

Marfan syndrome. Part 1: pathophysiology and diagnosis

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Abstract | Marfan syndrome is a connective-tissue disease inherited in an autosomal dominant manner and caused mainly by mutations in the gene *FBN1*. This gene encodes fibrillin-1, a glycoprotein that is the main constituent of the microfibrils of the extracellular matrix. Most mutations are unique and affect a single amino acid of the protein. Reduced or abnormal fibrillin-1 leads to tissue weakness, increased transforming growth factor β signaling, loss of cell–matrix interactions, and, finally, to the different phenotypic manifestations of Marfan syndrome. Since the description of *FBN1* as the gene affected in patients with this disorder, great advances have been made in the understanding of its pathogenesis. The development of several mouse models has also been crucial to our increased understanding of this disease, which is likely to change the treatment and the prognosis of patients in the coming years. Among the many different clinical manifestations of Marfan syndrome, cardiovascular involvement deserves special consideration, owing to its impact on prognosis. However, the diagnosis of patients with Marfan syndrome should be made according to Ghent criteria and requires a comprehensive clinical assessment of multiple organ systems. Genetic testing can be useful in the diagnosis of selected cases.

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Introduction

Marfan syndrome is a connective-tissue disorder caused mainly by heterozygous mutations in the gene that encodes fibrillin-1. This condition was first described in 1896 by the French pediatrician Antoine Bernard-Jean Marfan.¹ Since then, different ocular, skeletal, cardiovascular, pulmonary, cutaneous, and neurological abnormalities have been added to the description of this disease to delineate what we now call Marfan syndrome.² Diagnosis of Marfan syndrome can be challenging because many of its features are age-dependent, others are frequently seen in the general population, substantial phenotypic variability is commonly observed, and, finally, there is considerable overlap with other connective-tissue disorders. As Marfan syndrome is associated with premature death in untreated patients, making a correct and early diagnosis is of great importance.

Marfan syndrome has traditionally been considered to result from structural weakness of connective tissue. However, in the past decade, this idea about the pathogenesis of Marfan syndrome has dramatically changed. In this manuscript, we discuss the genetics and pathogenesis of Marfan syndrome, as well as the current strategy for diagnosis. Our improved knowledge of the molecular mechanisms underlying the pathogenesis of this disease has opened the door to more promising treatments, which are discussed in Part 2 of this Review.³

Competing interests

The authors declare no competing interests

Epidemiology

Marfan syndrome is one of the most common potentially lethal diseases inherited in Mendelian fashion.⁴ The true incidence of Marfan syndrome is difficult to determine because some of its manifestations become more evident with age and some are commonly seen in the general population. Furthermore, several changes in the diagnostic criteria of the disease have occurred over the past 20 years, which have resulted in some conditions originally classified as Marfan syndrome now being recognized as separate entities (for example, homocystinuria and Loeys–Dietz syndrome).⁴ The estimated prevalence of Marfan syndrome ranges from 1 in 5,000 to 1 in 10,000 live newborns, affecting each sex in equal numbers.^{5,6} Approximately 75% of patients with the classic Marfan syndrome phenotype have a family background of this disease. The remaining 25% have *de novo* mutations.⁴

Genetics

Marfan syndrome is an autosomal dominant disease characterized by high penetrance (that is, nearly all carriers develop the disease) and marked phenotypic heterogeneity.⁷ This heterogeneity is commonly seen both between and within affected families.⁸

The majority of cases of Marfan syndrome are caused by a mutation in the fibrillin-1 gene (*FBN1*) on chromosome 15 (15q21.1).⁸ Fibrillin-1 is a matrix glycoprotein widely distributed in elastic and nonelastic tissues. Fibrillin-1 monomers associate to form complex extracellular macroaggregates—termed microfibrils—which form part of elastic fibers. Over 1,000 such mutations

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Key points

- Marfan syndrome is an autosomal-dominant connective-tissue disorder usually caused by mutations in the gene that encodes fibrillin-1
- Fibrillin-1 is the major constituent of extracellular microfibrils and has structural and regulatory functions in the extracellular matrix
- Marfan syndrome phenotype is thought to be the result of structural abnormalities and dysregulation of transforming growth factor β signaling
- Marfan syndrome typically affects cardiovascular, skeletal, ocular, and neural systems and its diagnosis is based on clinical (Ghent) criteria
- Aortic root dilatation is the leading cause of morbidity and mortality in patients with Marfan syndrome
- Many connective-tissue disorders share phenotypic features with Marfan syndrome and should, therefore, be considered in the differential diagnosis

have been described to date, distributed throughout the sequence of *FBNI*.^{4,8} Although there is no robust genotype–phenotype correlation, mutations in exons 24–32 tend to predict more a severe phenotype. Moreover, most mutations that cause neonatal Marfan syndrome (the most severe form of the disease) are usually located in this region.⁶ The majority of mutations in *FBNI* are missense mutations that alter a single amino acid out of the 2,871 amino acids that constitute the protein, usually in the epidermal growth factor (EGF)-like domains of the protein (thus called because of their sequence homology with EGF) and affecting cysteine residues or amino acids implicated in calcium binding.⁹ Various effects at the protein level have been described, including altered secondary structure, delayed secretion or enhanced protease susceptibility.⁶ Premature truncation codon mutations, which are associated with severe skeletal and skin manifestations of disease, and mutations associated with exon skipping have also been identified.⁶

