

## Evaluation of the adolescent or adult with some features of Marfan syndrome

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Individuals who are suspected of having Marfan syndrome are often referred to a medical geneticist for further evaluation and diagnosis. However, there are a number of conditions that share physical manifestations with those of Marfan syndrome; therefore, an approach to diagnosis and evaluation is crucial to the proper long-term follow-up

of these individuals. This practice guideline provides guidance for the approach to this cadre of individuals.

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**Key Words:** aortic aneurysm; aortic dissection; fibrillin; Loeys–Dietz syndrome; marfanoid

### INTRODUCTION

A common reason for referral to cardiologists and medical geneticists is the tall, lanky individual who wants clearance for physical activities or who has vague complaints of discomfort in the back, chest, or joints. Obviously, concern for Marfan syndrome (MFS) is appropriate, but frequently the diagnosis cannot be established by the original “Ghent Criteria.”<sup>1</sup> The specialist often wonders whether or how to label such an individual, whether further testing (such as computed tomography (CT) of the spine) or molecular genetic testing is necessary, and whether to recommend follow-up evaluation. New diagnostic criteria for MFS have been published recently.<sup>2</sup> A practice guideline that addresses these issues in the context of the new criteria will assist a variety of clinicians in dealing more appropriately with such patients and reduce instances of overly restricting people who do not have MFS or inappropriately reassuring those who do.

The following list of disorders (with OMIM numbers in parentheses) presents considerable diagnostic challenges because of shared features, overlapping phenotypes, similar inheritance patterns, and, at least for some, causation by mutations in the same gene, *FBNI*.

- MFS (154700)
- Ehlers–Danlos syndrome, hypermobile type (EDS) (130020)
- Familial thoracic aortic aneurysm and dissection (reviewed in 607086)
- Loeys–Dietz syndrome (LDS) and other disorders of TGFβ receptors (reviewed in 609192)

- Congenital contractural arachnodactyly (CCA) (121050)
- MASS phenotype (604308)
- Familial arterial tortuosity syndrome (208050)
- Familial mitral valve prolapse (MVP) (157700)
- Familial ectopia lentis (129600)
- Bicuspid aortic valve sequence (109730)
- Familial tall stature
- Familial pectus excavatum (169300)
- Familial scoliosis (181800)
- Stickler syndrome (108300)

Diagnostic criteria for these related disorders are based entirely on expert opinion, but rarely have groups of experts collaborated on refining their ideas.<sup>1,3</sup> The entire field suffers from the lack of any systematic attempt to apply rigorous methodology to categorization. The focus of what follows is the evaluation for the MFS. Comments about the other disorders are included as an appendix.

Medical geneticists, cardiologists, and sports medicine physicians, among others, are frequently consulted about tall, thin children and adolescents out of concern for MFS. The main reason that primary-care providers are interested in ruling MFS in or out is the risk of progressive aortic dilatation and aortic dissection, particularly related to physical activity. In this regard, if the echocardiogram shows an aortic root dimension within the normal range for body surface area,<sup>4</sup> in almost all of the disorders to be considered, the risk of aortic dissection is very low. The one exception is LDS<sup>5</sup> and other phenotypes

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associated with mutations in *TGFBR1* and *TGFBR2*,<sup>6</sup> in some of which both the aorta and its major branches dissect in the absence of much, if any, dilatation. Thus, the echocardiogram is an essential test whenever any of these conditions is considered seriously and whenever concerns about modulating physical activity are raised. Likewise, a slit-lamp examination, with the pupils fully dilated, is essential to exclude ectopia lentis; when MFS is seriously suspected, this test should be performed by an ophthalmologist comfortable with the ocular features of MFS.

Because all of the conditions listed above (except arterial tortuosity syndrome, which is recessive) can be inherited as autosomal dominant traits, the family history is a crucial component of any diagnostic matrix. Historical information may suffice, but usually more detail is needed in the form of medical and autopsy records. Frequently, a grandparent dies of an “aneurysm” and the family does not know what vessel or what region of the aorta was involved. More so in the past than now, a relative who died of an ascending aortic dissection and had a postmortem examination that showed “cystic medial necrosis” was automatically said to have had MFS, even in the absence of any other physical features of that condition. Personally examining the sibs and parents of a child in whom MFS is suspected is at least as important as obtaining a complete family history. Many of the helpful diagnostic features, such as scoliosis, striae atrophicae, disproportionate stature, MVP, and aortic root dilatation are clinically silent and may not be apparent to the relative and those close to him or her.

