Genetics, Screening, and Management of Marfan Syndrome

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ABSTRACT
The purpose of this article is to discuss the genetics, testing, management considerations, and role of the APN caring for the patient with Marfan syndrome. Data sources are research articles, consensus statements, and treatment guidelines from professional literature in medicine and nursing. The diagnosis of Marfan syndrome is still largely clinically based. Knowledge of genetic patterns and physical criteria can aid in the diagnosis. Proper anticipatory guidance and management throughout the lifespan can improve the quality and length of life for the patient with Marfan syndrome. Varying phenotypic features of Marfan syndrome can make the diagnosis difficult, but early diagnosis is essential to avoid the often fatal consequences of untreated Marfan syndrome.

Keywords: connective tissue disease; musculoskeletal anomalies; cardiovascular anomalies; anticipatory guidance

Marfan syndrome is a genetic condition that affects connective tissue. Early diagnosis and proper management of Marfan syndrome are imperative to avoid the often-fatal aortic aneurysms that result from untreated disease. As primary care providers, nurse practitioners frequently do well-child checks and sports physicals. These are possible occasions for the initial discovery of Marfan syndrome.

Incidence of Marfan syndrome is estimated to be from 1 in 9,800 (Dean, 2002) to 3 in 10,000 people (Loeys, Nuytinck, Delvaux, De Bie, & De Paepe, 2001). Given the common appearance of marfanoid characteristics in the general population and difficulties with genetic testing, estimates of disease incidence are likely to vary. There is no preference for any race, geographic location, or gender in the distribution of the disease. The purpose of this article is to discuss the genetics, disease characteristics, screening, management considerations, and family impact of Marfan syndrome.

MOLECULAR GENETICS
Mutations in the fibrillin-1 gene (FBN-1) on chromosome 15 cause Marfan syndrome (Robinson & Godfrey, 2000). Fibrillin is a large glycoprotein and principal structural component of connective tissue microfibrils that link together to form elastin fibers. Figure 1 shows the fibrillin gene transcription and translation to microfibrils. The microfibrils then coalesce to form elastin fibers.

Primary sites of microfibrils and elastin fibers are in the extracellular matrix of the aorta, periosteum, ciliary muscles, and skin (Lipscomb, Clayton-Smith, & Harris, 1997). In the individual with Marfan syndrome the deranged microfibrillar assembly, and subsequently deranged elastin formation, create connective tissue malformations in these sites.

The gene that codes for fibrillin is quite large and there are many different types of mutations that can occur. Therefore, people with Marfan syndrome may have distinct mutations but all have a mutation of the FBN-1 gene. Mutations are found throughout the entire FBN-1 gene. There does not appear to be any hot spot or particular area where mutations commonly occur (Robinson & Godfrey, 2000).

In about a quarter of cases of Marfan syndrome, a spontaneous mutation of the FBN-1 gene occurs (Dean, 2002). An example pedigree, with the proband having a spontaneous mutation and subsequent children having inherited the condition, is shown in Figure 2. The proband is the individual with the initial diagnosis in the family. In the remaining cases, Marfan syndrome is
Figure 1. The fibrillin gene on chromosome 15 codes for a messenger RNA. The mRNA directs the production of a large protein called fibrillin. The individual fibrillin molecules coalesce to form microfibril. Microfibrils can exist by themselves or form elastic fibers.

Figure 2. Shaded symbols represent people with Marfan syndrome and open symbols are people without Marfan syndrome. In the first generation neither spouse has Marfan syndrome. So the affected male in generation II had a spontaneous mutation and has a 50% chance of passing the gene on to his offspring.
inherited via autosomal dominant transmission. So an affected parent has a 50% chance of having an affected offspring (Pyeritz & Gasner, 1994).

Although intrafamilial genotype will be the same, the phenotype can and does still vary. This may be a result of the pleiotropy and variability exhibited by FBN-1 mutations. Pleiotropy means that many seemingly unrelated effects result from a single gene change. Variability means that individuals with the same genetic mutation exhibit the phenotype differently (Pyeritz, 1996).

Various specific mutations have been identified and most are unique to the family in which they are found (Pyeritz & Gasner, 1994). So wide interfamilial variability in genotype and phenotype also exist.

