Marfan syndrome

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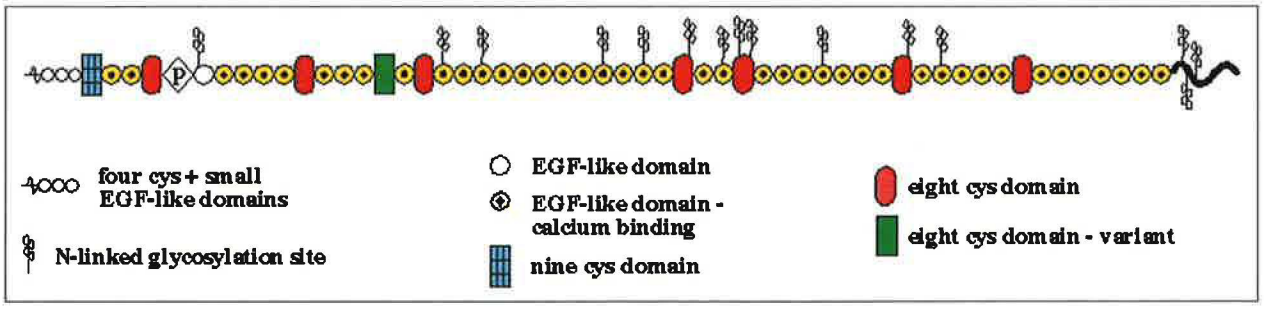


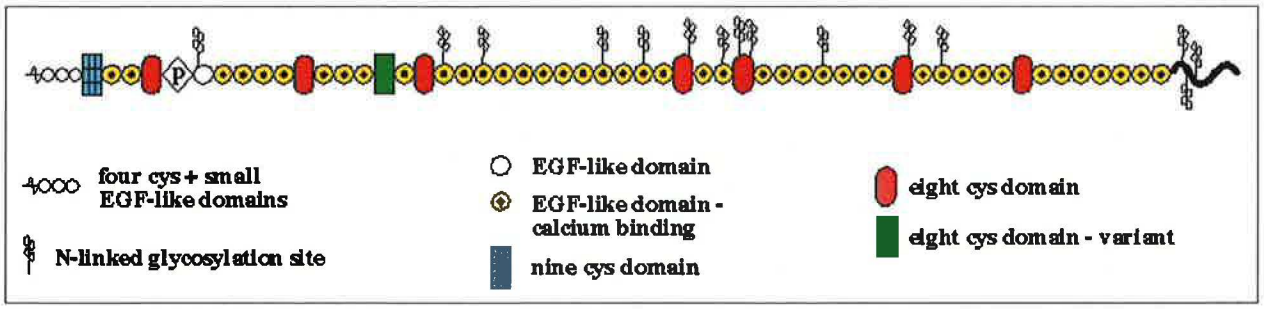
National Marfan Foundation

Biographical sketch: Dr. Brickner graduated from Ohio State University, completed an Internal Medicine Residency at the University of Michigan, and then completed her cardiology fellowship here at UT Southwestern. She has been a member of the faculty since 1991 in the division of Cardiology. Her clinical interests are in the diagnosis and treatment of adult congenital heart disease, Marfan syndrome and other genetic cardiovascular disorders, and valvular heart disease, as well as cardiac imaging by echocardiography.

Flo Hyman, a member of the US 1984 women's Olympic Volleyball team, died on the volleyball court in Japan in 1986 of aortic rupture. Initially, the cause of death was felt to be a heart attack but her family requested an autopsy which revealed a dilated ascending aorta with aortic rupture as the cause of death. There was evidence that the initial rupture had occurred several weeks prior to her death, with a retained clot "around the tear", suggesting that her initial dissection had occurred several weeks earlier. She was not known to have Marfan syndrome, although in retrospect her height (6'5"), very long arms, large hands and feet, and significant myopia were consistent with that diagnosis. Her family members were later examined by Dr. Reed Pyeritz at Johns Hopkins University where her brother was also found to have Marfan syndrome and underwent aortic surgery. Dr. Pyertiz then appeared on "Good Morning America" to discuss Marfan syndrome. This was followed by an article in Sports Illustrated which increased public awareness of this disorder.[i]

Marfan syndrome is an autosomal dominant disorder of connective tissue due to a mutation in the FBN1 gene on chromosome 15q21. The gene encodes for the glycoprotein fibrillin-1 which is a major component of extracellular matrix microfibrils. These microfibrils exist as isolated aggregates and in association with elastin fibrils where they play a critical role in the mechanical properties of elastic fibers. Abnormalities in the connective tissues of patients with Marfan syndrome result in abnormalities of the cardiac, ocular, and skeletal systems as well as involving other organ systems. This is a common disorder, occurring in 1 in 5,000 persons. The clinical presentation is highly variable and ranges from isolated features of the disorder to neonatal presentation with multiorgan system involvement and rapidly progressive disease. The clinical phenotype can be quite variable within individual families. Approximately 75% of affected persons with Marfan syndrome have an affected parent, while the remaining 25% of probands have a de novo mutation.

