Marfan syndrome

Key facts

- Marfan syndrome (MFS) is an autosomal dominant systemic disorder of connective tissue, presenting with skeletal, ocular, skin, and cardiovascular symptoms.
- MFS is mainly caused by pathogenic variants in the fibrillin-1 gene (*FBN1*) on chromosome 15.
- The condition has an estimated prevalence of 1 in 5000 individuals.
- The disorder has a very variable presentation with intra- and inter-familial differences in clinical features and severity.

Clinical features

- The signs and symptoms of MFS vary widely in severity, timing of onset and rate of progression.
- The features can become apparent at any time between infancy and adulthood, and range from mild to severe, including rapidly progressive neonatal multiorgan disease.
- Individuals with MFS are usually tall and slender, have elongated fingers and toes (arachnodactyly), loose joints and have an arm span that exceeds their body height.
- Other skeletal features can be present, for example, a long and narrow face, crowded teeth, scoliosis or kyphosis, skin striae (not related to weight gain or loss), and pectus excavatum or pectus carinatum.
- Cardiovascular findings, including dilatation of the aorta at the level of the sinuses of Valsalva, mitral valve prolapse with or without regurgitation, tricuspid valve prolapse and enlargement of the proximal pulmonary artery.
- Spontaneous pneumothorax may develop in some individuals.
- Ocular features include myopia, ectopia lentis and an increased risk for retinal detachment, early cataract and glaucoma.

Diagnosis

- Clinically, there is significant overlap between MFS and other presentations of systemic connective tissue disease, for example, Loeys–Dietz syndrome (LDS), Shprintzen-Goldberg syndrome (SGS) and the MASS (Mitral valve, Aorta, Skin, and Skeletal features) phenotype, and with non-syndromic aortic disease (known as familial thoracic aortic aneurysm and dissection (FTAAD)).
- Distinguishing MFS from other familial aortopathies is important. An international expert panel developed Ghent's nosology to provide criteria to facilitate the clinical diagnosis (Table 1).

Table 1: Revised Ghent nosology

Patient with positive family history	Ectopia lentis
	Systemic score >7 points
	Aortic root dilatation (z-score ≥2)

Isolated patient	Aortic root dilatation (z-score ≥2) and ectopia lentis
	Aortic root dilatation (z-score ≥2) and pathogenic FBN1 variant
	Aortic root dilatation (z-score ≥2) and systemic score >7 pts
	Ectopia lentis and pathogenic *FBN1* variant

Genetic basis and genetic testing

- MFS is an autosomal dominant disorder, with variants found primarily in the *FBN1* gene.
- A clear family history is apparent in approximately 75% of patients; MFS arises through de novo *FBN1* variants in about 25% of cases.
- Genetic testing is routinely performed by molecular genetic analysis of a small panel of genes, including *FBN1*, *TGFBR1*, *TGFBR2*, *TGFB2* and *SMAD3*, some of which are responsible for disorders that are phenotypically similar to MFS.
- Once the genetic diagnosis is made, predictive testing is available to at-risk relatives, so that affected individuals can undergo routine surveillance for early detection of medically significant complications. Where no genetic diagnosis can be made, at-risk relatives should undergo surveillance through clinical examination and investigation.
- Prenatal testing and preimplantation genetic diagnosis are available.

Clinical management

- Comprehensive management should be carried out by a multidisciplinary team, including a clinical geneticist, ophthalmologist, orthopaedic surgeon and cardiothoracic surgeon.
- Depending on the onset and severity of signs and symptoms, MFS can be fatal early in life. However, many affected individuals have normal lifespans with treatment.
- Prevention of primary manifestations, including medications that reduce haemodynamic stress on the aortic wall, such as ß-blockers or angiotensin receptor blockers.
- Surgical repair of the aorta is indicated when: the maximal measurement of the aortic root approaches 5cm in adults or older children, the rate of increase of aortic diameter approaches 0.5-1cm per year, or there is progressive and severe aortic regurgitation.
- Pregnant women with MFS should be assessed by a high risk obstetrician, both during pregnancy and through the postpartum period.
- Agents and circumstances to avoid include: contact sports, competitive sports, isometric exercise and agents that stimulate the cardiovascular system, or cause vasoconstriction.

Direction to further reading, guidelines and patient groups

- The Marfan Trust Charity
- Dietz H. Marfan Syndrome. 2001 [updated 2017]. In: Adam MP, Ardinger HH, Pagon RA et al. editors. GeneReviews. Seattle(WA): University of Washington, Seattle; 1993-2019. https://www.ncbi.nlm.nih.gov/books/
- Loeys BL, Dietz HC, Braverman AC et al. (2010) The revised Ghent nosology for the Marfan syndrome. J. Med Genet 47:476-485.

This information is intended for educational use and was current in September 2019. For clinical management, it is recommended that local guidelines and protocols are used.

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