**DISEASE CHARACTERISTICS**

The physical characteristics of Marfan syndrome are defined in the Revised Diagnostic Criteria for the Marfan Syndrome (De Paepe, Devereux, Dietz, Hennekam, & Pyeritz, 1996). Figure 3 is a checklist with all the physical characteristics that compose the diagnostic criteria. The nurse practitioner can use the checklist to diagnose Marfan syndrome. Once the diagnosis is made, or if a diagnosis is ambiguous, the nurse practitioner can refer to or collaborate with other health care providers as appropriate. The involvement of a geneticist and cardiologist would be necessary.

Physical characteristics can be present in the skeletal, ocular, cardiovascular, pulmonary, and integument systems. The anatomic requirements for diagnosis vary depending on whether a person has a family history of Marfan syndrome, a genetic test that reveals a mutation, or none of the above. The three diagnostic criteria categories and requirements are

- For a person with no known family history of Marfan syndrome to be diagnosed, disease characteristics that are major criteria must be present in two or more organ systems and involvement of a third organ system must be present. Diagnosis of a proband must be especially well documented, and the criteria must be more rigorous than subsequent cases that will make use of the diagnosis in the proband (Pyeritz, 1996).
- If a person has had genetic testing that reveals a mutation known to cause Marfan syndrome, then one major organ system and involvement of a second organ system must be present to confirm the diagnosis.
- If a person has a family history of Marfan syndrome, then he or she must have one major criterion in an organ system and involvement of a second organ system.

Physical characteristics for the diagnosis of Marfan syndrome are divided into major or minor criteria. Physical characteristics that are more highly correlated with Marfan syndrome and FBN-1 mutations are major criteria. Thus, if an individual possesses physical characteristics that are considered major criteria, the clinical diagnosis is more evident. Minor criteria are physical characteristics with a weaker correlation to Marfan syndrome. Minor criteria may contribute to the diagnosis, but the presence of major criteria is required for the diagnosis.

In a study of children with suspected Marfan syndrome, height in excess of the 97th percentile was the most common characteristic and usually presented by 2 years of age (Lipscomb et al., 1997). However, height is not on the diagnostic criteria and cannot be used as a clinical sign. Aortic root dilation was first detected at a mean age of 11 years. Many skeletal characteristics, such as pectus deformities, were exaggerated by puberty or did not develop until puberty. Therefore, absence of aortic root enlargement or skeletal features cannot be used to exclude a diagnosis of Marfan syndrome in a marfanoid child before growth is complete.

**SCREENING AND MONITORING**

The diagnostic criteria checklist should be used as a diagnostic and screening tool in children and adults suspected of having Marfan syndrome. Screening guidelines for marfanoid individuals who do not meet the diagnostic criteria have been suggested by Lipscomb and colleagues (1997). They recommended that, in the absence of cardiovascular or ocular manifestations, children with at least four skeletal features, particularly a pectus deformity, scoliosis, and limb disproportion, in association with tall stature, undergo periodic reevaluation, as more diagnostic features may become apparent with increasing age. These children should have an annual review of growth and skeletal abnormalities, annual slit lamp examination per ophthalmologist to evaluate for ectopia lentis until the age of 6, visual acuity yearly thereafter, and annual echocardiogram. They also suggested that adults with six or more skeletal features get continuing, periodic echocardiograms because cardiovascular features may develop for the first time in adulthood (Lipscomb et al., 1997).

**GENETIC TESTING CONSIDERATIONS**

Individuals who may want genetic testing are those with an ambiguous diagnosis, because an established diagnosis will guide the medical management plan. Couples planning a family may also want to confirm the diagnosis.
## Marfan Syndrome Checklist

### INDEX CASE:
- Major criteria in 2 different organ systems
- AND involvement of a third organ system

### RELATIVE OF INDEX CASE:
- 1 major criterion in family history
- AND 1 major criterion in an organ system
- AND involvement in second organ system

### SKELETAL
- Major (presence of at least 4 of the following manifestations)
  - pectus carinatum
  - pectus excavatum requiring surgery
  - reduced upper to lower segment ratio (Note 1)
  - OR arm span to height ratio > 1.05
- Height ___ Arm span ___ Upper segment ___ Lower segment ___
- wrist (Note 2) and thumb (Note 3) 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: 2 major criteria or 1 major and 2 minor

### OCULAR

#### Major
- ectopia lentis

#### Minor
- flat cornea
- increased axial length of the globe
- hypoplastic iris OR hypoplastic ciliary muscle causing decreased miosis
- Involvement: 2 minor criteria

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CARDOVASCULAR

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: 1 minor criterion

PULMONARY

Minor (only)
- spontaneous pneumothorax
- apical blebs
- Involvement: 1 minor criterion