The Fibrillin-1 gene



http://ef.wustl.edu/genes/FBN1.htm

From a historical perspective, the first published description of a patient with Marfan syndrome was published in 1876 in an ophthalmology journal. E. Williams published a case report of 2 siblings with ectopia lentis who were also particularly tall and loose jointed.[ii] In 1896, Antoine Bernard-Jean Marfan, a pediatrician in Paris, published the case history of "Gabrielle P." a 5 ½ year old girl with dolichostenomelia (disproportionally long extremities), scoliosis, and fibrous contractures of the fingers.[iii] While Marfan syndrome has come to bear his name, some authorities suspect that Marfan's original case description was actually a case of Beall syndrome or congenital contractural arachnodacytly, another inherited collagen vascular disorder. In 1912, Salle reported the first case of infantile Marfan syndrome, documenting the necropsy findings in a 2 ½ year old infant. In 1914, Beorger first reported the finding of ectopia lentis in association with other findings of Marfan syndrome. The genetic nature of Marfan syndrome was first described in 1931 by Weve, who named the constellation of findings "dystrophic mesodermalis congenital, typus marfanus". Cardiovascular complications (specifically, aortic complications) were first described in 1943 by physicians at Johns Hopkins – R.W. Baer, Helen Taussig, and Ella Openheimer. In 1955, Dr. John McKusick at Johns Hopkins established a formal classification of inherited connective tissue disorders, including Marfan syndrome. In 1986, an international panel of experts (including McKusick) defined a set of specific clinical criteria for the diagnosis of Marfan syndrome, the Berlin Nosology. [iv]

In 1991, the underlying gene defect in Marfan syndrome was defined with the identification of the FBN1 gene (encoding fibrillin -1). Dietz, et al. published their results in Nature.[v] Through genetic analysis, it was recognized that the Berlin criteria allowed for false positive diagnoses and more specific criteria were defined in 1996, the Ghent Nosology.[vi]

1996 Ghent criteria

The 1996 Ghent criteria focused on the presence of absence of a family history of Marfan syndrome and the observation of characteristic findings in multiple organ systems. The four clinical findings of major diagnostic significance were: Dilatation or dissection of the aorta at the level of the sinus of Valsalva, ectopia lentis, dural ectasia, and four of eight specific skeletal features as listed below.

Diagnostic criteria for the Skeletal System

Major criteria	Minor criteria
Pectus carinatum OR pectus excavatum requiring surgery*	Pectus excavatum of moderate severity*
Reduced upper to lower segment ration for age (< 0.85 for older children and adults) OR arm span to height ratio > 1.05*	Joint hypermobility**
Wrist (Walker-Murdoch) and thumb (Steinberg) signs*	Highly arched palate with tooth crowding**

Scoliosis of > 20° OR spondylolisthesis*	Facial appearance (dolicocephaly, malar hypoplasia, enopathalmos, retrognathia, down-slanting palpebral fissures)
Elbow extension < 170°	
Medial rotation of the medial malleolus causing pes planus	
Protrusio acetabuli (abnormally deep acetabulum with accelerated erosion) of any degree on x-ray	

*indicates criteria revised in the new 2010 Ghent criteria, **indicates criteria removed

Major involvement of the skeletal system in the 1996 criteria required ≥ 4 major criteria whereas minor involvement of the skeletal system required 2 major components or 1 major component and ≥ 2 minor criteria.

Diagnostic criteria for the Ocular System

Major criteria	Minor criteria
Ectopia lentis	Abnormally flat cornea (measured by keratometry)**
	Increased axial length of the globe*
	Hypoplastic iris or ciliary muscle causing decreased papillary miosis**

*indicates criteria revised in the new 2010 Ghent criteria, **indicates criteria removed

Major involvement of the ocular system required the presence of ectopia lentis, while minor involvement required ≥ 2 minor criteria.

Diagnostic criteria for the Cardiovascular System

Major criteria	Minor criteria
Dilatation of the ascending aorta involving the sinuses of Valsalva*	Mitral valve prolapse ± mitral regurgitation
Dissection of the ascending aorta	Dilatation of the main pulmonary artery without obvious cause at age < 40 years**
	Calcification of the mitral annulus at any age**
	Dilatation/dissection of the descending thoracic or abdominal aorta at age < 50 years**

*indicates criteria revised in the new 2010 Ghent criteria, **indicates criteria removed

Major involvement of the cardiovascular system required ≥ 1 major criterion, while minor involvement required ≥ 1 criterion.