In 1991, Boileau *et al.* described a large French family whose members exhibited some of the skeletal and cardiovascular features seen in patients with Marfan syndrome, but lacked others such as lens dislocation.¹⁰ This connective-tissue disorder was inherited also as an autosomal dominant trait, but no mutations in the fibrillin-1 gene were found.¹⁰ The gene responsible for this Marfan-like syndrome (referred to by the investigators as ‘Marfan syndrome type II’) was found to be located on chromosome 3 (3p24.2-25).¹¹ The same investigators later showed that this new gene, known as *TGFBR2*, coded for the type II subunit of the membrane receptor for transforming growth factor β (TGF- β).¹² Controversy still exists regarding the diagnosis of Marfan syndrome in this family, as they failed to meet the diagnostic criteria for this disorder.^{10,13} In addition, dissection and death occurred at smaller aortic dimensions, resembling the natural history of patients affected by Loeys–Dietz syndrome.¹³

The TGF- β receptor is a heterodimer involving the union between type I and II subunits (encoded by the genes *TGFBR1* and *TGFBR2*, respectively). To date, *TGFBR2* gene mutations have been found in patients with Marfan-like syndrome, in patients with Loeys–Dietz syndrome, and in some patients with familial aneurysm and aortic dissection.^{12,14–16} Although most mutations

are missense mutations that affect an intracellular kinase domain and reduce receptor signaling in response to TGF- β , all these patients show histological signs of TGF- β overactivity.¹⁷ The precise mechanisms underlying the increased TGF- β signaling remain unknown. TGF- β is a cytokine that takes part in the regulation of many different cell functions (proliferation, differentiation, and apoptosis) and has a central role in maintaining extracellular matrix homeostasis. Once synthesized, TGF- β is secreted into the extracellular medium where it is kept in an inactive state as a part of the large latent complex. These protein complexes, in which dimers of TGF- β are joined to latency associated peptide and large latent TGF- β 1 binding protein, binds to the microfibrils of the extracellular matrix, which act as a reservoir of inactive TGF- β molecules.^{17–19} After receiving certain physiological stimuli (such as mechanical stimuli, pH changes and signals from other cytokines), proteases release TGF- β molecules from the extracellular matrix, allowing their interaction with their receptors, initiating the process of signal transduction.¹⁷ Thus, fibrillin-1—the main constituent of the microfibrils—exercises control over the TGF- β signaling pathway. Reduced or mutated forms of fibrillin-1 lead to failed matrix sequestration of the large latent complex, with consequent excessive TGF- β activation and signaling.¹⁷

Physiopathology

Despite advances in our understanding of the genetics of Marfan syndrome and other related disorders, the molecular mechanisms that lead to the development of the phenotype are not fully elucidated. The evolution in our knowledge of the molecular pathogenesis of Marfan syndrome is discussed below.

In patients with Marfan syndrome, the medial layer of the aorta shows extensive abnormalities, including the fragmentation, disorganization and loss of the elastic lamina and its replacement by a basophilic material made up of glucosaminoglycans.²⁰ Areas with few cells and a lacunar appearance therefore develop. These lesions were termed ‘cystic medial necrosis’ by Erdheim in the 1920s.²¹ Although sometimes thought incorrectly to be pathognomonic of Marfan syndrome, this medial degeneration is nonspecific and can be seen in all types of thoracic aortic aneurysms.¹⁷

These early histological findings, and the identification of *FBNI* as the gene involved, led to the first theories on the pathogenesis of Marfan syndrome.^{22–24} Early hypotheses attributed a mere structural role to fibrillin-1. Mutations in *FBNI* were believed to cause structural weakness of the aortic wall, explaining the progressive dilation of the aortic root and the histological changes described above. Two mechanisms were proposed to explain this weakness. The first suggested that abnormal fibrillin-1 molecules, synthesized under the control of the mutated allele, interfered with the formation of fibrillin polymers, such that all the microfibrils of the extracellular matrix became structurally abnormal (that is, a dominant-negative effect).^{22,23} The second, more-plausible idea—given more-recently obtained results—proposed the

determining factor in the development of the phenotype to be a reduction in the overall production of fibrillin-1 to below a certain threshold (that is, haploinsufficiency).²⁴ Within the framework of this latter hypothesis, which focuses on the structural properties of fibrillin-1, certain manifestations of the disease—such as lens luxation, dural ectasia, or joint hyperlaxity—are easily explained as a consequence of connective-tissue weakness. However, this model cannot explain other phenotypic features of Marfan syndrome, such as the disproportionate growth of the long bones or myxoid changes in the mitral valve.

The development of several mouse models of the disease has contributed greatly to our current knowledge of the molecular pathogenesis of Marfan syndrome and other related disorders. These models have shown that fibrillin-1 is not essential in elastogenesis.²⁵ They have provided insights into the regulatory role of fibrillin-1 and into the implication of increased TGF- β signaling in the development of some manifestations of the disease, such as impaired pulmonary alveolar septation or myxomatous thickening of mitral valve.^{26,27} Notably, treatment of these fibrillin-deficient mice with TGF- β -neutralizing antibodies prevented or attenuated both manifestations.^{26,27}

In an elegant mouse model of Marfan syndrome, Habashi *et al.* showed that excessive TGF- β signaling also had a causal role in the development of aortic root aneurysms,²⁸ the most feared manifestation of Marfan syndrome. Again, the administration of TGF- β -neutralizing antibodies had a beneficial impact on the phenotype. The treated mice exhibited reduced fragmentation of the elastic fibers and slower growth of the aortic root, compared with the placebo group.²⁸

The various manifestations of Marfan syndrome are today considered to be the result of an overall abnormality in the homeostasis of the extracellular matrix, in which reduced or mutated forms of fibrillin-1 lead to alterations in the mechanical properties of tissues, increased TGF- β activity and signaling, and loss of cell–matrix interactions.¹⁷ The abnormal homeostasis is thought to result in vascular remodeling, characterized by an exaggerated elastolysis as a result of overexpression of matrix metalloproteinases (MMP-2 and MMP-9), and increased hyaluronan content.²⁹ In samples of dilated aortas of patients with Marfan syndrome, Nagashima *et al.* found that apoptosis of vascular smooth muscle cells might be part of the remodeling process that leads to cystic medial necrosis;³⁰ however the exact role of apoptosis is unknown.