SKIN AND INTEGUMENT

Minor (only)
- striae atrophicae
- recurrent or incisional hernia
- Involvement: 1 minor criterion

DURA

Major
- lumbosacral dural ectasia by CT or MRI

FAMILY/GENETIC HISTORY

Major
- first-degree relative who independently meets the diagnostic criterion

NAME ___________________________  

- presence of mutation in FBN-1 known to cause Marfan syndrome
- presence of haplotype around FBN-1 inherited by descent and unequivocally
  associated with diagnosed Marfan syndrome in the family

Notes
2. wrist sign—thumb overlaps the distal phalanx of the fifth digit when grasping the contralateral wrist.
3. thumb sign—entire nail of the thumb projects beyond the ulnar border of the hand when the hand is clenched without assistance.

Figure 3. Continued
to see if future children would be at risk. Figure 4 shows practical, social, and ethical concerns regarding genetic testing for Marfan syndrome. The decision to perform genetic testing should be based on the potential to benefit the patient to an equal or greater extent than simple diagnosis with anatomic criteria. Informed consent and genetic counseling are ethical imperatives.

Genetic testing found FBN-1 mutations in 66% of people who were clinically diagnosed with Marfan syndrome per the diagnostic criteria. So the diagnostic criteria are only 66% sensitive. Twelve percent of people with Marfanoid characteristics who did not meet the diagnostic criteria for a clinical diagnosis in fact had an FBN-1 mutation per genetic testing. So diagnostic criteria are 88% specific (Loeys et al., 2001).

**MANAGEMENT**

The main goal of health care providers in the management of Marfan syndrome is early identification of cases using the revised diagnostic criteria on the checklist. The management is much more successful, and possibly life saving, if initiated early in disease progression.

Management of Marfan syndrome must be viewed in terms of the natural history of the condition and considering the wide variability in the phenotype. Many characteristics may not be present initially, but emerge with time. Some characteristics may progress with time and require frequent follow-up. Most importantly, each case will be unique, so treatment must be tailored to the individual. Referral to a geneticist should be part of the plan as well. Management of specific disease characteristics—otic dilatation, mitral valve prolapse, ectopia lentis, and skeletal malformations—will be discussed here.

**Aortic Dissection**

Early identification of aortic root dilatation cannot be overstated. Death rates from surgical repair of aortic aneurysm were only 1.5% when done early, compared to 12% among patients who underwent emergency repair. That is an eightfold increase in death with emergency surgery (Gott et al., 1999). Also, dissection at the time of first aortic repair has been associated with the need for a second vascular surgery (Finkbohner, Johnston, Crawford, Coselli, & Milewicz, 1995), so prophylactic surgery should be considered.

Current guidelines for prophylactic aortic root replacement are aortic root diameter greater than 54 mm, positive family history of aortic dissections and aortic root

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**Issues Surrounding Genetic Testing for Marfan Syndrome**

<table>
<thead>
<tr>
<th>Practical Obstacles to Routine Testing</th>
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<tr>
<td>• Various FBN-1 mutations exist.</td>
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<td>• Most mutations are unique to a particular family. Thus, genetic testing may not yield more information than a thorough family history.</td>
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<tr>
<td>• Similar conditions and diseases also have FBN-1 mutations, like homocystinuria and congenital arachnodactyly.</td>
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<tr>
<td>• Linkage analysis is the most readily available method of genetic testing and requires the tested individual have family members with a definite diagnosis. It cannot be used for the diagnosis of a single individual.</td>
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<th>Social Concerns</th>
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<td>• Possible discrimination in employment, insurance coverage, and life activities</td>
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<td>• Genetic testing may cause anxiety or psychosocial difficulty</td>
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<td>• Possible stigmatization of people who genetically have the disease, whether or not they have physical characteristics</td>
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<th>Ethical Concerns</th>
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<td>• Does an individual with a genetic mutation, but no physical characteristics, have the disease?</td>
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<td>• Do the results of genetic testing have any bearing on the treatment plan?</td>
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<tr>
<td>• Is a genetic diagnosis anymore valuable than a clinical diagnosis?</td>
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Figure 4. Practical, social, and ethical considerations for genetic testing of Marfan syndrome.

diameter greater than 49 mm, or aortic root growth greater than 2 mm/year. Five-year survival following emergency and prophylactic repair of the aortic root was 51% and 97%, respectively (Groenink et al., 1999).