Diagnostic criteria for other organ systems

Pulmonary	
Major criteria	Minor criteria (≥1)
	Spontaneous pneumothorax
	Apical blebs on CXR**
Skin and integument	
Major criteria	Minor criteria (≥1)
	Stria atrophicae without obvious cause
	Recurrent or incisional hernia**
Dura	
Major criteria	
Lumbosacral dural ectasia (ascertained by CT or MRI)*	

*indicates criteria revised in the new 2010 Ghent criteria, **indicates criteria removed

Family and Genetic History criteria

Major criteria	**Minor criteria**
Parent, child, or sibling who meets diagnostic criteria independently	
FBN1 mutation known to cause Marfan syndrome*	
Haplotype around FBN1, inherited by descent, known to be associated with Marfan syndrome in the family (as ascertained by linkage analysis)	

*indicates criteria revised in the new 2010 Ghent criteria

Since the diagnosis of Marfan syndrome is associated with a risk for aortic aneurysm and dissection, there is a significant detriment to patients who are inappropriately given the diagnosis. Certainly, there is significant anxiety over potential health risks as well as increased health care expenditures associated with screening tests. In addition, patients may be denied or incur increased expense for health insurance and live insurance (usually denied), may be restricted from activities, and may make reproductive decisions on the basis of an incorrect diagnosis. In addition, a variety of conditions with overlapping cardiovascular features and systemic features has markedly broadened the differential diagnosis of Marfan syndrome. Thus, in 2010 an international panel convened and published a new nosology, the revised Ghent criteria. [vii]

The revised Ghent nosology (2010)

The revised Ghent nosology gave substantially more weight to the two cardinal features of the syndrome – aortic root aneurysm and/or dissection and ectopia lentis. All other findings (previously divided into organ systems) now contribute to a global "system score" which is applied when aortic disease is present but ectopia lentis is not. Some of the less specific clinical findings were either removed from the criteria entirely or given a less significant role in the diagnostic evaluation. The finding of aortic root dilatation has been more formalized, based on echocardiographic imaging. The criteria now require that the aortic dimension be measured at the level of the sinus of Valsalva and that the patient have a "Z score" ≥ 2 in order to meet diagnostic criteria. A Z score is a correction factor for predicted aortic root size, based on patient size and age. The reporting of Z scores has been well validated in pediatric echocardiography but is not commonly used in adult echocardiography and is less well validated. The Cornell data base formulae provide standards for children up to age 15, adults aged 20-40, and adults > 40 years of age.[viii]

For adults age 20-40
Mean predicted aortic root diameter (cm) for BSA = 0.97 + (1.12 x BSA)
SD = 0.24cm
Z = (measured root diameter – predicted AR) / 0.24
For adults age > 40
Mean predicted aortic root diameter (cm) for BSA = 1.92 + (0.74 x BSA)
SD = 0.37cm
Z = (measured root diameter – predicted AR) / 0037

A more prominent role is also assigned to genetic testing. The new criteria stress the utilization of testing for FBN1 mutations and other relevant genes (see section on differential diagnosis) but do not mandate such testing. FBN1 mutation testing does not yet have 100% sensitivity and specifity and thus, the absence of a FBN1 mutation despite complete gene screening is possible in Marfan syndrome. Finally, the new criteria specifically state that additional diagnostic testing is required for patients that meet the diagnostic criteria for Marfan syndrome but have unexpected findings or findings suggestive of a specific alternate diagnosis.

The new diagnostic criteria are simpler. If there is no family history of Marfan (suspected de novo mutation), then 4 rules apply.

Aortic root enlargement (defined as a Z score ≥ 2) and ectopia lentis = MFS*
Aortic root enlargement and a causal FBN 1 mutation = MFS
Aortic root enlargement and ≥ 7 points on the system score = MFS*
Ectopia lentis and a causal FNB mutation with known aortic dilatation (Z score < 2) = MFS

*without discriminating features of Shpritzen-Goldberg syndrome, Loeys-Dietz syndrome, or vascular, valvular and kyphoscoliotic types of Ehlers-Danlos AND after TGFBR1/1, collagen biochemistry, COL3A1 testing if indicated.

In the presence of a family history of Marfan syndrome, 3 rules apply.