Cardiovascular manifestations

The most notable phenotypic characteristics of patients with Marfan syndrome are listed in Table 1; Figure 1 illustrates some of these clinical manifestations. The cardiovascular manifestations of Marfan syndrome are the main cause of morbidity and mortality in patients with this disease. The most common of these manifestations is mitral valve prolapse, although aortic pathology has the greatest impact on prognosis. Indeed, the most feared complication of this disease is aortic dissection.

Aortic dilation in Marfan syndrome typically occurs in the sinuses of Valsalva—although it may extend to other

segments of the aorta—and has been reported in some 60–80% of all adults with Marfan syndrome.³¹ The typical localization of dilatation in the aortic root (by contrast to aneurysms of other etiology that affect the tubular portion of the ascending aorta) is explained by its higher elastic fiber content—the assembly of which involves fibrillin-1—and the wall stress and cyclic torsion to which this segment is subjected during ventricular ejection. The clinical presentation and diagnosis of aortic dilatation depends on the age of the patient, but in the most severe form of the disease it can begin during intrauterine life.³²

A lesser known cardiovascular manifestation of Marfan syndrome is the dilatation of the main pulmonary artery, which can occur in the absence of valve stenosis.³³ Dilatation usually occurs at the level of the root, a clear parallel of aortic dilatation. In addition, a strong correlation exists between the degree of aortic and main pulmonary artery dilatation.³³

As mentioned above, the most common cardiovascular finding in patients with Marfan syndrome is the involvement of the atrioventricular valves.³⁴ Prevalence of mitral valve prolapse ranges from 50–80% in patients with this disease, compared with about 2% in the general population.^{34,35} The histology and morphology of the mitral valve apparatus in patients with Marfan syndrome is different from that of patients with isolated mitral valve prolapse (myxomatous mitral valve disease).³⁵ Although posterior leaflet prolapse is the most common pathological finding in both conditions, patients with Marfan syndrome have a higher incidence of bileaflet prolapse or anterior leaflet prolapse. Moreover, although the valve leaflets are often thicker than normal in patients with Marfan syndrome, they are still longer and thinner than in those with myxomatous disease.³⁵ Regurgitation can result from mitral valve prolapse. In the most serious forms of Marfan syndrome, valve involvement can result in heart failure and pulmonary hypertension in the first years of life—the foremost cause of infant mortality among patients with Marfan syndrome.³⁴

Unlike mitral regurgitation induced by mitral valve prolapse, aortic regurgitation is a late manifestation, generally secondary to aortic dilation. Aortic valve leaflets are usually normal, although in some cases may be fenestrated.³⁴

An increased tendency for mitral valve annulus calcification has been reported for patients with Marfan syndrome.² An increased prevalence of dilated cardiomyopathy and ventricular dysfunction has also been reported in some studies of patients with Marfan syndrome;^{36,37} however, these findings are controversial and have not been confirmed in other studies.³⁸

Diagnostic criteria

The diagnostic criteria for Marfan syndrome has been,³⁹ and continues to be,² mainly clinical; diagnosis is dependent on the demonstration of the multisystem problems characteristic of the disease (based on clinical findings in different organs and systems) and the medical history of the patient's family. Notably, many of the manifestations of the disease may appear as variations of

Table 1 | Diagnostic criteria for Marfan syndrome*²

Organ system	Requirement for classification of organ system as meeting a major criterion	Requirement for classification of organ system as being 'involved'
Skeletal system	At least four of the following features: 1. Pectus carinatum 2. Pectus excavatum requiring surgery 3. Reduced upper to lower segment ratio or increased arm-span to height ratio (>1.05) 4. Positive wrist and thumb signs 5. Scoliosis (>20°) or spondylolithesis 6. Reduced extension of the elbows (<170°) 7. Medial displacement of the medial malleolus causing pes planus 8. Protrusio acetabulae of any degree	At least two features contributing to major criterion, or one feature from that list and two of the following minor criteria: 1. Pectus excavatum of moderate severity 2. Joint hypermobility 3. Highly arched palate with dental crowding 4. Characteristic facial appearance (dolicocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)
Ocular system	Ectopia lentis	At least two of the following minor criteria: 1. Abnormally flat cornea 2. Increased axial length of globe 3. Hypoplastic iris or hypoplastic ciliary muscle, causing decreased miosis
Cardiovascular system	At least one of the following features: 1. Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva 2. Dissection of the ascending aorta	At least one of the following minor criteria: 1. Mitral valve prolapse with or without regurgitation 2. Dilatation of the pulmonary artery, in the absence of valvular or peripheral stenosis or any other obvious cause, in individuals younger than 40 years of age 3. Calcification of the mitral annulus in individuals younger than 40 years of age 4. Dilatation or dissection of the descending thoracic or abdominal aorta annulus in individuals younger than 50 years of age
Pulmonary system	None	At least one of the following minor criteria: 1. Spontaneous pneumothorax 2. Apical blebs
Integumentary system	None	At least one of the following minor criteria: 1. Stretch marks not associated with marked weight changes, pregnancy or repetitive stress 2. Recurrent or incisional herniae
Dura	Lumbosacral dural ectasia by CT or MRI	None