Another reason for early identification of cases is the proven benefit of early chemoprophylaxis with beta-blockers. Long-term treatment with beta-blockers reduces the risk of aortic dissection, reduces the rate of aortic dilatation, and increases aortic distensibility. Those who respond best to beta blockade tend to have a smaller aortic diameter (less than 4 cm) and be younger. Studies indicate that early initiation of beta-blocker medications provide the best results (Shores, Berger, Murphy, & Pyeritz, 1994).

Aortic root dilatation and dissection is the most common cause of death in Marfan syndrome, and without treatment the average age of death is in the 30s and 40s (Pyeritz, 1996).

Yearly echocardiogram to track aortic enlargement, aortic regurgitation, and mitral valve prolapse should be part of the management plan. Measurement of the aorta should be indexed to a child’s body surface area to account for the growth of the child. The occasional use of a MRI to assess for aortic enlargement has also been promoted because an elliptical enlargement may not be easily detected by an echocardiogram. Additional reasons for MRI screening are a chest wall deformity precluding adequate imaging by ultrasound and three-dimensional images of the entire aorta to reveal distal aortic enlargement (Pyeritz, 1996).

Smoking and hypertension have been linked to the need for repeat aortic repair (Finkbohner et al., 1995). Thus, management of hypertension and smoking cessation are indicated.

Mitral Valve Prolapse

Mitral valve prolapse is more often found in females and tends to develop with age (Pyeritz, 1996). Mucopolysaccharide deposition on valve leaflets is thought to cause mitral valve prolapse in Marfan syndrome (Dean, 2002). If yearly echocardiogram reveals a mitral valve prolapse, prognosis for surgical repair is good with 80% requiring only a repair rather than a replacement (Gillinov et al., 1994).

Ectopia Lentis

Ectopia lentis develops in only 25% of patients with Marfan syndrome and is characterized by lens dislocation. The ectopic lens lying in the pupillary space may impair vision. However, the need for lens removal is rarely indicated. The condition may be present at birth, but is not likely to develop after the age of 6 years. Therefore, children should get a slit lamp evaluation yearly until age 6 (Lipscomb et al., 1997). Myopia, due to an elongated globe, and amblyopia, due to favoring an eye with better vision, are more common. Early correction of visual acuity in childhood prevents the development of amblyopia. Changes in visual acuity can occur rapidly with growth, so yearly eye exam and vision correction are indicated (Pyeritz, 1996).

Musculoskeletal Malformations

Decreased microfibrils cause perichondral and periosteal membranes to function poorly and affect bone growth. Long, misshapen bones result in skeletal malformation (Eaton & Meiner, 1999). Pectus deformities are likely to change dramatically with growth and cannot be considered stable until midadolescence. Therefore, surgery to correct a pectus deformity should be delayed at least until then (Pyeritz, 1996). Scoliosis is a common skeletal anomaly and when coupled with a chest wall deformity may cause lung restriction. Therefore, orthopedic consult for surgical correction or bracing may be indicated (Pyeritz). Ligamentous laxity is also a consequence of microfibrillar derangement. Children with ligamentous laxity may have subsequent motor milestone delays (Pyeritz). Back and joint pain are common in the adult with Marfan syndrome and may require physical therapy and pain control (Pyeritz).

SPECIAL CONSIDERATIONS

Pregnancy

Pregnancy can seriously endanger the life of a woman with Marfan syndrome and also carries a 50% chance of passing the condition on to the fetus. The hyperdynamic, hypervolemic state of pregnancy is not tolerated in aortic enlargement and aortic regurgitation. Estrogen also increases valvular deposits during pregnancy, worsening the progression of the disease (Dean, 2002).

Prior to becoming pregnant, a woman with Marfan syndrome should undergo a physical exam, an echocardiogram by a cardiologist to determine aortic root size, and have a consultation with a perinatologist and a genetic counselor. Aortic root enlargement is the single greatest predictor of pregnancy outcome.

Women with mild or no aortic dilatation should be advised to have children early in life. Women with aortic dimensions greater than 4.0 cm are at increased risk (Professional Advisory Board, 2004). Current guidelines recommend that women with aortic size greater than 5.0 cm not get pregnant due to the extreme risk to the mother and fetus. An obstetrician and cardiologist should
closely follow any woman with Marfan syndrome who becomes pregnant, with no less than an echocardiogram every 3 months. Women should also get an echocardiogram within 2 months postpartum (Professional Advisory Board of the National Marfan Foundation, 2004).