Almost all of the conditions listed above are “syndromes,” in that multiple features are required to establish the diagnosis. For those conditions caused by a mutation in a single gene, the syndromic features are pleiotropic manifestations of the mutation and the pathogenetic mechanisms that derive from it. However, a number of important caveats affect this interpretation. First, virtually all of the features are age dependent; when examining a young relative, usually fewer features will be evident than in older relatives. Second, all genetic syndromes show variable expression beyond age dependency, for reasons that are poorly understood. Third, many of the features of these conditions also occur “sporadically” in the general population for both genetic and nongenetic reasons. Examples are nearsightedness, tall stature, pectus excavatum, scoliosis, joint hypermobility, and MVP. Fourth, many of these same features are more likely to occur among relatives because of polygenic contributions to pathogenesis. Occasional families will show such frequent occurrence of one of these features that Mendelian inheritance is inferred; this led to some of the diagnoses listed above, although with rare exceptions the causative locus has not been identified. Examples are familial forms of pectus excavatum, scoliosis, tall stature, and what the rheumatologists term “familial benign joint hypermobility,” which is distinguished from forms of EDS by an absence of involvement of the skin.

The frequency of specific features in the general population contributes to their importance as diagnostic criteria in a

Bayesian sense. For example, lumbosacral dural ectasia occurs in very few conditions besides MFS and LDS and almost never in the absence of some systemic disorder. This prompted the inclusion of dural ectasia as a “major criterion” for the diagnosis of MFS in the Ghent scheme.<sup>1</sup> Similar reasoning was used to so distinguish ectopia lentis, aortic dissection, and aortic dilatation. But it is important to emphasize again that these decisions were based on expert opinion and are just beginning to be subjected to formal scrutiny. If the diagnosis of MFS is clear in a patient who has no back or radicular pain, then there is almost no need to image the lower spine. On the other hand, if the diagnosis of MFS hangs on whether dural ectasia is present, then the effort, expense, and radiation (if a CT scan is done) of imaging are warranted. The severity of dural ectasia is clearly age dependent, but no cross-sectional survey of a pediatric population has been performed to determine when radiographic features appear. In the new diagnostic criteria for MFS, the presence or absence of dural ectasia has been reduced in importance.

Some of the diagnoses are ones of exclusion. For example, a family history of aortic aneurysms and mild thoracic-cage abnormalities, with no one meeting criteria for MFS, warrants a label of familial aortic aneurysm (although that implies little about etiology). Likewise, a family history of MVP and mild joint hypermobility, in the absence of features of MASS such as striae, thoracic-cage abnormalities, and myopia, warrants a label of familial MVP. Familial pectus, familial tall stature, and familial ectopia lentis fall into this group. Occasionally, long-term follow-up of patients or introduction of relatives with a wider spectrum of features may prompt reevaluation of the initial diagnosis. This has happened rather often with familial ectopia lentis due to mutations in *FBNI*.

Because echocardiography is an expensive, if benign, test, physicians often wonder whether to rescreen and at what interval. Certainly in MFS, a maximum interval is annually; the larger the aortic root diameter, the more frequently the test should be performed. This holds for familial aortic aneurysm, bicuspid aortic valve with aneurysm, and LDS. For the tall, lanky adolescent with flat feet and myopia, if the family history is unremarkable and the initial echocardiogram is completely normal, the study might be repeated only if cardiovascular symptoms arise. A great many patients fall somewhere in between, and repeating an echocardiogram every 2 to 3 years, or whenever a major increase in physical exertion is planned, seems reasonable. Interestingly, patients followed by cardiologists tend to have echocardiograms more frequently.

Anyone with moderate or severe aortic root dilation and/or a *TGFBR1* or -2 mutation should be taught the signs and symptoms of aortic dissection and should consider wearing a medical alert bracelet.