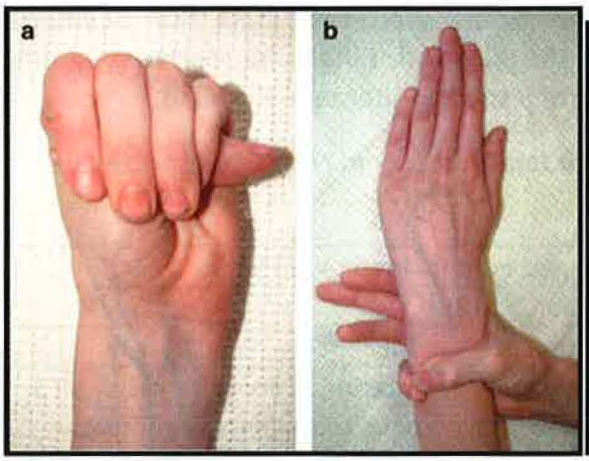
Ectopia lentis and a family history of MFS = MFS
Systemic score ≥ 7 points and a family history of MFS = MFS *
Aortic root enlargement (defined as a Z score ≥ 2) and a family history of MFS = MFS*

*without discriminating features of Shpritzen-Goldberg syndrome, Loeys-Dietz syndrome, or vascular, valvular and kyphoscoliotic types of Ehlers-Danlos AND after TGFBR1/1, collagen biochemistry, COL3A1 testing if indicated.

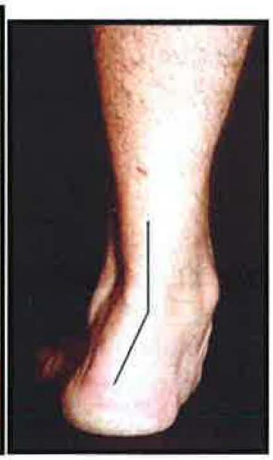
The scoring system for systemic features is listed below:

Wrist and thumb sign	3 pts	Wrist or thumb sign	1 pt
Pectus carinatum	2 pts	Pectus excavatum or chest asymmetry	1 pt
Hindfoot deformity	2 pts	Plain pes planus	1 pt
Pneumothorax	2 pts		
Dural ectasia	2 pts		
Protrusio acetabuli	2 pts		
Reduced US/LS and increased arm/height ratio with no severe scoliosis	1 pt		
Scoliosis or thoracolumbar kyphosis	1 pt		
Reduced elbow extension	1 pt		
Facial features (3/5)	1 pt		
Skin striae	1 pt		
Myopia > 3 diopters	1 pt		
Mitral valve prolapse	1 pt		

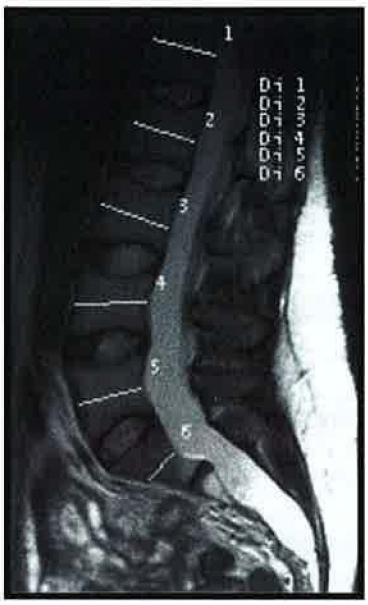
The maximum total points are 20. A score ≥ 7 indicates systemic involvement.



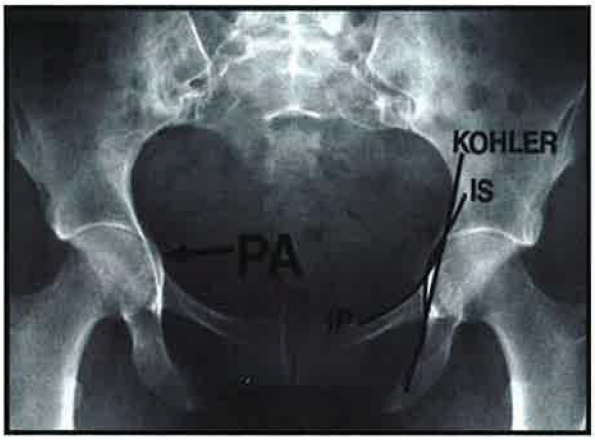
Wrist and thumb signs.