Beta-blockers should be continued throughout the pregnancy. Beta-blockers can help to minimize enlargement of the aortic root during pregnancy and there have been no reported cases of teratogenesis with beta-blockers. There have been some incidence of low birth weights, but the benefits to the mother far outweigh the risk to the infant (Professional Advisory Board, 2004).

Newborns of women with Marfan syndrome should be closely monitored for symptoms of Marfan syndrome, particularly mitral valve prolapse and extremely long limbs and digits. A dilated eye exam during the neonatal period to rule out lens dislocation should be performed well (Professional Advisory Board, 2004).

Physical Activity
The health care provider must consider the level of physical activity a person with Marfan syndrome should undertake (Eaton & Meiner, 1999). A person with Marfan syndrome should not engage in contact sports or sports with a high incidence of bodily collision like diving, basketball, and rugby. The risks of cardiovascular events, like aortic rupture, or lens dislocation are too great. Scuba diving increases the risk of pneumothorax due to pressure changes. Physical activity three or four times a week in a noncompetitive, noncontact sport like leisure bicycling, swimming, or dancing should be encouraged. Patients should be advised to monitor how they feel and their heart rates. The patients should be warned not to push themselves to the limit and stop immediately if they feel light-headed, dizzy, or very short of breath (Professional Advisory Board, 2004).

Bacterial Endocarditis Prophylaxis
The maintenance of good oral health and the use of antibiotic prophylaxis prior to dental or surgical procedures is recommended to avoid bacterial endocarditis. The American Heart Association’s (AHA) bacterial endocarditis antibiotic prophylaxis guidelines are recommended by the National Marfan Foundation Professional Advisory Board. The AHA (1997) recommends two grams (50 mg/kg for children) of amoxicillin orally 1 hour prior to procedures.

NURSE PRACTITIONER ROLE
Once the diagnosis is made, the NP’s role in managing a case would be to monitor the progression of the disease with frequent screening, manage the treatment plan, coordinate resources and referrals, and provide patient education. The NP may refer the child for further screening of physical characteristics or refer an ambiguous case to genetic counseling. The NP may have a role in prenatal counseling, advising on physical activity and safety, and promoting smoking cessation. Other educational issues that the NP may address with the patient are treatment options, the role of beta-blockers and medical therapy, the need for prophylactic antibiotics with dental work, the importance of frequent follow-up, symptoms of cardiac involvement, and lifestyle management. The patient will also require information on disease progression and life expectancy (Eaton & Meiner, 1999).

FAMILY IMPACT
People within a family are more likely to have similar characteristics of Marfan syndrome than are people from another family with Marfan syndrome. For this reason, it may be advisable for people in a family with Marfan syndrome to become good medical historians. When one relative develops a characteristic, such as aortic dissection, monitoring for the development of the characteristic in other family members can be initiated.

The family may be very anxious and confused at the initial diagnosis. They should be informed that, with proper management, individuals with Marfan syndrome have a median life expectancy of 72 years and can lead active, healthy lives (Silverman et al., 1995). Figure 5 gives the contact information for the National Marfan Foundation, which is a great resource for both patients and providers. Initial diagnosis will most likely be in childhood, so a commitment by parents to seek treatment for children is a must. As with any chronic disease the diagnosis of Marfan syndrome will add the burden of cost, take time to plan and coordinate care, and increase family stress. The obligations of the disease

National Marfan Foundation
A good source for more information on Marfan Syndrome is the National Marfan Foundation. This is a resource for both patients and providers. The website for the organization is www.marfan.org. The phone number is 1-800-8MARFAN. The address is National Marfan Foundation, 22 Manhasset Avenue, Port Washington, NY 11050.

Figure 5. The National Marfan Foundation is a rich resource for both patients and providers.
will eventually transfer from the parents to the individual with Marfan syndrome.

Family planning will also be impacted. The family will have to make decisions regarding whether to risk pregnancy in the case of a female with Marfan syndrome. In either gender the individual will have to decide if a 50% risk of passing on the condition is acceptable or if fetal screening is desired.

CONCLUSION

Marfan syndrome is a rare yet potentially fatal genetic disorder. The APN can assist families and individuals through early identification and lifelong management. Current research is expanding genetic knowledge, screening techniques, and treatment options for families. The life expectancy of people with Marfan syndrome has improved dramatically. With proper treatment, people with Marfan syndrome can lead healthy, productive lives.

REFERENCES


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