Challenges in the diagnosis of Marfan syndrome

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The multidisciplinary diagnostic Marfan Clinic at Prince Charles Hospital in Brisbane has assessed over 600 individuals from more than 300 families since 1995. It is staffed by a nurse coordinator, two cardiologists, an ophthalmologist, a paediatrician specialising in clinical genetics, two genetic counsellors and a molecular geneticist. Referrals for assessment of Marfanoid habitus arise primarily from general practitioners and paediatricians. The clinic also receives referrals from cardiologists because of aortic dilatation or dissection and from ophthalmologists because of dislocated lenses.

All individuals referred to the clinic are assessed by the current diagnostic criteria (Box 1), with particular attention to the possibility of other conditions that have symptoms and signs in common with Marfan syndrome (Box 2). Box 3 and Box 4 show some of the skeletal and ocular characteristics of Marfan syndrome. Four families are detailed below to demonstrate the potential range of diagnostic dilemmas faced by physicians who consider Marfan syndrome (MFS) as a provisional diagnosis for a patient or family.

ABSTRACT

- Marfan syndrome (MFS) is a multisystem disorder of connective tissue that is inherited in an autosomal dominant fashion, and results from mutations in the *FBN1* gene on chromosome 15.
- Diagnosis is challenging as it requires definition of diverse clinical features and input from a variety of specialists.
- Genetic testing of *FBN1* is time consuming, expensive and complex, and may not solve the diagnostic dilemma.
- Failure to make a diagnosis or making an inappropriate diagnosis of MFS has social, lifestyle and medical consequences for the individual as well as the family.

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Family 1: Homocystinuria diagnosed as Marfan syndrome

The proband presented with lens subluxation and minor skeletal signs of MFS (long limbs). There were no cardiovascular signs. She had normal intelligence. No other family members were affected. Blood levels of homocysteine were found to be elevated at 220 μmol/L (normal range, < 15 μmol/L), and a diagnosis of homocystinuria was made. She responded well to treatment with pyridoxine and betaine. Homocystinuria shares the predisposition of lens subluxation with Marfan syndrome (Box 2), and we have seen a number of other cases at the Marfan clinic. The correct diagnosis ensured that this patient received both appropriate treatment and accurate genetic counselling for her autosomal recessive condition.

Family 2: Role of DNA testing in classic Marfan syndrome

The proband was a man in his thirties who had classical features of MFS with lens subluxation, aortic dilatation (requiring surgery) and marked skeletal abnormalities. He had experienced social difficulties as a child and teenager, suffering from bullying and negative body image because of his skeletal deformities. His father appeared normal and his mother had mild chest wall asymmetry. His brother had long limbs, greater than 20° scoliosis, striae and an inguinal hernia. These musculoskeletal features were consistent with MFS, but insufficient to satisfy the diagnostic criteria. The family requested DNA testing to clarify the status of the proband's brother. DNA from the proband had a splice acceptor site mutation that was absent in his parents and his brother, indicating a spontaneous mutation. Current evidence suggests that spontaneous mutation accounts for at least 25% of MFS cases.[2] Risks to family members are different depending on whether the mutation is inherited or spontaneous. For this family, genetic testing confirmed the genetic status of the proband and provided reassurance for other members of the family.

Family 3: Variable phenotype in Marfan syndrome

Thirteen members of one sibship and their offspring were examined. The main clinical presentation was lens subluxation with minor skeletal features of MFS. The family was initially said to have familial isolated ectopia lentis (Box 2). However, our examination showed that several children required surgery for mitral valve prolapse, and two adults had aortic dilatation. Linkage to *FBN1* was found, indicating that the family was likely to have a mutation in this gene. One adult, whose children had lens subluxation, had few signs of MFS, but was a mutation carrier based on DNA haplotype analysis and family status. This adult is manifesting low expressivity of the mutation. For this family, the confounding variability of phenotype meant that detection of the *FBN1* mutation in a young patient had little prognostic value, but did identify individuals who required regular surveillance. This family demonstrates that some carriers of the same *FBN1* gene mutation in a family may not fit the diagnostic criteria for Marfan syndrome but nevertheless have a significant risk of aortic dilatation and its consequences. Therefore, echocardiography needs to be performed for all individuals suspected of having MFS.