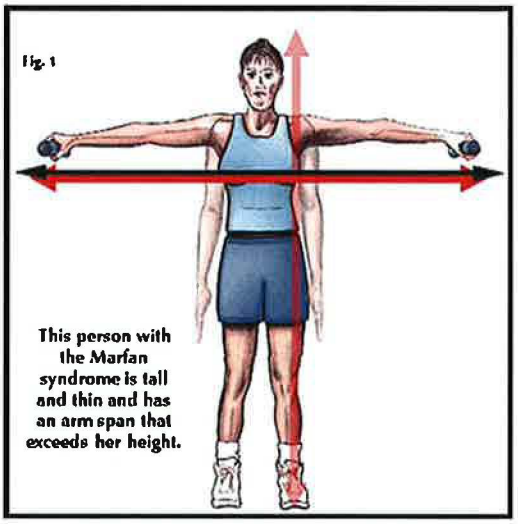
Hindfoot deformity



Dural ectasia by MRI



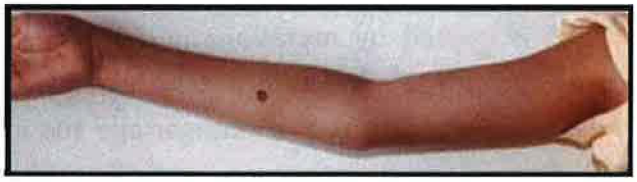
Protrusio acetabuli



Reduced upper to lower segment ratio:
< 0.85 for white adults
< 0.78 in black adults

and

Arm span to height ratio > 1.05



Reduced elbow extension

The criteria for a causal mutation are listed below.

Mutation previously shown to segregate in Marfan family	
De novo mutation (with proven paternity and absence of disease in parents)	
	Nonsense mutation
	Inframe and out of frame deletion/insertion
	Splice site mutations affecting canonical splice sequence or shown to alter splicing on mRNA/cDNA level
	Missense affecting/creating cysteine residues
	Missense affecting conserved residues of the EGF consensus sequence
Other missense mutations with segregation in the family if possible and absence in 400 ethnically matched control chromosomes. If no family history, absence in 400 ethnically matched control chromosomes.	
Linkage of haplotype for n ≥ 6 meiosis to the FBN1 locus	

The differential diagnosis for Marfan syndrome has expanded considerably (see table). Among the major diagnostic considerations are Ectopia Lentis syndrome with lack of aortic root dilatation, MASS phenotype (requires at least of the following: myopia, mitral valve prolapse, borderline aortic root enlargement, skin and minor skeletal criteria), and mitral valve prolapse syndrome (often with pectus excavatum, scoliosis, and mild arachnodactyly – no aortic root dilatation and no ectopia lentis. Bicuspid aortic valves (seen in 2% of the general population) may be associated with aortic root dilatation but lack the skeletal and ocular features seen in Marfan syndrome. Bicuspid valves (with or without aortic dilatation) may be familial.[ix] [x] [xi] Loeys-Dietz syndrome is an autosomal dominant syndrome that includes many of the features of Marfan syndrome (including facial features, arachnodactyly, dural ectasia, translucent skin, easy bruising, and aortic root enlargement) but also includes unique features such as hypertelorism, a bifid uvula, cleft palate, cervical spine instability, craniosynostosis , and generalized arterial tortuosity and aneurysms. LDS is caused by mutations in TGFBR1 or TGFBR2 (subunits of the transforming growth factor-β receptor).[xii] The natural history of aortic disease in LDS tends to be more aggressive, with dissections occurring at a younger age and at smaller aortic dimensions (< 40mm).[xiii] Familial thoracic aortic aneurysm and dissection syndrome (FTAAD) refers to a heterogeneous group of disorders with a variety of genetic causes. Ehlers-Danlos Vascular type (formerly EDS IV), with mutations in COL3A1, the gene coding for type III collagen, is usually associated with dissection or rupture in medium size