*For a diagnosis of Marfan syndrome in patients with no family background of this disease, two different organ systems must be classified as meeting the major criteria and there should be data suggesting at least the 'involvement' of a third system. In patients with a family history of Marfan syndrome, only one major criterion need be met, along with data suggesting the involvement of a second system.

normality or are shared with other inheritable diseases of the connective system.²

The current diagnostic criteria for Marfan syndrome date back to 1996 and, like their forerunners, are based on the presence of major and minor clinical criteria for each of the organ systems that might be affected (Table 1).^{2,39} Within each of the systems shown, the major criteria are considered to be clinical manifestations that are highly specific of the disease, that is, they are uncommon in other diseases of the connective tissue and rarely seen in the general population. These major criteria carry the greatest weight in the diagnosis of Marfan syndrome. Notably, in the skeletal system, at least four clinical manifestations are required for a major criterion to be met. If insufficient manifestations have been recorded for a major criterion to be met, however, a system can still be regarded as 'involved'; the minor criteria required for this classification are also listed in Table 1.

Since Marfan syndrome is a disease that affects multiple systems, its diagnosis requires multiple systems to show clinical manifestations. The requirements for establishing a definitive diagnosis in any particular

patient vary depending on whether that patient has a family history of the disease.² In patients with no family background of Marfan syndrome, two different systems must be classified as meeting the major criteria, and there should be data suggesting at least the 'involvement' of a third system.² For example, if a patient presents with no family history of Marfan syndrome, but who meets a major criterion in the skeletal system (such as having dolichostenomelia, wrist and thumb signs, spondylolithesis, and pectus carinatum), a diagnosis of Marfan syndrome would require another major criterion be met in another system (for example, dilation of the aortic root), plus data suggesting the involvement of a third system (for example, the presence of atrophic stretch marks in the skin). In patients with a family history of Marfan syndrome, only one major criterion need be met, along with data suggesting the involvement of a second system. A patient is considered to have a family history of Marfan syndrome if he or she has a direct relative (parent, child, or sibling) who independently meets the criteria for diagnosis of the disease, if he or she is a carrier of one of the mutations of the fibrillin-1 gene known to cause the

disease, or if he or she is a carrier of the haplotype that is associated with the disease in his or her family (that is, genetic linkage).²

Clinical assessment for diagnosis

Given the multisystem nature of Marfan syndrome, all patients suspected of having the disease should undergo multidisciplinary assessment. The initial study should include investigation of the patient's family history of the disease and an extensive physical examination, including a transthoracic echocardiogram and an ophthalmological assessment. Complementary tests should be performed in line with the findings made in the initial study. A radiological study (an X-ray of the spine and an antero-posterior X-ray of the pelvis) should allow the detection of deformities of the vertebral column and protrusio acetabuli, but should only be performed if insufficient diagnostic criteria have been met in the initial assessment but Marfan syndrome is still suspected. Similarly, CT or MRI of the lumbar spinal column can be very helpful in detecting dural ectasia, which is considered a major criterion and may aid in establishing the definitive diagnosis. The diagnosis of children is often a challenge, since many of the manifestations of the disease do not develop until adulthood. Young patients who do not fulfill the diagnostic criteria, but have a family history of Marfan syndrome or have no family history but present with Marfan-like syndrome, should, therefore, be examined periodically until the age of 18 years. We and others recommend that these children are at least assessed at 5, 10, and 15 years of age.⁴⁰

Cardiovascular assessment

Transthoracic echocardiography is the main imaging technique used in the diagnosis of cardiovascular involvement. To assess aortic dilatation, the projection of choice is the long axis from the parasternal window.⁴¹ According to the recommendations of the American Society of Echocardiography, the aortic diameters should be measured (in two-dimensional or M mode) at end-diastole, using the leading-edge technique.⁴¹ Measurements should be taken at the aortic valve annulus (hinge point of aortic leaflets), at the sinuses of Valsalva, at the sinotubular junction, and at the tubular portion of the ascending aorta (Figure 2). All measurements need to be strictly perpendicular to the long axis of the aorta to avoid oblique overestimates and should be compared with indexed nomograms that take into account the patient's age and body surface area (Figure 3).^{2,41,42} Aortic dilation is defined as a normalized diameter greater than the mean plus two standard deviations (z -score >2).^{2,41} Unfortunately, however, individuals with heights greater than the 95th percentile were poorly represented in the group of healthy individuals on which the currently available nomograms are based. Consequently, there is some doubt regarding the upper normal limit for the aortic diameters of this tallest subgroup, to which the majority of patients with Marfan syndrome belong. Reed *et al.* showed that the relationship between anthropometric variables and aortic diameters is not linear in