Family 4: Familial aortic dissection

The proband was a woman in her fifties with dissection of the ascending aorta, aortic arch and abdominal aorta. Her family history was notable for a number of cases of aortic aneurysm or rupture. Some affected individuals had minor skeletal abnormalities, but none had lens subluxation. The family did not meet the diagnostic criteria for MFS and may have an autosomal dominant familial aneurysmal condition. Several genetic loci, including *FBN1*, have been implicated in familial aneurysms (see Box 2), and one of these may be mutated in the affected individuals. This family illustrates the issues involved in offering DNA testing to families who do not meet the criteria for Marfan syndrome. In such cases, DNA testing is likely to be costly and complex, and may not ultimately result in a molecular diagnosis.

Routine evaluation at Marfan Clinic

Evaluation at Marfan Clinic routinely involves cardiological assessment including echocardiography, and ophthalmological review

1 Diagnostic criteria for Marfan syndrome[1]

Skeletal system

Major criterion

- Presence of at least four of the following manifestations:
  - ➢ Pectus carinatum
  - ➢ Pectus excavatum requiring surgery
  - ➢ Reduced upper to lower segment ratio, or arm span to height ratio greater than 1.05
  - ➢ Arachnodactyly
  - ➢ 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 criteria

- Pectus excavatum of moderate severity
- Joint hypermobility
- Highly arched palate with crowding of teeth
- Facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)

For the skeletal system to be involved, at least two of the components of the major criterion or one component of the major criterion plus two of the minor criteria must be present.

Ocular system

Major criterion

- Ectopia lentis

Minor criteria

- Abnormally flat cornea (as measured by keratometry)
- Increased axial length of globe (as measured by ultrasound)
- Hypoplastic iris or hypoplastic ciliary muscle causing a decreased miosis

For the ocular system to be involved, at least two of the minor criteria must be present.

Cardiovascular system

Major criteria

- Dilatation of the ascending aorta with or without aortic regurgitation, and involving at least the sinuses of Valsalva
- Dissection of the ascending aorta

Minor criteria

- Mitral valve prolapse with or without mitral valve regurgitation
- Dilatation of the main pulmonary artery in the absence of valvular or peripheral pulmonary stenosis or any other obvious cause under the age of 40 years
- Calcification of the mitral annulus under the age of 40 years
- Dilatation or dissection of the descending thoracic or abdominal aorta under the age of 50 years

For the cardiovascular system to be involved, at least one minor criterion must be present.

Dura

Major criterion

- Lumbosacral dural ectasia by computed tomography or magnetic resonance imaging scan

Minor criteria

- None

Pulmonary system

Major criteria

- None

Minor criteria

- Spontaneous pneumothorax
- Apical blebs (ascertained by chest radiography)

For the pulmonary system to be involved, one of the minor criteria must be present.

Skin and integument

Major criteria

- None

Minor criteria

- Striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy or repetitive stress
- Recurrent or incisional herniae

For the skin and integument to be involved, one of the minor criteria must be present.

Family/genetic history

Major criteria

- Having a parent, child or sibling who meets these diagnostic criteria independently
- Presence of a mutation in *FBN1* known to cause Marfan syndrome
- Presence of a haplotype around *FBN1*, inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family

For the family/genetic history to be contributory, one of the major criteria must be present.

