *FBN1* gene is large (over 600 kb) and the coding sequence is highly fragmented (65 exons). The promoter region is large and poorly characterized. High evolutionary conservation of intronic sequence at the 5' end of the gene suggests the presence of intronic regulatory elements. Three exons at the extreme 5' end of the gene are alternatively utilized and do not appear to contribute to the coding sequence.

Pathologic allelic variants: Over 200 *FBN1* mutations that cause Marfan syndrome or related phenotypes have been described [Vollbrandt et al 2004]. No common mutation exists in any population. (For more information, see Genomic Databases table above.)

Normal gene product: Fibrillin 1 is an extracellular matrix protein that contributes to large structures called microfibrils. Microfibrils are found in both elastic and nonelastic tissues. They participate in the formation and homeostasis of the elastic matrix, in matrix-cell attachments, and possibly in the regulation of selected growth factors. Studies in animal models of Marfan syndrome have demonstrated that microfibrils regulate the matrix sequestration and activation of the growth factor TGFbeta. Excess TGFbeta signaling has been observed in the developing lung, the mitral valve and the ascending aorta [Neptune et al 2003, Ng et al 2004, Loeys et al 2005]. TgFbeta antagonism in vivo has been shown to rescue the pulmonary emphysema and myxomatous changes of the mitral valve seen in fibrillin-1 deficient mice. 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].

Abnormal gene product: Mutant forms of fibrillin 1 are believed to have dominant-negative activity. That is, the mutant forms can interfere with the utilization of the normal protein derived from the opposite allele. A hallmark feature of the Marfan syndrome is a severe reduction of microfibrils in explanted tissues and in the matrix deposited by cultured dermal fibroblasts. The residual level of protein is generally far below the 50% level predicted by the presence of a wild-type copy of *FBN1* in all affected individuals.

Marfan syndrome and related disorders can also be caused by mutations, such as premature termination codons, that reduce expression from the mutant allele. Thus, haploinsufficiency may also contribute to the pathogenesis of disease. Animal studies suggest that half-normal amounts of fibrillin-1 (i.e., haploinsufficiency) may be insufficient to initiate productive microfibrillar assembly [Judge et al 2004]. Polymorphic variation regulating the output of the wild-type allele can contribute to the severity of disease in the haploinsufficient state [Hutchinson et al 2003].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select*  *for the most up-to-date Resources information.*—ED.

Canadian Marfan Association
Centre Plaza Postal Outlet
128 Queen Street South
PO Box 42257
Mississauga, Ontario, L5M4Z0, Canada
Phone: 866-722-1722 (toll-free); 905-826-3223
Fax: 905-826-2125
Email: info@marfan.ca
www.marfan.ca

National Library of Medicine Genetics Home Reference
Marfan syndrome

National Marfan Foundation
22 Manhasset Avenue
Port Washington, NY 11050
Phone: 800-8-MARFAN (800-862-7326); 516-883-8712
Fax: 516-883-8040
Email: staff@marfan.org
www.marfan.org

NCBI Genes and Disease
Marfan syndrome

Medline Plus
Connective Tissue Disorders

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Aoyama T, Francke U, Gasner C, Furthmayr H. Fibrillin abnormalities and prognosis in Marfan syndrome and related disorders. Am J Med Genet. 1995;58:169–76. [PubMed: 8533811]

Booms P, Pregla R, Ney A, Barthel F, Reinhardt DP, Pletschacher A, Mundlos S, Robinson PN. RGD-containing fibrillin-1 fragments upregulate matrix metalloproteinase expression in cell culture: a potential factor in the pathogenesis of the Marfan syndrome. Hum Genet. 2005;116:51–61. [PubMed: 15517394]

Brenn T, Aoyama T, Francke U, Furthmayr H. Dermal fibroblast culture as a model system for studies of fibrillin assembly and pathogenetic mechanisms: defects in distinct groups of individuals with Marfan's syndrome. Lab Invest. 1996;75:389–402. [PubMed: 8804362]

Bunton TE, Biery NJ, Myers L, Gayraud B, Ramirez F, Dietz HC. Phenotypic alteration of vascular smooth muscle cells precedes elastolysis in a mouse model of Marfan syndrome. Circ Res. 2001;88:37–43. [PubMed: 11139471]