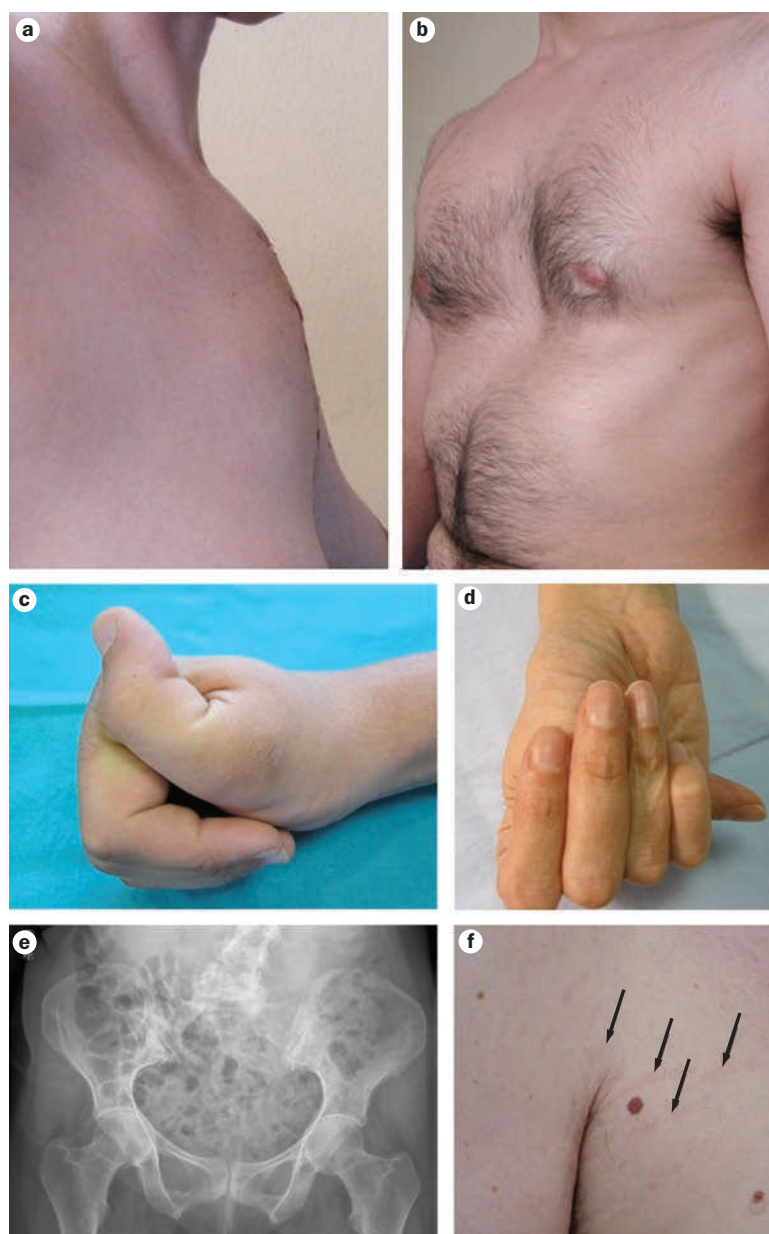


Figure 1 | Typical phenotypic manifestations associated with Marfan syndrome. **a** | Pectus carinatum (protrusion of the sternum and ribs). **b** | Pectus excavatum (sunken sternum and ribs). **c** | Joint hypermobility. **d** | Arachnodactyly (overgrowth of the fingers). Steinberg or thumb sign. Arachnodactyly leads to two characteristics signs: the Steinberg or thumb sign (the distal phalanx of the thumb fully extends beyond the ulnar border of the hand when folded across the palm), and the Walter-Murdoch or wrist sign (full overlap of the distal phalanges of the thumb and fifth finger when wrapped around the contralateral wrist). **e** | Protrusio acetabulae (medial displacement of the femoral head into the pelvic cavity). **f** | Stretch marks (arrows).

people of this height; rather, the slope tends to flatten out.⁴³ Assuming linearity thus leads to overestimation of what might be considered normal.⁴³

Some authors have proposed more rapid and simple methods for the screening of aortic dilatation.⁴⁴ One of these methods involves determining the ratio between the diameter at the sinuses of Valsalva and that at the aortic annulus.⁴⁴ In healthy people, the rate of growth of the aortic root is proportional to the rate of growth of the

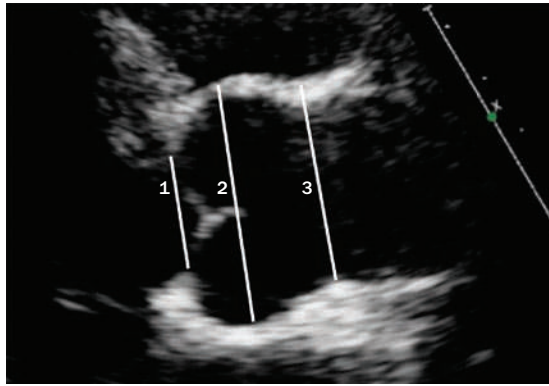


Figure 2 | Echocardiography of the aortic root. Components analyzed during assessment of aortic root dilatation are the aortic annulus (1), the sinuses of Valsalva (2), and the sinotubular junction (3). The tubular portion of the ascending aorta should also be assessed.

aortic annulus. Consequently, this ratio tends to remain constant and is independent of age, body weight, and height. In patients with Marfan syndrome, aortic dilation usually begins in the sinuses of Valsalva and this ratio is altered at an early age; therefore, determining this ratio may be useful in screening for aortic dilation in the pediatric population. In children, a ratio of ≥ 1.45 predicts the existence of aortic dilation with high sensitivity (0.82) and specificity (1.00).⁴⁴ However, in the subgroup of patients that present with dilation of the aortic annulus, the ratio tends to normalize and, therefore, loses its usefulness.⁴⁴ Additionally, in patients with a small aortic annulus, it can lead to false positives.

Some investigators have found that the extension of dilation beyond the sinuses of Valsalva might be a predictor of cardiovascular complications (including progressive aortic dilation, aortic dissection, and severe aortic regurgitation).⁴⁵ However, this observation remains to be validated.

