MARFAN SYNDROME

Epidemiology

Marfan syndrome is a generalized connective tissue disease affecting approximately 1 in 5000 to 10,000 individuals, with no racial, gender, or geographic predilection. Whereas most affected individuals will have a family history of the disease, approximately 25 percent will not, suggesting de novo mutations.

Etiology and Pathogenesis

Routine histopathologic examination of biopsies do not show significant changes. However, ultrastructurally the dermis of Marfan patients demonstrates abnormal collagen fibrils with varied thickness, whirl- and wave-formed disarray, and twisted fibrils with flower-like shapes with zigzagged margins, similar to EDS. In addition, the ratio of collagen I-collagen III content is decreased.

Marfan syndrome is typically an AD disorder caused by heterozygous mutations in the gene for
fibrillin 1 (FBN1), localized to 15q21.1. More than 500 mutations in the FBN1 gene have been reported that span the entire coding region of the gene (65 exons). Some, but not all, mutations result in the classical features of Marfan syndrome, and a few genotype-phenotype correlations are possible. Most missense mutations in the EGF domains result in the classic form of the disease. Patients with dramatic structural rearrangements, such as exon skipping (approximately 10 percent of the total), have comparatively severe forms of the disease. Patients with mutations that lead to premature stop codons and reduced mRNA transcripts from the mutant allele have a surprisingly wide range of clinical severity, which is unlike the clear differences seen between OI patients with dominant-negative mutations and loss-of-function mutations (null alleles). The only established genotype-phenotype correlation is that of severe neonatal onset with mutations clustered in the middle of the FBN1 gene.

FBN1 is a major constitutive element of ECM microfibrils throughout the body. It is abundant in tissues affected in Marfan syndrome—the ascending aorta, suspensory ligament of the lens, periosteum, and the skin. Fibrillin plays a major role in the normal functioning of microfibrils, which are critical structural components of many tissues. The fibrillin molecule is spanned by cysteine-rich repeats interspersed with latent transforming growth factor-β (TGF-β)-binding protein-like and EGF-like motifs.

Genetic alterations in FBN1 produce a spectrum of clinical abnormalities well beyond the classic Marfan phenotype, the so-called fibrillopathies. The spectrum includes the severe neonatal Marfan phenotype at one end, extending to isolated aortic root dilatation or marfanoid skeletal features lacking cardiovascular involvement or ectopia lentis at the other. Other phenotypes that can result from mutations in FBN1 include: the mitral, aortic, skin, and skeletal manifestations (MASS) phenotype; bicommissural aortic valve with ascending aortic aneurysm; Shprintzen-Goldberg syndrome; MVP syndrome; familial ectopia lentis; isolated marfanoid habitus, and Weill-Marchesani syndrome.

MARFAN SYNDROME AT A GLANCE
Marfan syndrome

- Incidence: 1 in 5000 to 10,000.

- Autosomal dominant inheritance with mutations in fibrillin 1 (FBN1; chromosome 15q21.1).

- Cutaneous features include striae distensae (two-thirds of patients), inguinal or incisional hernias, and, rarely, elastosis perforans serpiginosa.

- Extracutaneous manifestations include hyperextensible joints, upward lens displacement, skeletal abnormalities, and cardiac aberrations, such as aortic aneurysm and rupture.


Mutations in the FBN2 gene on chromosome 5q23 can result in an AD disorder that resembles neonatal Marfan syndrome, especially in its skeletal manifestations—congenital contractural arachnodactyly (Beals syndrome). It is characterized by multiple flexion contractures (especially elbow, knee, and finger joints), arachnodactyly, severe kyphoscoliosis, crumpled pinnae, and muscular hypoplasia. Aortic root dilatation and the ocular manifestations of Marfan syndrome do not tend to be associated.

Heterozygous mutations in the TGF-β receptor 2 on chromosome 3p24.2-25 have also been described in a subset of patients with prominent aortic dilatation but without ocular abnormalities.
Clinical Findings

Marfan syndrome is a generalized disorder of connective tissue that has primary manifestations in the skeletal, ocular, and cardiovascular systems. Patients with Marfan syndrome may have major abnormalities primarily in three organ systems: in the eye—most characteristically dislocation of the lenses; in the skeletal system—excessive length of extremities, loose-jointedness, kyphoscoliosis, and anterior chest deformity; and in the cardiovascular system—most characteristically aortic aneurysm and mitral valve redundancy. Skin manifestations consist of striae distensae, a common finding, and elastosis perforans serpiginosa, a rare finding.