## EVALUATION FOR MFS

MFS is characterized by autosomal dominant inheritance of features in the skeletal, ocular, cardiovascular, and pulmonary

systems, along with muscular and adipose hypoplasia, dural ectasia, and hernias.<sup>7</sup> As individuals with MFS live longer with aggressive and prophylactic management of their cardiovascular disease, additional features are emerging, such as renal and hepatic cysts.<sup>8</sup> Because about one-third of patients have parents unaffected by MFS, more features are required in them to be certain of the diagnosis. Mutations in *FBNI*, the gene that encodes the large glycoprotein, fibrillin-1, cause MFS, but also cause many of the related conditions. Conversely, conditions that have been confused with MFS, such as CCA and LDS, are due to mutations in genes that encode either related proteins (e.g., fibrillin-2) or proteins involved in pathogenesis of common features (e.g., TGF $\beta$  receptors). There is no case of classic, bona fide MFS due to mutations in a gene other than *FBNI*. However, current clinical molecular testing of *FBNI* successfully detects mutations in such unequivocal patients in only about 90–95% of cases.<sup>9</sup> For all of these reasons, searching for mutations in *FBNI* continues to have a circumscribed role in the diagnosis of equivocal cases. Said differently, MFS remains, by and large, a clinical diagnosis.

#### Diagnostic criteria

If there is no family history of MFS, then the subject has the condition under any of the following four situations:

- A dilated aortic root (defined as greater than or equal to two standard deviations above the mean for age, sex, and body surface area, i.e., a Z-score of  $> +2$ ) and ectopia lentis
- A dilated aortic root and a mutation in *FBNI* that is clearly pathologic
- A dilated aortic root and multiple systemic features (see below) or
- Ectopia lentis and a mutation in *FBNI* that has previously been associated with aortic disease

If there is a positive family history of MFS (independently ascertained with these criteria), then the subject has the condition under any of the following three situations:

- Ectopia lentis
- Multiple systemic features (see below) or
- A dilated aortic root (if over 20 years, greater than two standard deviations; if younger than 20, greater than three standard deviations)

The scoring system for systemic features involves the following:

- 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
- Protrusion acetabuli = 2

- Reduced upper-to-lower segment ratio AND increased arm/height AND no severe scoliosis = 1
- Scoliosis or thoracolumbar kyphosis = 1
- Reduced elbow extension = 1
- Facial features (three of five including dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, and retrognathia) = 1
- Skin striae = 1
- Myopia  $>3$  diopters = 1
- Mitral valve prolapse (all types) = 1
- Maximum total: 20 points; score of 7 or more indicates systemic involvement

#### Diagnostic evaluation

1. Physical exam
2. Family history
3. Echocardiogram
4. Dilated eye exam
5. Consider CT or magnetic resonance imaging for evidence of lumbosacral dural ectasia and protrusion acetabulae
6. Consider *FBNI* gene sequencing

#### Management

**Cardiovascular:** (recommend management by a skilled cardiologist)

- A. *Aortic root dilation and/or diagnostic criteria met for MFS:*  
 Annual echocardiogram for root diameter  $<4.5$  cm in an adult and rate of increase  $<0.5$  cm/year  
 $\beta$ -Blocker therapy.<sup>10</sup> A randomized controlled trial of losartan versus atenolol is under way, but the results are potentially not available until 2013–14.<sup>11</sup> The final *N* of 604 subjects was reached at the end of January 2011.  
 Echocardiogram every 6 months if diameter is  $>2$  SD in an adult or rate of increase in size is  $>0.5$  cm/year  
 Surgical repair for measurements  $>4.5$  cm, rate of increase in size  $>1$  cm/year, or progressive aortic regurgitation  
 Magnetic resonance angiography or CT of the entire aorta starting in young adulthood. Repeat annually if there is a history of aortic root replacement or dissection, less frequently if not

- B. *Normal aortic root size with systemic involvement of another system with a positive family/genetic history:*  
 Annual echocardiogram

- C. *Normal aortic root size with systemic involvement with a negative family/genetic history:*  
 Repeat echocardiogram every 2 to 3 years until adult height is reached. Then repeat if symptomatic or when a major increase in physical activity is planned. The diameter of the aortic root is slightly larger in men than women of the same body size and, in both sexes, increases very slightly and gradually in normal individuals with age, but should not exceed the general upper limit of normal of 40–42 mm, even in tall individuals.

## APPENDIX

## EDS HYPERMOBILE TYPE

Joint hypermobility in this condition may mimic that in MFS. The skin may be mildly hyperextensible whereas it rarely is in MFS. Aortic root dilation, usually mild, occurs in one-quarter to one-third of individuals with EDS classic and hypermobility types.<sup>12</sup> There is not thought to be a risk of dissection without significant aortic root dilatation. Long-term prognosis is not known. Other features include joint laxity, easy bruising, functional bowel disorders, osteoporosis, and chronic pain.

**Diagnostic criteria**

Diagnosis is based on clinical evaluation and family history. A small subset of individuals with the hypermobile form of EDS have an insertion or deletion in the *TNXB* gene.