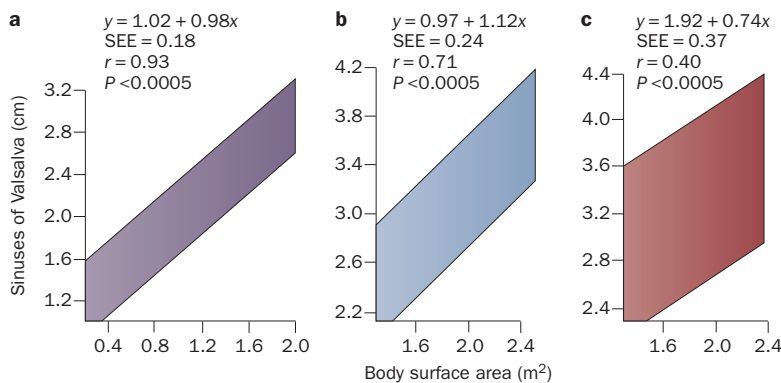


Figure 3 | Normal range of aortic root dimensions. 95% CI for diameter at the sinuses of Valsalva normalized to body size and age. **a** | Children and adolescents. **b** | Adults younger than 40 years of age. **c** | Adults older than 40 years of age. Correlations between aortic root diameter and body surface area are indicated on each normogram. Reprinted from Roman, M. J., Devereux, R. B., Kramer-Fox, R. & O’Loughlin, J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. *Am. J. Cardiol.* **64**, 507–512, ©1989 with permission from Elsevier.

In patients with a poor transthoracic window, or who require an overall assessment of aortic involvement, a CT or MRI scan should be performed. Both these imaging techniques are very important in the monitoring of patients who undergo surgery on the ascending aorta.³¹

Ophthalmological assessment

The ophthalmological assessment of a patient with suspected Marfan syndrome requires a slit lamp examination following dilation of the pupils. This strategy allows complete visualization of the lens and exploration of the retina for the identification of possible retinal detachments.⁴⁶ Luxation of the lens (ectopia lentis) is seen in 60% of patients with Marfan syndrome,⁴⁶ but is not exclusive to this disease. One or both eyes may be affected, usually in the superior quadrant, but corrective surgery is not usually required.⁴⁶ Keratometry is used to assess the curvature of the cornea, which can be reduced in patients with Marfan syndrome. The anteroposterior diameter of the eye is determined via ocular biometry.

Assessment of dural ectasia

The diagnosis of dural ectasia (that is, dilatation of the dural sac) can be performed both qualitatively and quantitatively, and requires a CT or MRI of the lumbosacral column (Figure 4). In severe cases a simple X-ray might show some indirect signs of this manifestation, such as the erosion of the vertebral bodies, which typically occurs in the mid portion of the posterior surface.⁴⁷ Such alterations to the vertebral channel can lead to the herniation of the nervous roots and even the meningoceles. Notably, dural ectasia does not cause symptoms in most patients with Marfan syndrome and has been described in patients with other hereditary diseases.

Qualitative assessment of whether dural ectasia exists is less precise than quantitative assessment, and is based on the existence, or not, of dural sac dilatation, scalloping (central erosion of the vertebral body as seen in the sagittal plane), or meningoceles. In healthy individuals, the diameter of the dural sac (in the sagittal plane) normally gets progressively smaller, until it is obliterated at the level of the mid sacrum. A greater dural sac diameter (measured in the mid section of the vertebral body) at S1 than at L4 demonstrates that the dural sac is not tapering and is highly suggestive of dural ectasia.⁴⁸

Quantitative assessment is more complex than qualitative assessment, and requires determination of the ratio between the dural sac diameter and the anteroposterior diameter of each vertebral body from L1 through to S1 (known as the dural sac ratio). The dural sac diameter is measured from the posterior surface of the vertebral body to the posterior wall of the vertebral canal. The anteroposterior diameter of the vertebral body is measured perpendicular to the long axis of the vertebral column in the mid section of the vertebral body, using penetration of the artery into the posterior surface as a point of reference. Oosterhof *et al.* established dural sac ratio cut-off values for the adult population.⁴⁹ A dural sac ratio at L3 of >0.47 or at S1 of >0.57 diagnoses dural ectasia in adults with Marfan syndrome with 95% sensitivity and



Figure 4 | Dural ectasia. Sagittal view of the lumbar column of a patient with Marfan syndrome. The diameter of dural sac at S1 is clearly larger than at L4, which suggests dural ectasia.

98% specificity.⁴⁹ These diagnostic criteria have been validated in pediatric and adolescent populations.⁴⁸ The most useful criteria for diagnosing dural ectasia in patients of any age might be the presence of a greater dural sac diameter at S1 than at L4 and an abnormal dural sac ratio at L5 and S1.

The role of genetics in diagnosis

Mutations of the *FBNI* gene can be detected in 90–95% of patients who meet the clinical criteria of Marfan syndrome (Ghent nosology, 1996).⁴ However, the use of genetic studies for diagnostic purposes has important limitations. Firstly, more than 90% of the mutations described to date are unique, that is, the majority of mutations are not repeated among nongenetically related patients. The absence of known mutations in a patient in whom Marfan syndrome is clinically suspected does not, therefore, exclude the possibility that Marfan syndrome is present; the patient may be carrying a mutation that is presently unknown.⁵⁰ Complete sequencing of the coding regions of the gene might thus be considered desirable; however, the financial cost of such an undertaking is high. Additionally, although this strategy can identify mutations of *FBNI* in a high proportion of patients with the classic Marfan syndrome phenotype (high sensitivity), mutations in noncoding regions (regulators) would not be detected with current techniques.⁴