Virtually all patients with Marfan syndrome have myopia as the result of an abnormally long anterior-posterior axis of the orbit and relatively flat corneas. In addition, approximately 70 percent of affected patients have ectopia lentis, with the lens usually displaced upward. In an examination after the dilation of the pupil, the margin of the lens is usually visible in the lower part of the pupil. Dislocation of the lens into the anterior chamber or trapping of the lens in the pupil sometimes occurs, and acute glaucoma may result. Detection of mild ectopia lentis requires full dilation of the pupils and slit-lamp examination for redundancy of the suspensory ligament of the lens. Therefore, clinical exclusion of ectopia lentis in an individual suspected of having Marfan syndrome must include a slit-lamp examination after dilation of the pupils. Strabismus and cataracts may also develop.

The skeletal features, particularly the long, narrow extremities, figured prominently in Marfan's initial description in 1896 of the syndrome that now bears his name. Patients with Marfan syndrome are usually taller than their same-sex siblings. There is skeletal disproportion, with the most consistent and reliable measure being an abnormally low ratio of the upper segment (height minus lower segment) to the lower segment (measured from the pubic symphysis to the floor). The arm span (fingertip to fingertip when expanded) is usually longer than the height by several centimeters. These discrepancies may be magnified by associated kyphoscoliosis. The ribs appear to undergo the same excessive longitudinal growth, as do the bones of the extremities. Depression of the sternum (pectus excavatum) or projection (pectus carinatum) or an asymmetric deformity of the anterior chest results.
Joint hyperextensibility is present in some, but not all, patients with Marfan syndrome. Flat-footedness, hyperextensibility at the knees (genu recurvatum) and elbows, and occasional dislocation of joints are manifestations of the loose-jointedness. Because of joint hyperextensibility and long, narrow extremities, the patient is often able to touch his or her umbilicus with the right hand passed around the back and approaching the umbilicus from the left. A relatively narrow palm of the hand with a long thumb and hyperextensibility is the basis of Steinberg's sign, in which the thumb propped across the palm extends well beyond the ulnar margin of the hand.

The cardiovascular manifestations of Marfan syndrome are by far the most clinically significant and account for the overwhelming majority of morbidity and mortality associated with this disorder. The two major cardiovascular manifestations are MVP and aortic root dilatation. MVP is a consequence of the redundancy of the valve leaflets, the stretching of the chordae tendineae, and dilatation of the valve annulus. The prevalence of MVP in Marfan syndrome increases with age and is present in approximately 75 percent of individuals. MVP can occasionally be associated with abnormal electrocardiograms, regurgitation, and cardiac arrhythmias that can lead to sudden death.

Dilatation of the proximal aorta is progressive and, in some cases, may even occur in utero. Dilatation is often first seen in the sinuses of Valsalva, but is often discontinuous and unpredictable. Patients with Marfan syndrome should be monitored on a yearly basis, as aortic complications of Marfan syndrome do not occur in aortas that are normal for age or in adults in aortas less than 40 mm in diameter. The aortic pathology of Marfan syndrome is almost always in the proximal (ascending) aorta; distal pathology is usually a result of forward progression of a dissecting lesion. Premature death in Marfan syndrome is a result of its cardiovascular complications: proximal aortic dilatation associated with aortic valve incompetence, aortic rupture, or aortic dissection. Other manifestations of this syndrome include a high-arched palate and crowding of the anterior teeth, emphysema, spontaneous pneumothorax, and dural ectasia.

Cutaneous lesions develop in approximately two-thirds of patients with Marfan syndrome and represent minor diagnostic signs in the revised 1996 Ghent criteria. These include striae distensae (more prominent during adolescence and on the buttocks, thighs, breasts, abdomen, and thighs) and inguinal or incisional hernias. Histology reveals abnormal elastic fibers with a moth-eaten appearance and collapsed, distorted adipocytes.

The large size of the gene, along with the absence of mutational hot spots and the heterogeneity of these mutations preclude sensitive testing for FBN1 mutations. Clinical assessment remains the current diagnostic method, but in individuals with a familial phenotype,
mutational or linkage analysis may yield positive results.

Treatment

Management of patients with Marfan disease should be multi-disciplinary, targeting each affected organ system.

Prevention

Patients with aortic dilatation are encouraged to avoid caffeine, stressful circumstances, and vigorous exercise. Contact sports or heavy lifting should be avoided. Early use of either a valvesaving aortic repair or composite graft placement is now prudent because of significant improvements in the success of these procedures and the well-known difficulties in managing an acute aortic dissection in Marfan patients. To prevent pneumothorax, patients should avoid smoking and activities that involve rapid changes in pressure such as flying or scuba diving.