Requirements for the diagnosis of Marfan syndrome

For the index case:

- In the absence of significant family history: at least two major criteria in different organ systems and involvement of a third organ system
- If an *FBN1* gene mutation or linkage haplotype previously confirmed to cause Marfan syndrome 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/genetic history category and one major criterion in an organ system and involvement of a second organ system ◆

including dilatation of the pupils for slit-lamp examination and keratometry. In patients with subluxated lenses, the possibility of homocystinuria is excluded by measurement of plasma homocysteine. Patients are assessed by a clinical geneticist by examination for skeletal and skin features, and the role of DNA testing is discussed. A genetic counsellor records genetic and medical family history and constructs a three-generation pedigree to identify individuals at risk. Because at least 25% of cases of MFS result from spontaneous mutations,[2,3] the absence of other confirmed cases in the family does not rule out MFS. The genetic counsellor also provides support for addressing psychosocial issues that may have arisen because of the condition.

Defining skeletal features of Marfan syndrome

Skeletal features of MFS can be difficult to define. Normal reference graphs of upper/lower body segment ratio, which is age-

2 Genetic conditions which have features in common with Marfan syndrome (MFS)

Name	Gene	Chromosome	Inheritance pattern	Features in common with MFS	Features distinct from MFS
Genetic conditions unlikely to involve *FBN1*					
MFS2, Loeys–Dietz syndrome	Transforming growth factor beta receptors (*TGFBR2*, *TGFBR1*)	3, 9	AD	Cardiovascular and skeletal features	Intellectual disability in Loeys–Dietz syndrome
Congenital contractural arachnodactyly	Fibrillin 2 (*FBN2*)	5	AD	Arachnodactyly, contractures, long arms and legs	Ocular and cardiovascular signs rare
Homocystinuria	Cystathionine beta synthase (*CBS*)	21	AR	Lens subluxation, scoliosis, other skeletal features	Venous thrombosis
Bicuspid aortic valve	Unknown	Not mapped	AD?	Dilatation and dissection of ascending aorta	Other organ systems not involved
Familial thoracic aneurysm	Unknown	3, 5, 11	AD?	Thoracic aneurysm and dissection	Other systems rarely involved
Stickler syndrome	Collagens (*COL11A1*, *COL11A2*, *COL2A1*)	1, 6, 12	AD	Joint flexibility, long axial length of globe	Cleft palate
Ehlers–Danlos syndrome	Collagen (*COL3A1*)	2	AD	Rupture of large arteries	Increased skin elasticity, fine translucent skin (type IV), bowel rupture (type IV)
Klinefelter syndrome		Aneuploidy	Chromosomal	Skeletal features	Cryptorchidism, gynaecomastia, 47XXY karyotype
Genetic conditions caused by mutations in *FBN1* which do not meet the diagnostic criteria for Marfan syndrome					
MASS phenotype	Fibrillin 1 (*FBN1*)	15	AD	Cardiovascular, skeletal and skin features	Ocular signs rare, cardiovascular signs milder than MFS
Familial ectopia lentis	*FBN1*	15	AD	Lens subluxation	Other organ systems not involved
Isolated skeletal features of MFS	*FBN1*	15	AD?	Skeletal features	Other organ systems not involved

AD = autosomal dominant. AR = autosomal recessive. ◆

dependent, are generally not widely available. Some existing graphs provide mean values without standard deviations, which may limit interpretation. Milder degrees of pectus carinatum or pes planus can be challenging to evaluate. Specific imaging is only performed when identification of dural ectasia or protrusio acetabulae is required to confirm a diagnosis of MFS.

It is worth noting that the Marfanoid features which most commonly lead to referral are tall and thin body habitus with hyperextensible joints, but these features have a low specificity and are not included in the major diagnostic criteria. Box 3 shows some of the skeletal features mentioned in Box 1 which are included in the major criterion for the skeletal system.

Defining cardiovascular features of Marfan syndrome

Normal reference graphs of ascending thoracic aortic diameter related to age and body size are available.[4] Individuals with aortic dilatation are referred to a separate clinic for monitoring and ongoing management. Patients with a dilated aorta undergo magnetic resonance angiography. An affected individual's siblings and offspring with normal cardiac status are reviewed at 1–5-year intervals until age 20. Individuals with aortic diameters at the upper limit of normal are reviewed annually.