*Major diagnostic criteria*<sup>13</sup>

All of the following criteria should be met to establish a diagnosis of EDS, hypermobility type:

1. Joint hypermobility confirmed by a score of 5 or more on the 9-point Beighton scale:<sup>14</sup>
  - Passive dorsiflexion of each fifth finger >90 degrees (1 point each side)
  - Passive apposition of each thumb to the flexor surface of the forearm (1 point each side)
  - Hyperextension of each elbow >10 degrees (1 point each side)
  - Hyperextension of each knee >10 degrees (1 point each side)
  - Place palms flat on the floor when bending over with knees fully extended (1 point)
2. Soft or velvety skin with normal or slightly increased extensibility
3. Absence of skin or soft tissue fragility (suggestive of other EDS subtypes)

*Minor diagnostic criteria*

These criteria are supportive but not sufficient to establish the diagnosis.

1. Autosomal dominant family history of similar features without skin abnormalities
2. Recurrent joint dislocation or subluxation
3. Chronic joint or limb pain
4. Easy bruising
5. Functional bowel disorders (functional gastritis, irritable bowel syndrome)
6. Neurally mediated hypotension or postural orthostatic tachycardia
7. High, narrow palate
8. Dental crowding

**Diagnostic evaluation**

1. Physical exam
2. Family history
3. Echocardiogram to evaluate for aortic root dilatation
4. Dilated eye exam (to exclude MFS)

**Management**

*Cardiovascular: (recommend management by a skilled cardiologist)*

*A. Normal aortic root size:*

Repeat echocardiogram every 2–3 years until adult height reached. If no dilatation present, repeat echocardiogram if cardiovascular symptoms develop or when a major increase in physical activity is planned. If dilatation present, follow as described in the next section.

*B. Aortic root dilation:*

Echocardiogram every 6 months if diameter is >4.5 cm in an adult or rate of increase in size is >0.5 cm/year. Annual echocardiogram for root diameter <4.5 cm in an adult and rate of increase is <0.5 cm/year

*C. Bone Density:*

Encourage calcium and vitamin D supplementation  
Low-impact weight-bearing exercise  
Order DXA scan for height loss greater than one inch

*D. Gastrointestinal:*

Gastritis and reflux may require a proton pump inhibitor, H-2 blocker, and sucralfate.  
Delayed gastric emptying may require a promotility agent  
Irritable bowel is treated with antispasmodics, antidiarrheals, and laxatives as needed

*E. Musculoskeletal:*

Low-resistance exercise is recommended to improve joint stability by increasing muscle tone. Physical therapy for myofascial release is often necessary to facilitate participation in low-resistance exercise. A pain management specialist is a crucial participant in the care of a patient with EDS hypermobile type with chronic pain. Due to a general decrease in the degree of stabilization and pain reduction and the duration of improvement as compared with those without EDS hypermobile type, orthopedic surgery should be delayed, if possible, in favor of physical therapy and bracing.  
Vitamin C is a cofactor for cross-linking of collagen fibrils and may improve hypermobility

**FAMILIAL THORACIC AORTIC ANEURYSM AND DISSECTION (FAA)**

Some families show an autosomal dominant predisposition to developing aneurysms in the thoracic aorta whereas others develop dilatation anywhere in the aorta. The larger the dilatation, the greater the risk of dissection. In other families, a risk of dissection exists with minimal or no dilatation. Several genetic

loci have been mapped in families with aortic aneurysm, but most of the genes are yet to be identified. *TGFBR2* mutations have been reported in a few families. Two splicing and one missense mutation in the *MYH11* gene have been described in two families with FAA and patent ductus arteriosus.<sup>15</sup> Occasionally, patients with aortic aneurysm will have deformity of the thoracic cage (scoliosis, pectus excavatum). These skeletal changes are also seen in people with bicuspid aortic valve sequence, which raises the question of whether patients with only ascending aortic aneurysms are simply failing to express the bicuspid valve.

#### Diagnostic evaluation<sup>16</sup>

1. Physical examination
2. Family history
3. Echocardiogram
4. Dilated eye exam (to exclude MFS)
5. Consider gene sequencing
6. Imaging of the vasculature, including the cerebral vasculature, for those with a genetic mutation that predisposes to diffuse arteriopathy

#### Diagnostic criteria

Autosomal dominant family history of dilation or dissection of the aortic root, ascending aorta, or descending aorta in the absence of major criteria for the diagnosis of MFS or another connective tissue disorder.