Since no clear genotype–phenotype correlation exists for Marfan syndrome, the severity of disease cannot be predicted from the type of mutation.⁵ From a clinical point of view, therefore, the identification of a mutation is mainly useful in those patients with suspected Marfan

Box 1 | Differential diagnosis of Marfan syndrome

Hereditary connective tissue disorders

Fibrillinopathies

- MASS phenotype
- Familial ectopia lentis
- Familial mitral valve prolapse
- Familial arachnodactyly
- Shprintzen–Goldberg syndrome

Nonfibrillinopathies

- Ehlers–Danlos syndrome
- Loeys–Dietz syndrome
- Arterial tortuosity syndrome

Nonsyndromic familial aortic aneurysms

- Bicuspid aortic valve
- Familial aortic aneurysms and dissection (genetic loci TAAD1, TAAD2, TAAD3, TAAD4, TAAD5, TAAD-patent ductus arteriosus, FAA1)

Abbreviation: MASS, mitral valve, aorta, skeleton, skin.

syndrome who do not meet sufficient clinical criteria at the time of initial examination, in individuals who belong to a family with classic Marfan syndrome in which the causal mutation is known (presymptomatic diagnosis), and also in patients who have an atypical phenotype, so that other connective-tissue disorders—particularly Loeys–Dietz syndrome—can be ruled out. Unfortunately, however, some mutations of *FBNI* are associated with other phenotypes, including MASS (mitral valve, aorta, skeleton, skin) syndrome, familial mitral valve prolapse syndrome, and familial ectopia lentis.

Given the associated technical problems, the fact that *FBNI* mutations are not specific to Marfan syndrome, and that the absence of a known mutation in this gene does not rule out Marfan syndrome, molecular diagnosis is currently considered an appendix to clinical evaluation.^{2,3}

Differential diagnosis

Several diseases of the connective tissue share some of the features and manifestations of Marfan syndrome, and should be considered in the differential diagnosis (Box 1). Some of these diseases are also hereditary and associated with mutations in the fibrillin gene; therefore, they are all (including Marfan syndrome) generically classified as fibrillinopathies. The marked overlap of their phenotypes and the progressive nature of many of their manifestations render differential diagnosis a challenge, and periodic re-evaluation is often necessary. Table 2 summarizes the most important features of the different syndromes that should be considered during the differential diagnosis of Marfan syndrome.

Some of the most complex diseases showing notable analogy to Marfan syndrome include the MASS phenotype or syndrome, and Loeys–Dietz syndrome. The acronym ‘MASS’ was suggested by Glesby *et al.* to describe a subgroup of patients with enough signs to consider that a systemic connective-tissue disorder may be present,

Table 2 | Hereditary syndromes with aortic aneurysm considered in the differential diagnosis of Marfan syndrome

Characteristic	Marfan syndrome	Congenital contractural arachnodactyly* ^{2,57}	Type I Loeys–Dietz syndrome ^{14,52}	Type II Loeys–Dietz syndrome ^{14,52}	Ehlers–Danlos syndrome (vascular or type IV) ³⁹	Shprintzen–Goldberg syndrome ^{†58}	Arterial tortuosity syndrome ^{59,60}
Phenotype	Skeletal manifestations, ectopia lentis, aortic aneurysms and dissection, dural ectasia, skin and pulmonary involvement	Dolicoestenomelia, arachnodactyly, scoliosis, multiple joint contractures, crumpled ears, no ocular manifestations, mild and nonprogressive aortic dilatation	Hypertelorism and cranio-synostosis, cleft palate and/or bifid uvula, arterial tortuosity and aneurysms	Absence of facial manifestations, except for bifid uvula, similar to type IV Ehlers–Danlos Syndrome (easy bruising, visceral fragility or rupture, etc)	Easy bruising, thin, translucent and velvety skin, joint hypermobility, spontaneous visceral rupture, obstetrical complications, characteristic facial appearance	Craniosynostosis, severe exophthalmos, maxillary and mandibular hypoplasia, low-set ears, arachnodactyly, abdominal hernias, mental retardation	Tortuosity of aorta and large arteries, localized arterial stenoses, hernias, joint laxity, elongated face
Genes known to be mutated	<i>FBN1</i> and <i>TGFBR2</i>	<i>FBN2</i>	<i>TGFBR1</i> and <i>TGFBR2</i>	<i>TGFBR1</i> and <i>TGFBR2</i>	<i>COL3A1</i>	<i>FBN1</i>	<i>SLC2A10</i>
Prevalence	1 in 3,000–5,000	Unknown	Unknown	Unknown	1 in 25,000 (type IV accounts for 4% of cases)	Unknown	Unknown
Inheritance	AD	AD	AD	AD	AD	AD	AD
Pathophysiology	Altered synthesis of fibrillin-1 and increased TGF- β signaling	Altered synthesis of fibrillin-2	Increased TGF- β signaling	Increased TGF- β signaling	Abnormal synthesis of type III collagen	Altered synthesis of fibrillin-1	Deficiency of glucose transporter (GLUT10) and increased TGF- β signaling
Diagnosis	Ghent criteria \pm genetic testing	Clinical assessment \pm genetic testing	Clinical assessment \pm genetic testing	Clinical assessment \pm genetic testing	Clinical assessment (Villefranche criteria), biochemical diagnosis or genetic testing	Clinical assessment \pm genetic testing	Clinical assessment \pm genetic testing
Prognosis	Median survival if treated = 70 years	Not well established; normal lifespan unless cardiovascular problems arise	Median survival = 37 years; mean age at death = 26 years	Median survival = 37 years; mean age at death = 26 years	Median survival with no treatment = 48 years; high risk of surgical complications	Not well established	Not well established
Treatment	β -B/ARBs; surgery [§] if diameter \geq 50 mm or rapid progression of dilation	Physical therapy, cardiovascular monitoring on yearly basis	β -B/ARBs; surgery [§] if diameter \geq 40 mm	β -B/ARBs; surgery [§] if diameter \geq 40 mm	Surgery [§] if diameter \geq 40 mm	Cardiovascular monitoring and prophylactic surgery if dilated; orthopedic treatment.	Vascular surgery if needed