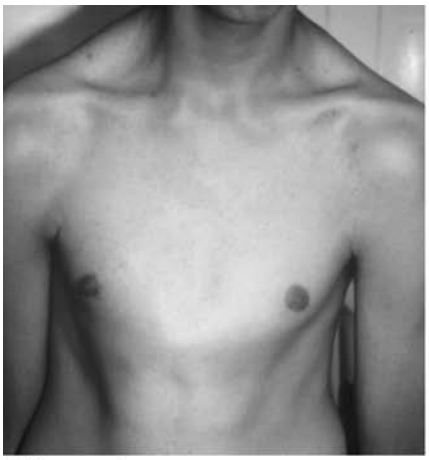
Defining ophthalmic features of Marfan syndrome

Subluxation of the lens is the major ophthalmic criterion for the diagnosis of Marfan syndrome. The lens is usually displaced superotemporally (Box 4). The zonule fibres are stretched, but still present, resulting in myopic astigmatism. Other minor criteria include iris hypoplasia, displaying a featureless iris, a flat corneal curvature and increased axial length. Other features described previously, including glaucoma, retinal detachment and lens opacity, appear to be a secondary effect of lens subluxation and not a primary effect of Marfan syndrome. Amblyopia occurs in small children as an effect of lens subluxation and resultant refractive error. Lens subluxation may be absent in young children and develop as they age.

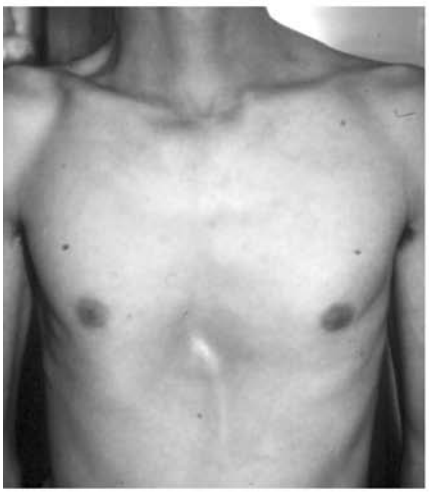
Genetic testing for Marfan syndrome

As there are no common mutations, genetic testing involves screening the entire *FBN1* gene. This process is expensive and only available privately in Australia. With a success rate of 70%–80%, DNA testing cannot exclude a diagnosis of MFS. In the family of an individual with confirmed MFS, the genetic status of other family members can be difficult to ascertain on the basis of the clinical

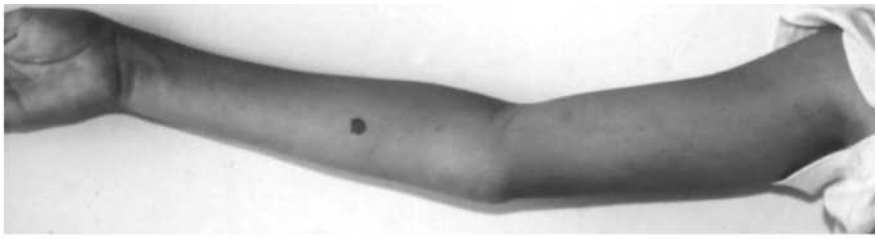
3 Skeletal signs in Marfan syndrome



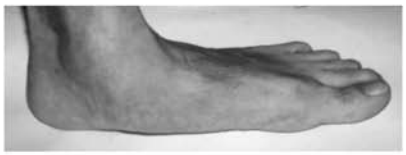
A: Pectus carinatum.