Burke LW, Pyeritz RE. Prenatal diagnosis of connective tissue disorders. In: Milunsky A (ed) Genetic Disorders and the Fetus: Diagnosis, Prevention and Treatment, 4 ed. Johns Hopkins Univ Press, Baltimore, pp 612-34. 1998

De Bie S, De Paepe A, Delvaux I, Davies S, Hennekam RC. Marfan syndrome in Europe. Community Genet. 2004;7:216–25. [PubMed: 15692197]

De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet. 1996;62:417–26. [PubMed: 8723076]

Dietz HC, Pyeritz RE. Marfan syndrome and related disorders. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The Metabolic and Molecular Bases of Inherited Disease, 8 ed. McGraw-Hill, New York, pp 5287-311. 2001

Dietz HC, McIntosh I, Sakai LY, Corson GM, Chalberg SC, Pyeritz RE, Francomano CA. Four novel FBN1 mutations: significance for mutant transcript level and EGF-like domain calcium binding in the pathogenesis of Marfan syndrome. Genomics. 1993;17:468–75. [PubMed: 8406497]

Erkula G, Jones KB, Sponseller PD, Dietz HC, Pyeritz RE. Growth and maturation in Marfan syndrome. Am J Med Genet. 2002;109:100–15. [PubMed: 11977157]

Faivre L, Gorlin RJ, Wirtz MK, Godfrey M, Dagoneau N, Samples JR, Le Merrer M, Collod-Beroud G, Boileau C, Munnich A, Cormier-Daire V. In frame fibrillin-1 gene deletion in autosomal dominant Weill-Marchesani syndrome. J Med Genet. 2003;40:34–6. [PubMed: 12525539]

Foran JR, Pyeritz RE, Dietz HC, Sponseller PD. Characterization of the symptoms associated with dural ectasia in the Marfan patient. Am J Med Genet A. 2005;134:58–65. [PubMed: 15690402]

Giske L, Stanghelle JK, Rand-Hendrikssen S, Strom V, Wilhelmsen JE, Roe C. Pulmonary function, working capacity and strength in young adults with Marfan syndrome. J Rehabil Med. 2003;35:221–8. [PubMed: 14582554]

Halliday DJ, Hutchinson S, Lonie L, Hurst JA, Firth H, Handford PA, Wordsworth P. Twelve novel FBN1 mutations in Marfan syndrome and Marfan related phenotypes test the feasibility of FBN1 mutation testing in clinical practice. J Med Genet. 2002;39:589–93. [PubMed: 12161601]

Hayward C, Porteous ME, Brock DJ. Identification of a novel nonsense mutation in the fibrillin gene (FBN1) using nonisotopic techniques. Hum Mutat. 1994;3:159–62. [PubMed: 7911051]

Hutchinson S, Furger A, Halliday D, Judge DP, Jefferson A, Dietz HC, Firth H, Handford PA. Allelic variation in normal human FBN1 expression in a family with Marfan syndrome: a potential modifier of phenotype? Hum Mol Genet. 2003;12:2269–76. [PubMed: 12915484]

Judge DP, Biery NJ, Keene DR, Geubtner J, Myers L, Huso DL, Sakai LY, Dietz HC. Evidence for a critical contribution of haploinsufficiency in the complex pathogenesis of Marfan syndrome. J Clin Invest. 2004;114:172–81. [PubMed: 15254584]

Korkko J, Kaitila I, Lonnqvist L, Peltonen L, Ala-Kokko L. Sensitivity of conformation sensitive gel electrophoresis in detecting mutations in Marfan syndrome and related conditions. J Med Genet. 2002;39:34–41. [PubMed: 11826022]

Loeys B, De Backer J, Van Acker P, Wettinck K, Pals G, Nuytinck L, Coucke P, De Paepe A. Comprehensive molecular screening of the FBN1 gene favors locus homogeneity of classical Marfan syndrome. Hum Mutat. 2004;24:140–6. [PubMed: 15241795]

Loeys B, Nuytinck L, Van Acker P, Walraedt S, Bonduelle M, Sermon K, Hamel B, Sanchez A, Messiaen L, De Paepe A. Strategies for prenatal and preimplantation genetic diagnosis in Marfan syndrome (MFS). Prenat Diagn. 2002;22:22–8. [PubMed: 11810645]

Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, Holm T, Meyers J, Leitch CC, Katsanis N, Sharifi N, Xu FL, Myers LA, Spevak PJ, Cameron DE, De Backer J, Hellemans J, Chen Y, Davis EC, Webb CL, Kress W, Coucke P, Rifkin DB, De Paepe AM, Dietz HC. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet. 2005;37:275–81. [PubMed: 15731757]

Milewicz DM, Grossfield J, Cao SN, Kielty C, Covitz W, Jewett T. A mutation in FBN1 disrupts profibrillin processing and results in isolated skeletal features of the Marfan syndrome. J Clin Invest. 1995;95:2373–8. [PubMed: 7738200]

Mizuguchi T, Collod-Beroud G, Akiyama T, Abifadel M, Harada N, Morisaki T, Allard D, Varret M, Claustres M, Morisaki H, Ihara M, Kinoshita A, Yoshiura K, Junien C, Kajii T, Jondeau G, Ohta T, Kishino T, Furukawa Y, Nakamura Y, Niikawa N, Boileau C, Matsumoto N. Heterozygous TGFBR2 mutations in Marfan syndrome. Nat Genet. 2004;36:855–60. [PubMed: 15235604]

Neptune ER, Frischmeyer PA, Arking DE, Myers L, Bunton TE, Gayraud B, Ramirez F, Sakai LY, Dietz HC. Dysregulation of TGF-beta activation contributes to pathogenesis in Marfan syndrome. Nat Genet. 2003;33:407–11. [PubMed: 12598898]

Ng CM, Cheng A, Myers LA, Martinez-Murillo F, Jie C, Bedja D, Gabrielson KL, Hausladen JM, Mecham RP, Judge DP, Dietz HC. TGF-beta-dependent pathogenesis of mitral valve prolapse in a mouse model of Marfan syndrome. J Clin Invest. 2004;114:1586–92. [PubMed: 15546004]

Nijbroek G, Sood S, McIntosh I, Francomano CA, Bull E, Pereira L, Ramirez F, Pyeritz RE, Dietz HC. Fifteen novel FBN1 mutations causing Marfan syndrome detected by heteroduplex analysis of genomic amplicons. Am J Hum Genet. 1995;57:8–21. [PubMed: 7611299]

Nollen GJ, Mulder BJ. What is new in the Marfan syndrome? Int J Cardiol 97 Suppl. 2004;1:103–8. [PubMed: 15590086]

Robinson PN, Godfrey M. The molecular genetics of Marfan syndrome and related microfibrillopathies. J Med Genet. 2000;37:9–25. [PubMed: 10633129]

Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. Am J Cardiol. 1989;64:507–12. [PubMed: 2773795]

Rossiter JP, Repke JT, Morales AJ, Murphy EA, Pyeritz RE. A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. Am J Obstet Gynecol. 1995;173:1599–606. [PubMed: 7503207]

Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term beta- adrenergic blockade in Marfan's syndrome. N Engl J Med. 1994;330:1335–41. [PubMed: 8152445]

Sood S, Eldadah ZA, Krause WL, McIntosh I, Dietz HC. Mutation in fibrillin-1 and the Marfanoid-craniosynostosis (Shprintzen-Goldberg) syndrome. Nat Genet. 1996;12:209–11. [PubMed: 8563763]

Tynan K, Comeau K, Pearson M, Wilgenbus P, Levitt D, Gasner C, Berg MA, Miller DC, Francke U. Mutation screening of complete fibrillin-1 coding sequence: report of five new mutations, including two in 8-cysteine domains. Hum Mol Genet. 1993;2:1813–21. [PubMed: 8281141]

Vollbrandt T, Tiedemann K, El-Hallous E, Lin G, Brinckmann J, John H, Batge B, Notbohm H, Reinhardt DP. Consequences of cysteine mutations in calcium-binding epidermal growth factor modules of fibrillin-1. J Biol Chem. 2004;279:32924–31. [PubMed: 15161917]

Yetman AT, Bornemeier RA, McCrindle BW. Usefulness of enalapril versus propranolol or atenolol for prevention of aortic dilation in patients with the Marfan syndrome. Am J Cardiol. 2005;95:1125–7. [PubMed: 15842990]

Chapter Notes

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