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ISSUES IN THE DIAGNOSIS OF MARFAN SYNDROME: VARIABLE
CLINICAL PHENOTYPE IN GENETIC DISEASE

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ABSTRACT

Marfan syndrome (MFS) is a multisystem disorder of connective tissue that is inherited in an autosomal dominant fashion and results from mutation in the *FBNI* gene on chromosome 15. Diagnosis is challenging both in defining the clinical features and for the variety of specialists required for input. Genetic testing of *FBNI* 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.

Clinical record

The multidisciplinary diagnostic Marfan Clinic at Prince Charles Hospital in Brisbane has assessed over 600 individuals from more than 300 families. Referrals arise from general practitioners and paediatricians primarily for assessment of Marfanoid habitus. The clinic also receives referrals from cardiologists because of aortic dilatation or dissection and from ophthalmologists because of dislocated lenses. All individuals are assessed by the current diagnostic criteria (Box 1). Four families are detailed below to demonstrate the potential range of diagnostic dilemmas faced by physicians attempting to determine whether Marfan syndrome (MFS) is present.

Family 1

The proband presented with lens subluxation and minor skeletal signs (scoliosis, long limbs and digits) of MFS. There were no cardiovascular signs. She had normal intelligence. No other family members were affected. Blood levels of homocysteine were found to be elevated and a diagnosis of homocystinuria was made. She responded well to treatment with pyridoxine and betaine. Determination of the correct diagnosis allowed appropriate treatment and genetic counselling for this recessive condition.

Family 2

The proband was a man in his thirties who had classical features of MFS with lens subluxation, aortic dilation (requiring surgery) and marked skeletal abnormalities. He had experienced social difficulties as a child and teenager, suffering from bullying and negative body image due to his skeletal deformities. His brother and parents had minor musculoskeletal features of MFS. The family requested DNA testing to clarify the status of his brother. DNA from the proband had a splice acceptor site mutation

that was absent in his parents and his brother, indicating a spontaneous mutation in the proband. Genetic testing has provided reassurance for other members of the family.

Family 3

13 members of a sibship of 15 individuals and their offspring were examined. The main clinical presentation was lens subluxation with minor skeletal features of MFS. However, several children had required surgery for mitral valve prolapse and two adults had aortic dilatation. Linkage to *FBNI* 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 has low penetrance of the mutation. For this family the confounding variability of phenotype meant that detection of the *FBNI* mutation in a young patient had little prognostic value, but did identify individuals to be monitored.

Family 4

The proband was a woman in her fifties with aortic dissection affecting the ascending aorta, aortic arch and abdominal aorta. 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 *FBNI*, have been implicated in familial aneurysms and one of these may be mutated in this family. DNA testing would therefore be complex and may not result in a molecular diagnosis.

Discussion

Evaluation at the Marfan Clinic involves cardiological assessment including echocardiography, slit-lamp examination through dilated pupils and keratometry by an ophthalmologist, assessment by a clinical geneticist with examination for skeletal and skin features, construction of a family pedigree to identify individuals at risk, blood collection and discussion of DNA testing. Because at least 25% of cases result from spontaneous mutations⁴ the absence of other confirmed cases in the family does not rule out MFS. Specific imaging is only performed when identification of dural ectasia or protrusio acetabulae is required to confirm a diagnosis of MFS. Subjects undergo magnetic resonance angiography when a dilated aorta is present. In patients with subluxated lenses, the possibility of homocystinuria should be excluded by measurement of plasma homocysteine. Skeletal features of MFS can be difficult to define. Graphs for upper/lower body segment ratio, which is age-dependant, are generally not widely available and existing tables provide mean values without standard deviations making interpretation difficult. Milder degrees of pectus carinatum or pectus excavatum can be difficult to diagnose. 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 are not discriminatory and are not included in the major diagnostic criteria. Graphs of ascending thoracic aortic diameter related to age and body size are available. Individuals with aortic dilatation are referred to a separate clinic for monitoring and further management. An affected individual's siblings and offspring with normal cardiac status are reviewed at 1-5 years. Individuals with aortic diameters at the upper limit of normal are reviewed at 1 year.