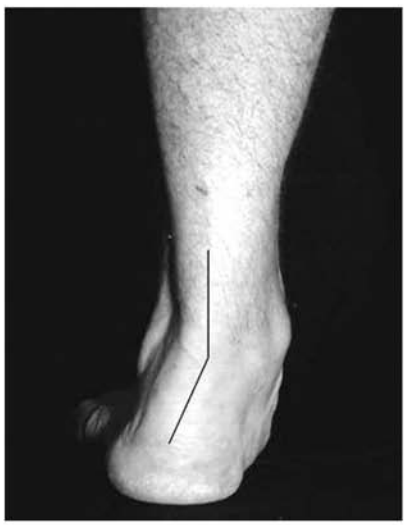


B: Pectus excavatum. This must "require surgery" to be included in the major criterion (Box1).

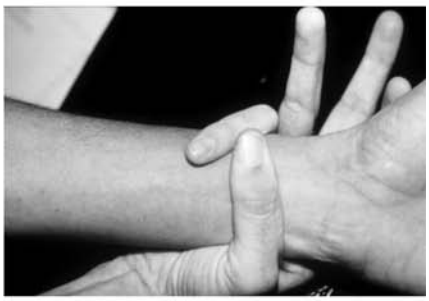


C: Fixed flexion of the elbow.





D: Pes planus. This is best diagnosed by examining the foot from behind. A valgus deviation of the hindfoot indicates pes planus.

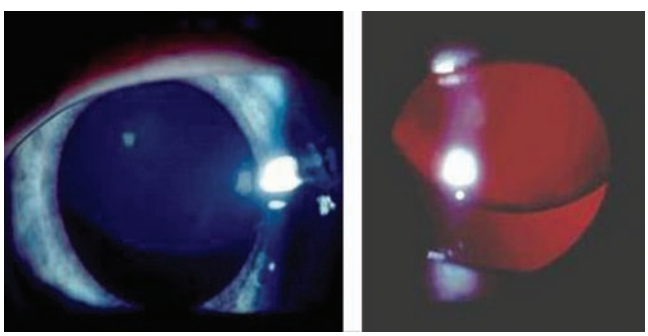


E: Arachnodactyly — the wrist sign.

F: Arachnodactyly — the thumb sign. ◆

features alone. We reserve DNA testing for such families to enable more accurate identification of individuals at risk. This allows family members shown to be non-carriers to cease intensive surveillance protocols, as in Family 2. However, owing to variation in clinical expression of MFS, it is not possible to predict severity in family members shown to carry the familial mutation, as was the case for Family 3. Because of the difficulties in diagnosing MFS and the cost of DNA testing, we believe a recommendation for DNA testing should come from a multidisciplinary clinic or geneticist after full review of the family.

4 Ophthalmic signs in Marfan syndrome



Superotemporal subluxation of the lens. ◆

Diagnostic rate at Marfan clinic

At least one individual in 22% of the families seen at the Prince Charles Hospital Marfan Clinic satisfied the international diagnostic criteria for MFS (see Box 1[1]). Additionally, 18% of the families were given other diagnoses, as for Family 1. Box 2 outlines other conditions that share clinical features with MFS. We consider that the 22% diagnostic rate represents an appropriate referral pattern, because of the difficulties in diagnosis and because treatments are available (such as prophylactic β-blockers which may delay aortic dilatation, and pre-emptive surgery which can prevent rupture of an aortic aneurysm, often a fatal event).

As the prevalence of MFS is relatively high (about 1 in 5000[5]), and isolated features of the condition are even more common, many clinicians will encounter potential cases. A diagnosis of MFS raises the possibility of early death from the complications of aortic

dilatation and dissection,[3] and patients are advised to make lifestyle adjustments to minimise these risks. Pregnancy must be closely monitored in affected women. Patients diagnosed with MFS may find it difficult to obtain life insurance. Misdiagnosis of MFS raises the possibility of inappropriate discrimination by insurance companies and employers, and can lead to improper treatment and surveillance. As outlined above, full cardiovascular, ophthalmological and musculoskeletal evaluation of patients suspected of having Marfan syndrome ensures appropriate diagnosis and circumvents these potential problems.

Competing interests

None identified.

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