#### Management (recommend management by a skilled cardiologist)

Aortic dissection is rare in early childhood, but aortic dilation may be present. In most adults, the risk of aortic dissection or rupture becomes significant at diameters >5.0 cm. However, mutations in some genes (*TGFBR1* and -2) predispose to dissection at smaller and even normal aortic diameters. Persons with mutations in *MYH11*, *SMAD3*, and *ACTA2* should be considered for repair with a diameter between 4.5–5.0 cm.

Annual echocardiograms for individuals with small aortic dimensions and slow rate of increase of the dilation in the absence of a *TGFBR* mutation

Echocardiograms at least every 6 months if the root exceeds 4.5 cm in an adult, the rate of aortic growth exceeds 0.5 cm/year, or significant aortic regurgitation occurs.

Imaging of the entire aorta every 2–3 years

β-blockade for aortic root dilation. No randomized controlled trial of angiotensin receptor blockade is planned.

Prophylactic surgical repair if the rate of dilation approaches 1 cm/year, if there is progression of aortic regurgitation, if the diameter approaches 5 cm in those with a mutation known to predispose to earlier dissection, when the diameter is 5.0 cm in those with bicuspid aortic valve, and for a diameter of 5.0–5.5 cm for all others.

### LDS

The features include characteristic facial features, craniosynostosis, bifid uvula or cleft palate, tortuosity of the

aorta and its branches, aortic dilatation and dissection, and joint hypermobility.<sup>5</sup> Patients have had mutations in one or another of the receptors for TGFβ. When this condition is suspected, echocardiography must be augmented by a CT or magnetic resonance angiogram of the thorax, abdomen, and pelvis. Because dissection tends to occur at smaller aortic diameters than in MFS, earlier prophylactic aortic root repair is indicated. A variant of LDS strongly resembles the vascular form of Ehlers–Danlos syndrome, especially in terms of thin skin.

#### Diagnostic evaluation

1. Physical exam
2. Family history
3. Echocardiogram
4. Dilated eye exam (to exclude MFS)
5. Magnetic resonance angiography of the head, neck, thorax, abdomen, and pelvis
6. *TGFBR1* and *TGFBR2* gene sequencing

#### Diagnostic criteria

In a patient found to have consistent facial features, bifid uvula, and arterial tortuosity, the diagnosis can be confirmed with *TGFBR* testing. Tortuosity can sometimes be isolated (e.g., found only in the head and neck), requiring the magnetic resonance angiography of the head, neck, thorax, abdomen, and pelvis for a complete evaluation.

#### Management (recommend management by a skilled cardiologist)

Craniosynostosis is treated in the standard manners

Annual echocardiogram if no aortic root dilation

Echocardiogram at least every 6 months if aortic root dilation is detected

Annual magnetic resonance angiography of the head, neck, thorax, abdomen, and pelvis

β-blockade. There is no randomized controlled trial of angiotensin receptor blockade under way.

Aortic dilation and dissection in childhood is a feature of LDS, but not for all patients with a mutation in *TGFBR1* or *TGFBR2*. There is a low threshold for prophylactic aortic grafting in LDS. If the progression is rapid, aortic root replacement is recommended at 2.0 cm.<sup>17</sup>

### CCA, BEALS SYNDROME

This condition shows congenital contractures of the elongated digits, elbows, and knees that can improve with physical therapy. Scoliosis develops during childhood and can become severe. The helix of the ear shows overfolding. There is no ectopia lentis. There is a Marfan-like habitus. Originally, the cardiovascular system was said to be unaffected, but first MVP and more recently aortic dilatation have been described. Every patient thought to have CCA should have echocardiography, perhaps on a regular basis, at least during childhood and adolescence. Congenital contractures, typically of the digits and

elbows, also occur in MFS. Some “crumpling” of the ear is also not uncommon in the general population. Therefore, diagnosis of CCA can be difficult. The role of examining the *FBN2* locus for mutations is unclear.

## Diagnostic evaluation

1. Physical exam
2. Family history
3. Echocardiogram
4. Dilated eye exam (to exclude MFS)
5. Consider *FBN2* gene sequencing

## Diagnostic criteria

Individuals with CCA typically have a marfanoid habitus; flexion contractures of multiple joints including elbows, hips, knees, and fingers; kyphoscoliosis; muscular hypoplasia; and abnormal pinnae (“crumpled” outer helices).<sup>18</sup>

## Management

Physical therapy for joint manifestations and surgical release of severe contractures

Bracing and/or surgical correction of kyphoscoliosis

Echocardiogram every 2 years until adult height reached. If no dilation present, repeat if symptomatic or when a major increase in physical activity is planned.