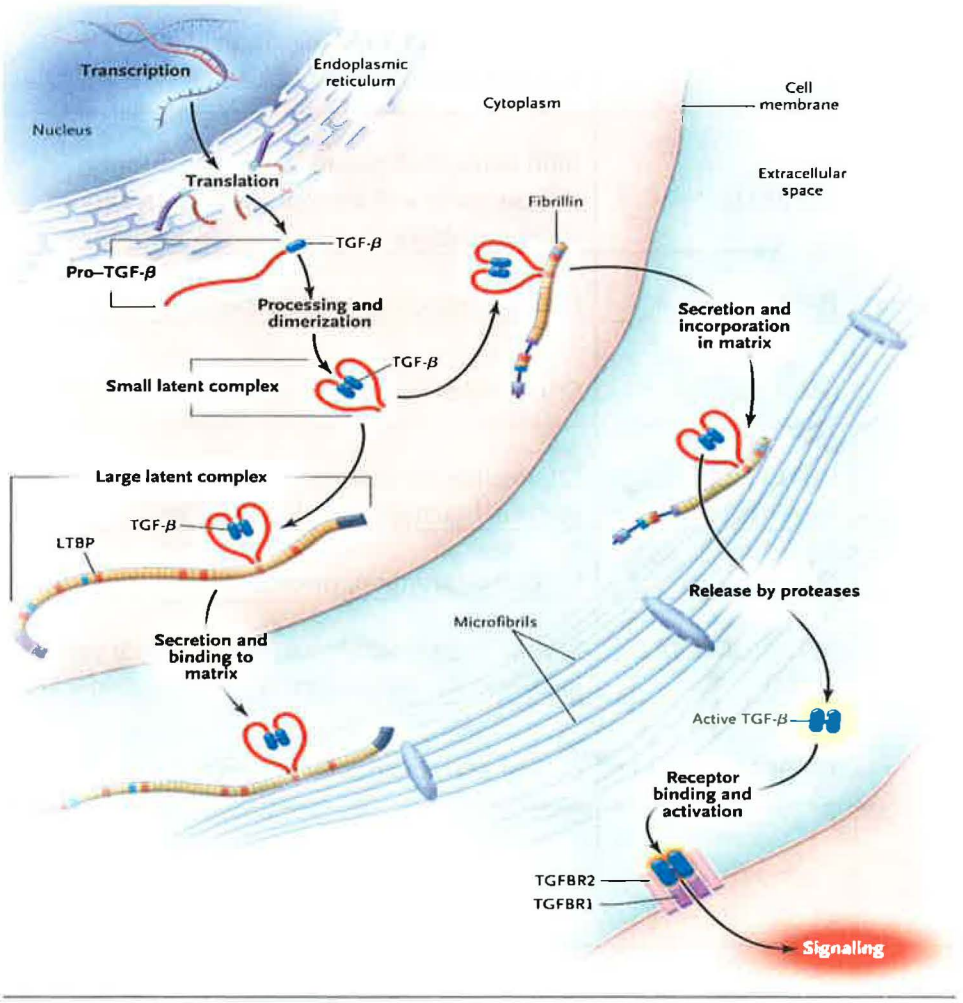
arteries but aortic involvement may be seen. Other features suggestive of this form of Ehlers-Danlos include translucent skin, dystrophic scars, easy bruising, and a predisposition to intestinal or uterine rupture.[xiv] Other rare forms of Ehlers-Danlos syndrome (kyphoscoliotic type, cardiac valvular subtype) may also be associated with vascular disease, including aortic dilatation and dissection.

Differential Diagnosis for Marfan syndrome (from reference 7)

Syndrome	Gene	Discriminating features
Ectopia lentis syndrome	FBN1, LTBP2, ADAMTA10	No aortic root dilatation
MASS phenotype	FBN1 in some	Myopia, MVP, borderline aortic root enlargement, skin and minor skeletal criteria
MVP syndrome	Not defined, autosomal dominant	Pectus excavatum, scoliosis, mild arachnodactyly common
Loeys-Dietz syndrome (LDS)	TGFBR1/2	Bifid uvula/cleft palate, arterial tortuosity, diffuse aortic and arterial aneurysms, cervical spine instability
Shprintzen-Goldberg syndrome	FBN1 and other	Craniosynostosis, mental retardation
Congenital contractural arachnodactyly	FBN2	Crumpled ears, contractures
Weill-Marchesani syndrome	FBN1 and ADAMTS10	Microspherophakia, lens dislocation, short stature, brachydactyly, joint stiffness
Homocystinuria	CBS	Mental retardation, thrombosis, lens dislocation
Ehlers-Danlos syndromes	COL3A1, COL1A2, PLOD1	Middle sized arterial aneurysms, severe valvular insufficiency, translucent skin, dystrophic scars
Familial thoracic aortic aneurysm syndrome	TGFBR1/2, ACTA2	Lack of Marfanoid skeletal features
Familial thoracic aneurysm syndrome with bicuspid aortic valve		
Arterial tortuosity syndrome	SLC2A10	Generalized arterial tortuosity, arterial stenosis, facial dysmorphism

Treatment goals for patients with Marfan syndrome focus on preventing complications, particularly the cardiovascular complications. This requires routine surveillance exams, particularly of the aorta and the eyes. Focusing on the cardiovascular system, an echocardiogram focusing on aortic dimensions is a critical part of the initial evaluation. In addition, all individuals who meet the criteria for Marfan syndrome should have at least annual echocardiograms. For those patients whose aortic dimensions are approaching a surgical threshold (≥ 4.5cm in an adult population) or have demonstrated rapid change (defined as ≥ 0.5cm/year) should have more frequent imaging. Echocardiography is the focus of the new Ghent criteria, but CT or MRI imaging can certainly be used for those patients with inadequate transthoracic echo windows.