*Also known as Beals syndrome. †Also referred as to marfanoid craniosynostosis syndrome. §Refers to prophylactic aortic surgery. Abbreviations: β -B, β -blockers; AD, autosomal dominant; ARB, angiotensin II receptor blocker; TGF- β , transforming growth factor β .

but that couldn't be diagnosed of any of the known syndromes.⁵¹ MASS phenotype is characterized by the following manifestations: myopia, mitral valve prolapse, mild aortic dilation, skin and skeletal abnormalities.^{2,51} Although it involves multiple systems, the cutaneous and skeletal manifestations are nonspecific and aortic dilation is always mild and nonprogressive.² Diagnosis always requires at least two systems to be affected.² The MASS phenotype has been associated with mutations in the *FBN1* gene; MASS is, therefore, a fibrillinopathy.

Loeys–Dietz syndrome is an autosomal dominant connective-tissue disorder that was first described in 2005.¹⁴ Affected patients exhibit a variety of features, mainly involving the cardiovascular, musculoskeletal, and central nervous systems.¹⁴ Mutations in the TGF- β receptor type I (*TGFBR1*) and type II (*TGFBR2*) genes have been linked to the disease.¹⁴ Approximately two-thirds of patients with Loeys–Dietz syndrome have heterozygous mutations in *TGFBR2*. From a clinical point of

view, Loeys–Dietz syndrome is characterized by a triad of arterial tortuosity and aneurysms, hypertelorism, and bifid uvula or cleft palate.¹⁴ Recently, Loeys–Dietz syndrome has been subdivided in type I (if craniofacial involvement consisting of cleft palate, hypertelorism, or craniosynostosis was observed) and type II (absence of craniofacial involvement, but isolated bifid uvula).⁵² Patients with more severe craniofacial abnormalities tend to develop more severe and aggressive arterial disease.⁵² Arteriopathy, in particular aortic dilatation and dissection, represents the main cause of death.^{14,52,53} Unlike Marfan syndrome, in which arteriopathy seems to be confined to the ascending aorta, tortuosity and dilatation of abdominal aorta, pelvic vessels, and intracranial vessels can develop in patients with Loeys–Dietz syndrome.^{14,52,53} Aortic dilatation and dissection occur at an earlier age and at smaller aortic diameters than in patients affected of Marfan syndrome.^{52,53} Early diagnosis and prophylactic aortic surgery are crucial in the management of these

patients.⁵³ Given the aggressiveness of aortic pathology, surgery is considered at smaller diameters than those recommended for patients with Marfan syndrome and a stricter follow-up is advocated.⁵³

Finally, it is important to point out that aortic aneurysms and dissection can occur in multiple members of an affected family that has no other syndromic manifestations.^{17,54} Furthermore, the literature reports 11–19% of patients referred for surgery for aortic aneurysm to have direct relatives with aortic aneurysms.⁵⁴ These familial nonsyndromic aneurysms usually have an autosomal dominant pattern of inheritance with decreased penetrance and variable expression. Although the age of presentation and the severity of the phenotype is very variable, these aneurysms tend to appear at an earlier age than sporadic aneurysms (mean age of presentation 56.8 years compared with 64.3 years).⁵⁴ Aneurysms generally involve the ascending aorta, but can be accompanied by other aneurysms in different locations (such as the descending aorta, cerebral arteries, carotid arteries, and popliteal arteries). To date, seven genetic loci have been linked to familial nonsyndromic aneurysms and dissection: TAAD1, TAAD2, TAAD3, TAAD4, TAAD-patent ductus arteriosus, TAAD5 and FAA1.¹⁷ However, only four genes have been identified: *TGFBR2* in TAAD2, *TGFBR1* in TAAD5, *ACTA2* in TAAD4, and *MYH11* in TAAD-patent ductus arteriosus.^{17,54} The *ACTA2* gene encodes smooth muscle α_2 -actin, and might be the most

common cause of familial aortic aneurysms and dissections.⁵⁵ *MYH11* encodes smooth muscle β MHC, a specific contractile protein in vascular smooth muscle cells.⁵⁶ The existence of familial forms of aneurysm of the ascending aorta in more than 10% of individuals belonging to a population without Marfan syndrome justifies a systematic review of their direct relatives, particularly if they are young and there is no history of hypertension.

Conclusions

Marfan syndrome is the most common form of syndromic aortic aneurysms and is associated with high morbidity and mortality in untreated patients. Diagnosis remains essentially clinical, although genetic testing can be useful in selected cases. Advances in the understanding of the genetic and molecular basis of the disease have challenged our traditional definition of the disease as a structural connective-tissue disorder.

Review criteria

This article is based on a comprehensive search of original articles and reviews in the PubMed database. Search terms included “Marfan syndrome”, “genetics”, “fibrillin” and “aneurysm”. The cited papers were selected on the basis of their relevance. We also searched the reference lists of identified articles as a source for additional relevant papers in the field.

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