I - Revised Ghent criteria for the diagnosis of Marfan syndrome (MFS) and related conditions


In the absence of a family history:
(1) Ao (Z ≥ 2) AND EL = MFS
(2) Ao (Z ≥ 2) AND FBN1 = MFS
(3) Ao (Z ≥ 2) AND Syst (≥7 points) = MFSa
(4) EL AND FBN1 with known Ao = MFS
EL with or without Syst AND with an FBN1 not known with Ao or no FBN1 = ELS
Ao (Z < 2) AND Syst (≥5) with at least one skeletal feature without EL = MASS
MVP AND Ao (Z < 2) AND Syst (>5) without EL = MVPS

In the presence of a family history:
(5) EL AND FH of MFS (as defined above) = MFS
(6) Syst (≥7 points) AND FH of MFS (as defined above) = MFSa
(7) Ao (Z ≥ 2 above 20 years old, ≥ 3 below 20 years) + FH of MFS (as defined above) = MFSa

Systemic score

• Wrist AND thumb sign –3 (Wrist OR thumb sign –1)
• Pectus carinatum deformity –2 (pectus excavatum or chest asymmetry –1)
• Hindfoot deformity –2 (plain pes planus –1)
• Pneumothorax –2
• Dural ectasia –2
• Protrusio acetabuli –2
• Reduced US/LS AND increased arm/height AND no severe scoliosis –1
• Scoliosis or thoracolumbar kyphosis –1
• Reduced elbow extension –1
• Facial features (3/5) –1 (dolichocephaly, enophtalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
• Skin striae –1
• Myopia > 3 diopters –1
• Mitral valve prolapse (all types) –1

Maximum total: 20 points; score ≥ 7 indicates systemic involvement

Ao, aortic diameter at the sinuses of Valsalva above indicated Z-score or aortic root dissection; EL, ectopia lentis; ELS, ectopia lentis syndrome; FBN1, fibrillin-1 mutation; FBN1 not known with Ao, FBN1 mutation that has not previously been associated with aortic root aneurysm/dissection; FBN1 with known Ao, FBN1 mutation that has been identified in an individual with aortic aneurysm; FH, family history; MASS, myopia, mitral valve prolapse, borderline (Z < 2) aortic root dilation, skeletal findings, striae; MFS, Marfan syndrome; MVPS, mitral valve prolapse syndrome; Syst, systemic score; US/LS, upper segment/lower segment ratio; Z, Z-score.

aCaveat: without discriminating features of Shprintzen-Goldberg syndrome (SGS), Loeys-Dietz syndrome (LDS) or vascular Ehlers-Danlos syndrome (vEDS) AND after TGFBR1/2, collagen biochemistry, COL3A1 testing if indicated. Other conditions/genes will emerge with time.
**Criteria for causal FBN1 mutation**

- Mutation previously shown to segregate in Marfan family
- De novo (with proven paternity and absence of disease in parents) mutation (one of the five following categories)
- 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
  
  \[(D/N)X(D/N)(E/Q)Xm(D/N)Xn(Y/F)\] with \(m\) and \(n\) representing variable number of residues; D aspartic acid, N asparagine, E glutamic acid, Q glutamine, Y tyrosine, F phenylalanine
- Other missense mutations: segregation in family if possible + absence in 400 ethnically matched control chromosomes, if no family history absence in 400 ethnically matched control chromosomes
- Linkage of haplotype for \(n \geq 6\) meioses to the FBN1 locus
II - Ghent criteria for the diagnosis of Marfan syndrome

Skeletal

Major (presence of at least 4 of the following manifestations)
- pectus carinatum
- pectus excavatum requiring surgery
- reduced upper to lower segment ratio OR arm span to height ratio >1.05
- wrist and thumb signs
- scoliosis of >20° or spondylolisthesis
- reduced extension at the elbows (<170°)
- medial displacement of the medial malleolus causing pes planus
- protrusio acetabulae of any degree (ascertained on radiographs)

Minor
- pectus excavatum of moderate severity
- Joint hypermobility
- high arched palate with crowding of teeth
- facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)

Involvement: at least 2 major criteria or 1 major and 2 minor

Ocular

Major
- ectopia lentis

Minor
- abnormally flat cornea (as measured by keratometry)
- increased axial length of the globe (as measured by ultrasound)
- hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis

Involvement: at least 2 minor criteria

Cardiovascular

Major
- dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva
- dissection of the ascending aorta

Minor
- mitral valve prolapse with or without mitral valve regurgitation
- dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonic stenosis below the age of 40 years
- calcification of the mitral annulus below the age of 40 years
- dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50 years
Involvement: at least 1 minor criterion

**Pulmonary**

**Minor (only)**
- spontaneous pneumothorax
- apical blebs (ascertained by chest radiography)

Involvement: at least 1 minor criterion

**Skin and integument**

**Minor (only)**
- striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy or repetitive stress
- recurrent or incisional hernias

Involvement: at least 1 minor criterion

**Dura**

**Major**
- lumbosacral dural ectasia by CT or MRI

Involvement: 1 major criterion

**Family/genetic history**

**Major**
- first degree relative who independently meets the diagnostic criteria
- presence of mutation in FBN1 known to cause Marfan syndrome
- presence of haplotype around FBN1 inherited by descent and unequivocally associated with diagnosed Marfan syndrome in the family

Involvement: at least 1 major criterion

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**Diagnostic criteria interpretation**

**For the index case:**
- If family/genetic history is not contributory, major criteria in at least 2 different organ systems and involvement of a third organ system
- If a mutation known to cause Marfan syndrome in others is detected, one major criterion in an organ system and involvement of a second organ system

**For a relative of an index case:**
- Presence of a major criterion in the family history and one major criterion in an organ system and involvement of a second organ system