Marfan Syndrome Diagnostic Criteria

What is Marfan syndrome?

Marfan syndrome is a genetic disorder impacting the body's connective tissue, which supports bones, muscles, organs, and tissues, resulting in developmental complications. It is caused by mutations in a particular gene and is usually passed down from parents (National Institute of Arthritis and Musculoskeletal and Skin Diseases, 2019; The Marfan Foundation, 2022).

How is Marfan syndrome diagnosed?

Marfan syndrome is diagnosed through a combination of medical and family history assessment, physical examinations, and specific diagnostic tests such as echocardiography, electrocardiogram, genetic testing for fibrillin-1 (FBN-1) gene mutations, and eye examinations using a slit-lamp. Screening for the disorder extends to family members, even those without symptoms, to identify potential carriers or affected individuals (National Heart, Lung, and Blood Institute, 2022; The Marfan Foundation, n.d-a).

To decrease the risk of premature or missed diagnosis, Ghent nosology, an updated clinical criteria was introduced in 2010 in the Journal of Medical Genetics. This criteria emphasizes cardiovascular signs such as aortic root aneurysm and ectopia lentis (dislocated lenses) (The Marfan Foundation, n.d.-b).

The 2010 revised Ghent nosology for Marfan syndrome

In the absence of family history

1. Aortic root dilatation Z score ≥ 2 AND ectopia lentis = Marfan syndrome
2. Aortic root dilatation Z score ≥ 2 AND FBN1 = Marfan syndrome
3. Aortic root dilatation Z score ≥ 2 AND Systemic score ≥ 7pts = Marfan syndrome
4. Ectopia lentis AND a FBN1 mutation associated with aortic root dilatation = Marfan syndrome

In the presence of family history

1. Ectopia lentis AND family history of Marfan syndrome (as defined above) = Marfan syndrome
2. A systemic score ≥ 7 points AND family history of Marfan syndrome (as defined above) = Marfan syndrome
3. Aortic root dilatation Z score ≥ 2 above 20 yrs. old, ≥ 3 below 20 yrs. old + family history of Marfan syndrome (as defined above) = Marfan syndrome

Calculation of systemic score is done by evaluating the presence of the features below (The Marfan Foundation, n.d.-c):

Feature	Value	Description
Wrist AND thumb sign	3	The thumb sign is positive when the entire distal phalanx of the adducted thumb extends beyond the ulnar border of the palm with or without the assistance of the patient or examiner to achieve maximal adduction. The wrist sign is positive when the tip of the thumb covers the entire fingernail of the fifth finger when wrapped around the contralateral wrist.
Wrist OR thumb sign	1	
Pectus carinatum deformity	2	Pectus carinatum is believed to be more specific for MFS than pectus excavatum and is assigned two points. Subjective qualifiers in the original Ghent criteria such as “requiring surgery” have been eliminated but the examiner should be confident that a positive finding (pectus excavatum or chest wall asymmetry) extends beyond normal variation of chest contour in the general population before assigning one point.
Pectus excavatum or chest asymmetry	1	
Hindfoot deformity	2	Hindfoot valgus in combination with forefoot abduction and lowering of the midfoot (previously referred to as medial rotation of the medial malleolus) should be evaluated from anterior and posterior view. The examiner should distinguish this from the more common “flat foot” (one point) without significant hindfoot valgus.
Plain flat foot (pes planus)	1	
Pneumothorax	2	Any spontaneously-occurring pneumothorax.
Dural ectasia	2	For the detection of lumbosacral dural ectasia, no preferred method (CT or MRI) or uniformly accepted cut-offs have emerged from the literature and local standards should apply.
Protrusio acetabulae	2	On X-ray anterior-posterior pelvis angle, the medial protrusion of the acetabulum above 3 mm beyond the ilio-ischial (Kohler) line is diagnostic. Criteria on CT or MRI are not precisely defined but involve loss of the normal oval shape of the pelvic inlet at the level of the acetabulum.

Feature	Value	Description
Reduced upper segment (US) to lower segment (LS) AND increased arm span to height ratios	1	The combined presence of reduced upper to lower segment ratio (for white adults <0.85; <0.78 in black adults; no data have been assessed in Asians) and increased armspan to height ratio (for adults >1.05) in the absence of significant scoliosis contributes one point to the systemic score. In Asians the incidence of an enlarged armspan to height ratio in Marfan patients was noted to be lower (25) and prior studies of Asian (and also Afro-Caribean) populations demonstrated different distributions of armspan and height, so one should consider these ethnic differences when using cut-off values (26). For the US/LS ratio in children, abnormal ratios are US/LS < 1 (for age 0-5 yrs), US/LS < 0.95 (for 6-7 yrs), US/LS < 0.9 (8-9 yrs old) and < 0.85 (above age 10 yrs). The lower segment is defined as the distance from the top of the symphysis pubis to the floor in the standing position and the upper segment is the height minus the lower segment. Importantly, neither of these ratios provides an accurate measurement of bone overgrowth in the presence of severe scoliosis or kyphosis.
Scoliosis or thoracolumbar kyphosis	1	Scoliosis can be diagnosed either clinically if, upon bending forward, a vertical difference of least 1.5 cm between the ribs of the left and right hemithorax is observed or if a Cobb's angle (angle between a line drawn along the superior end plate of the superior end vertebra and a second line drawn along the inferior end plate of the inferior end vertebra of the scoliosis measured on anterior-posterior view of the spine) of at least 20° is seen on radiographs. In the absence of scoliosis, one point can be contributed by the presence of an exaggerated thoracolumbar kyphosis.
Reduced elbow extension	1	Elbow extension is considered reduced if the angle between the upper and lower arm measures 170 degrees or less upon full extension.
3 of 5 facial features	1	One point can be assigned based upon facial characteristics if the patient shows at least three of the five typical facial characteristics including dolichocephaly, downward slanting palpebral fissures, enophthalmos, retrognathia and malar hypoplasia.

Feature	Value	Description
Skin striae	1	Striae atrophicae are considered significant as a diagnostic feature if they are not associated with marked weight changes (or pregnancy) and if they have an uncommon location such as the mid-back, lumbar region, the upper arm, axillary region or thigh.
Myopia	1	Given that myopia is very common in MFS, is routinely monitored, and tends to show early onset, high severity and rapid progression, myopia of greater than 3 diopters contributes to the systemic score for diagnosis. However, since myopia is quite common finding in the general population we have only attributed one point to it in the systemic score.
Mitral valve prolapse	1	Mitral valve prolapse should be defined by echocardiography as protrusion of one or both of the mitral valve leaflets across the plane of the mitral annulus during systole. This is best detected in parasternal long-axis or apical long-axis 3-chamber or 2-chamber views. There are no special criteria for diagnosing MVP in MFS and standard practices should be applied.

For a more comprehensive calculation and evaluation of features, the Marfan Foundation provides a systemic calculator, detailed descriptions, accompanying photos and other tools to guide the process.

Additional notes

Treating Marfan syndrome can be challenging, but after diagnosis, the following can be done:
Regular medical check-ups
Lifestyle modifications
Genetic counseling and genetic testing

References

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