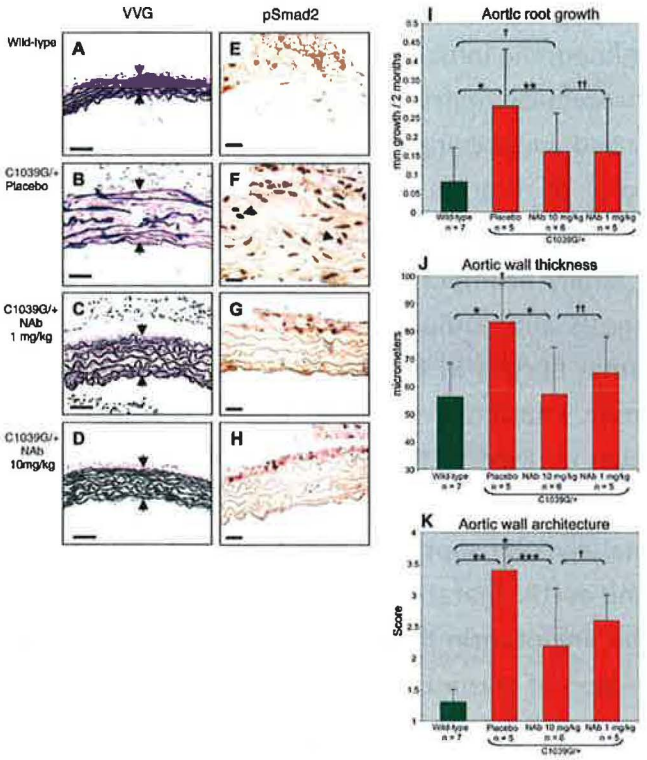
In terms of medical therapy, beta-blockers have been the mainstay of medical treatment for Marfan patients, based on very small clinical trials.[xv] Small trials of ACE-inhibitor therapy have also suggested some utility but are not considered the standard of therapy.[xvi]



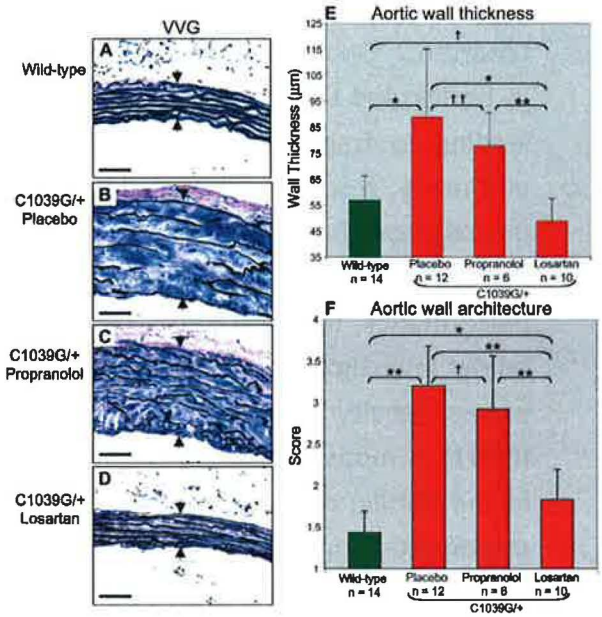
Gelb, NEJM 2006;355:841

One of the most exciting potential therapies is the use of the angiotensin receptor blocker, Losartan. Once the fibrillin gene defect was defined, the initial thought was that abnormalities in fibrillin led to increased susceptibility of extracellular matrix myofibrils to proteolysis, thus leading to fragmentation of the microfibrils and weakening of the connective tissues to ultimately result in the clinical manifestations of Marfan syndrome. More recently, investigators have demonstrated that the fibrillin appears to play a significant role in the regulation of transforming growth factor β, a family of important cytokines that help to cell performance, differentiation, tissue morphogenesis and homeostasis. [xvii] [xviii] [xix] Dietz and his fellow investigators postulated that the abnormal fibrillin in Marfan patients might result in excess activity of TGF-β. [xx] By introducing gene mutations into the mouse fibrillin-1 gene (FBN1), a mouse model of Marfan syndrome was created to test possible treatment options. In the fibrillin deficient mouse model, excessive TGF-β signaling caused aortic root dilatation, myxomatous mitral valve changes, and abnormal alveolar septation in the mice.[xxi] Treatment with TGF-β neutralizing antibodies prevented the aortic dilatation and myxomatous changes in post-natally treated mice. Signaling through the angiotensin II type I receptor (AT1) increases expression of TGF-β ligands and induces expression of thrombospondin, a potent activator of TGF-β. In contrast, signaling through the angiotensin II type II receptor (AT2) antagonizes many of the effects promoted by AT1 signaling. Losartan is an angiotensin II type I receptor blocker, which can antagonize AT1 signaling. In the mouse model, prenatal administration of losartan prevented aortic wall thickening and aortic root dilatation, compared to administration of propanolol or placebo. Additionally, post-natal administration of Losartan over a 2 month treatment halted further aortic dilatation and elastin fragmentation in the post-natal mice, more effectively than beta-blocker therapy.[xxii] This exciting work has led to the development of an NIH sponsored trial (run by the Pediatric Health Network) with a planned enrollment of 604 children and young adults (up to age 25) with Marfan syndrome to compare treatment with Losartan versus Atenolol for the prevention of aortic root dilatation.[xxiii] The primary trial outcome is the rate of change of the aortic root BSA-adjusted Z score. Secondary outcome measures include a variety of other measures of the rate of change of aortic dimensions, first occurrence of aortic dissection, aortic root surgery, or death, changes in somatic growth, weight, and body mass index, and the incidence of adverse drug reactions. This trial is still recruiting participants with an estimated completion date in 2013.