As there are no common mutations, genetic testing involves screening the entire *FBNI* gene. This process is expensive and only available privately. 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 family members can be difficult to ascertain on the basis of the clinical features. 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 follow-up protocols. However, because of variation in clinical expression of MFS it is not possible to predict severity in family members shown to have a mutated gene, as was the case for Family 3. Because of the difficulties in diagnosis of MFS and the cost of DNA testing, we believe a recommendation for DNA testing should come from a multidisciplinary clinic or geneticist following full review of the family. In 20% of the families seen at the Prince Charles Hospital Marfan Clinic, at least one individual satisfied the international diagnostic criteria for MFS⁴. A small proportion of the remainder were given other diagnoses.

Since the prevalence of MFS is high (at least 1 in 10,000⁴) and isolated features of the condition are even more common, many clinicians will be presented with potential cases. A diagnosis of MFS raises the possibility of early death due to the complications of aortic dilatation and dissection⁴ and patients are advised to make lifestyle adjustments to minimize these risks. In affected females, pregnancy must be planned and closely monitored. Subjects diagnosed with MFS may not be able to obtain life insurance. Misdiagnosis of MFS can result in inappropriate treatment and surveillance and opens the possibility of inappropriate discrimination by insurance

companies and employers. Box 2 outlines other conditions that share clinical features with MFS.

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Box 1 Diagnostic Criteria for Marfan Syndrome (after De Paepe, 1996)**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 $>20^\circ$ or spondylolisthesis
- Reduced extension at the elbows ($<170^\circ$)
- 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 considered involved, at least two of the components comprising the major criterion or one component comprising 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; or
- 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; or
- Dilatation or dissection of the descending thoracic or abdominal aorta under the age of 50 years.

For the cardiovascular system to be involved only one major or minor criterion need be present.

Dura

Major criterion

- Lumbosacral dural ectasia by CT or MRI scan

Minor criteria

- None

For the dura to be involved the major criterion must be present.

Pulmonary system

Major criteria

- None

Minor criteria

- Spontaneous pneumothorax; or
- 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; or
- 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 sib who meets these diagnostic criteria independently
- Presence of a mutation in *FBNI* known to cause the Marfan syndrome; or
- Presence of a haplotype around *FBNI*, 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 a *FBNI* 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.

Box 2 Genetic Conditions with Features in Common with Marfan Syndrome

Name	Gene	Chromosome	Inheritance pattern ^a	Features in common with MFS	Features distinct from MFS
Genetic conditions unlikely to involve <i>FBN1</i>					
MFS2, Loays Dietz syndrome,	<i>TGFBR2</i> <i>TGFBR1</i>	3 9		Aneurysm disease	
Congenital contractural arachnodactyly	<i>FBN2</i>	5	AD	Arachnodactyly, contractures, long arms and legs	Ocular and cardiovascular signs rare
Homocystinuria	Cystathionine beta synthase	21	AR	Lens subluxation, scoliosis, other skeletal features	Venous thrombosis
Bicuspid aortic valve			AD?	Dilatation and dissection of ascending aorta	Other organ systems not involved
Familial thoracic aneurysm		3, 5, 11	AD?		
Stickler syndrome	<i>COL11A1</i> , <i>COL11A2</i> , <i>COL2A1</i>	1, 6 12	AD	Joint flexibility, long axial length of globe	Cleft palate
Ehlers Danlos syndrome	<i>COL3A1</i>	2	AD	Rupture of large arteries	Fine translucent skin, bowel rupture
Klinefelter syndrome		Aneuploidy	Chromosomal	Skeletal features	Cryptorchidism Gynaecomastia 47XXY Karyotype
Genetic conditions caused by mutations in <i>FBN1</i> which do not meet the diagnostic criteria for Marfan syndrome					
MASS phenotype	<i>FBN1</i>	15	AD	Cardiovascular, skeletal and skin features	Ocular signs rare, cardiovascular signs milder than MFS
Familial ectopia lentis	<i>FBN1</i>	15	AD	Lens subluxation	Other organ systems not involved
Isolated skeletal features of MFS	<i>FBN1</i>	15	AD?	Skeletal features	Other organ systems not involved