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

(Loeys BL et al., J Med Genet 2010; 47:476-485 doi:10.1136/jmg.2009.072785)

In the absence of a family history:
(1) Ao ($Z \geq 2$) AND EL = MFS
(2) Ao ($Z \geq 2$) AND *FBN1* = MFS
(3) Ao ($Z \geq 2$) AND Syst (≥7 points) = MFS[a]
(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) = MFS[a]
(7) Ao ($Z \geq 2$ above 20 years old, ≥ 3 below 20 years) + FH of MFS (as defined above) = MFS[a]

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 hyoplasia, 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.

[a]Caveat: 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 ≥ 6 meioses to the *FBN1* locus

II - Ghent criteria for the diagnosis of Marfan syndrome

(De Paepe A et al., Am J Med Genet. 1996 Apr 24; 62(4):417-26)

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

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