Annual evaluation by physical exam for scoliosis until adult height reached

Aortic root dilation is treated as described above for MFS

## MASS PHENOTYPE

The acronym stands for mitral valve prolapse and myopia, an aortic root that may be at the upper limits of normal in caliber, striae atrophicae, and skeletal features reminiscent of, but less severe than, MFS.<sup>19</sup> A few patients designated as having MASS have had mutations in *FBN1*, but most do not. This condition is termed a “phenotype” because there are undoubtedly multiple causes. Importantly, almost all patients diagnosed as having MASS over a decade showed no progressive aortic root dilatation or aortic dissection (Pyeritz unpublished).

This diagnosis cannot be made with certainty in the absence of a multigenerational family history documenting no progression of aortic root dilation. Therefore, a child who appears to have the MASS phenotype without a family history should be followed as described above for MFS.

## FAMILIAL ARTERIAL TORTUOSITY SYNDROME

This condition was first described as a severe condition of infancy. Recently, a pleiotropic condition of adults that shows autosomal recessive inheritance was described.<sup>6</sup> Patients have marked tortuosity of the aorta and its branches, and there is a predisposition to dissection. They also have telangiectases of the cheeks, lax skin, high palate, and joint laxity. When this condition is suspected, echocardiography must be augmented by a CT or magnetic resonance angiogram of the thorax, abdomen,

and pelvis. Mutations in a nuclear glucose transporter encoded by the *SLC2A10* gene have been found.<sup>20</sup>

Monitoring guidelines are the same as those described above for LDS.

## MVP

In some families, MVP occurs as an autosomal dominant trait, either isolated or in association with an asthenic habitus. Because the pathogenesis of MVP is varied, the valvular abnormality is seen in a number of other hereditary syndromes, including dilated cardiomyopathy, myotonic dystrophy, fragile-X syndrome, and some in this Appendix, including MASS, various EDS types, bicuspid aortic valve, and Stickler syndrome.

A child with MVP and an asthenic habitus should have aortic root measurements taken when MVP monitoring echocardiograms are done. If dilation of the aortic root is found, the child should be followed as described above for MFS.

## FAMILIAL ECTOPIA LENTIS

Some families show variable skeletal manifestations of MFS along with ectopia lentis. Initially, these cases were said not to have aortic dilatation, but subsequently some have developed this feature and are more appropriately said to have MFS. Mutations near the 3′-end of *FBN1* have been associated with this autosomal dominant condition. If ectopia lentis and 3′ mutation are observed, follow the cardiovascular system as described above for MFS.

## BICUSPID AORTIC VALVE SEQUENCE

Left-sided flow defects show more familial predisposition than any other general class of congenital heart disease other than conotruncal defects. The causes are unknown, but a defect of the neural crest is suspected. The features that show variable expression in families with this sequence are congenital bicuspid aortic valve, dilatation of the ascending aorta (not usually the sinuses of Valsalva), aortic coarctation, MVP, and thoracic-cage deformity. Heterozygosity for mutations in *NOTCH1* has been reported in a few families and in 4% of sporadic cases of bicuspid aortic valve.<sup>21</sup>

## FAMILIAL TALL STATURE

One family distinguished by pectus excavatum and tall stature in the proband and tall stature in the relatives had a mutation in *FBN1*. No one had cardiovascular problems. There has been no systematic survey of disproportionately tall individuals for other features of MFS or mutations in *FBN1*.

## FAMILIAL PECTUS EXCAVATUM

Pectus excavatum occurs as an autosomal dominant trait in occasional families. The literature is silent on whether pectus carinatum or combined anterior chest defects also occur, probably because ascertainment has typically been through surgeons consulted to repair the excavatum defects. There has been no systematic survey for other features of MFS or mutations in *FBN1*.

## FAMILIAL SCOLIOSIS

“Idiopathic” scoliosis clearly shows familial predispositions.<sup>22,23</sup> There has been no systematic survey for other features of MFS or mutations in *FBNI*.

## STICKLER SYNDROME

Occasionally, the person with Stickler syndrome will be considered initially as having MFS or another connective tissue disorder. The features that overlap include retrognathia, high-grade myopia and retinal detachment, and MVP.

## DISCLOSURE

The author declares no conflict of interest.

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