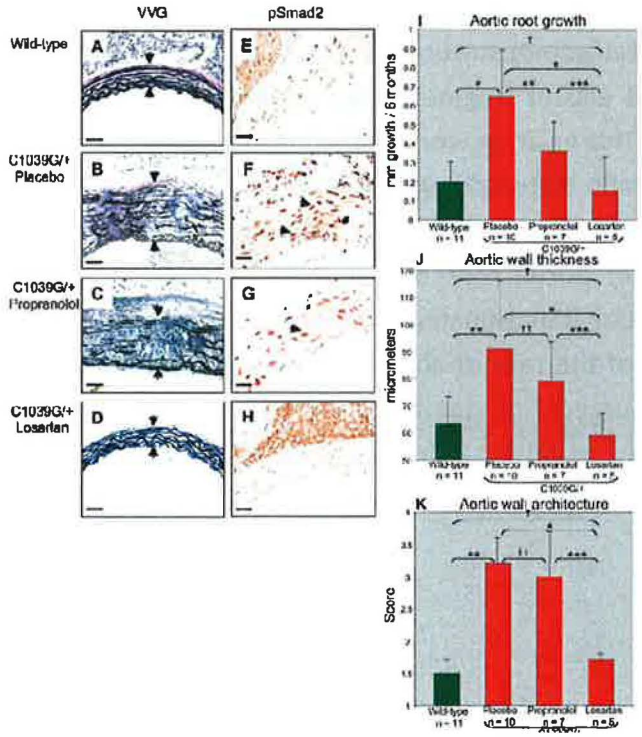
Post natal treatment with TGF-β neutralizing Ab



Prenatal treatment with Losartan and Propanolol



Post natal treatment with Losartan and Propranolol



From reference xxii.

Finally, new guidelines have been published by a joint committee of the American College of Cardiology Foundation, the American Heart Association Task force on Practice Guidelines, the American Association for Thoracic Surgery, the American College of Radiology, the American Stroke Association, the Society of Cardiovascular Anesthesiologists, the Society for Cardiovascular Angiography and Interventions, the Society of Inteventional Radiology, the Society of Thoracic Surgeons, and the Society for Vascular Medicine for the diagnosis and management of patients with thoracic aortic disease.[xxiv] In general, the threshold for surgical intervention in patients with an asymptomatic degenerative thoracic aortic aneurysm of the ascending aorta is an ascending aortic diameter of 5.5cm. In patients with Marfan syndrome or other genetically mediated disorders (including familial thoracic aortic aneurysms, Vascular type Ehlers-Danlos, bicuspid aortic valves, or Turner syndrome) should have elective operation at a smaller diameter (between 4.0 and 5.0cm). If there is evidence of rapid growth (greater than 0.5cm/year, a family history of aortic dissection at a diameter less than 5.0cm, or significant aortic regurgitation), earlier repair is usually indicated.[xxv] After repair of the ascending aorta, patients with Marfan syndrome remain at risk for later onset aneurysms and dissection of other areas of the thoracic aorta and require ongoing surveillance.[xxvi] Pregnant women with an aortic diameter greater than 4.0cm have an increased risk of aortic dissection and rupture with pregnancy. Prophylactic aortic surgery may be considered at this level in a woman planning pregnancy.

In summary, significant advances have been made in the diagnosis and treatment of Marfan syndrome, due in large part to the identification of the underlying genetic disorder and beginning to understand its biological implications. The differential diagnosis of Marfan syndrome has expanded, while the diagnostic criteria for the syndrome have become better defined and the role of genetic testing has become more important. While properly time aortic surgery remains the major means of preventing vascular catastrophes, emerging medical therapies may well revolutionize the natural history of this disease.

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