

GENETIC TESTING AND MARFAN SYNDROME

Genetic testing for mutations in fibrillin-1 (FBN1) and other genes has become an important and reliable option to aid in the diagnosis of Marfan syndrome and related disorders. However, the results of genetic testing for the diagnosis of disorders are not always straightforward. Therefore, working with a medical geneticist (a physician with training in genetics) or a genetic counselor is often necessary. By understanding some basic information about genetic testing for Marfan syndrome, you can have a more meaningful discussion with your healthcare professionals and better comprehend the advantages and limitations of the testing process and the results.

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Genetic testing can be used to confirm a suspected diagnosis of Marfan syndrome, identify the genetic causes of aortic aneurysms in some families, distinguish between those who inherited the altered copy of a gene in a family from those who inherited the normal copy, and increase reproductive options in families with Marfan syndrome and related disorders. However, the financial and psychosocial implications for these individuals and their families must be considered, along with the medical implications. Comprehensive clinical evaluation remains a vital step in diagnosing Marfan syndrome, determining the need for genetic testing, and creating a plan for treatment, follow-up and long-term evaluation.

Proper interpretation of genetic testing results requires association with accurate clinical information. Inappropriate interpretation can result in misleading or even dangerous recommendations; therefore, it is important to have a doctor who is knowledgeable about Marfan syndrome interpret the results of the genetic test.

- For people with a family history of Marfan syndrome, genetic testing can help confirm or rule out the diagnosis.
- Some of the features of Marfan syndrome can be found in other related disorders; therefore, genetic testing may be helpful when a diagnosis cannot be determined through a clinical evaluation.
 - Even if an individual's diagnosis remains uncertain after clinical evaluation and genetic testing, his or her features can still be treated effectively.
- Genetic testing can be useful for family planning purposes and may help facilitate discussion regarding preimplantation genetic diagnosis (PGD) and prenatal diagnosis, and allow for an accurate reproductive risk assessment.
 - Identification of an FBN1 gene mutation in the person with Marfan syndrome is necessary to pursue prenatal diagnosis, preimplantation genetic diagnosis (PGD), or diagnosis of a pre-symptomatic family member by gene-based studies.

How is Marfan syndrome inherited?

It is important to understand how Marfan syndrome is inherited to understand how genetic tests are used. Each person has two copies of most genes in their cells. When a couple has a child, each parent transmits only one copy to the child. Disorders in which there is a mutation, or change, in one copy of a gene that produce a medical condition are called dominant disorders. Marfan syndrome is a dominant disorder in which one copy of the FBN1 gene has a mutation that affects the function of the protein, fibrillin-1, produced under the direction of the gene. If a potential parent has Marfan syndrome, each child born to that parent has a 50 percent chance of inheriting the mutated copy of the gene and, therefore, of having Marfan syndrome. If the child inherits the normal copy of the gene from the affected parent, then he or she is not at risk of developing Marfan syndrome and does not have an altered copy to pass to his or her children. About 25 percent of people with Marfan syndrome do not have an affected parent. They are the first person in their family who has Marfan syndrome. This change in the gene is called a spontaneous mutation, and it almost always occurs during the course of the egg or the sperm being made.

How is genetic testing done?

A gene is made up of DNA, which has four building blocks, called nucleotides (known by their abbreviated names: A, C, G, and T). The cell uses the nucleotides as instructions to make a specific protein. If there is a mutation or change in the nucleotide sequence, the protein may not function properly and cause a medical condition such as Marfan syndrome. Genetic testing looks for mutations or changes in the nucleotides. If a mutation or change is found in a gene, that person may have the medical condition associated with that gene mutation.

If no mutation is found during the gene sequencing (genetic testing) and a person has clinical features of the disease, then a whole part of the gene could be missing. This is called a deletion. Further testing is required for confirmation.

Here are some common questions about genetic testing.

- Does the failure to identify a mutation in the FBN1 gene exclude the diagnosis of Marfan syndrome? No, current best estimates suggest that no mutation is found in about 5–10 percent of people with clear-cut Marfan syndrome. This occurs because of the nature of the change in the gene (mutation) or a variety of technical problems.
- Does the presence of an FBN1 gene mutation establish the diagnosis of Marfan syndrome? No, FBN1 gene mutations can be found in many disorders that have some clinical overlap with Marfan syndrome (see table on page 5). This is why a thorough clinical evaluation and review of family history are essential to make a diagnosis. In addition, some sequence changes in the gene are innocent; that is, they do not disrupt protein function or cause a medical condition.
- Does the type or location of the mutation predict whether someone has or will develop Marfan syndrome? Only to an extent. There is no clearly defined relationship between the location of a mutation and the severity of the condition that will result. Mutation identification currently has some limited value, but it has not been proven to reliably guide clinical management. When a clinical diagnosis of Marfan syndrome is made based on the strict diagnostic criteria (*J Med Genet* 2010;47:476-485), genetic testing does not alter clinical management.

In what situations might genetic testing be recommended?

There are several instances when genetic testing may be beneficial.

- Adults with Marfan syndrome who are considering having children often consider genetic testing to pursue preimplantation or prenatal diagnosis options. Pursuing these options is a personal decision. Technology today allows couples to prescreen embryos using in-vitro fertilization and implant embryos that do not carry the FBN1 gene mutation found in one of the parents. However, this method is only a screening tool and confirmatory testing should be completed during the pregnancy. Additionally, genetic testing of an already established pregnancy is available through prenatal testing. This can be done by two different methods. The first is called chorionic villus sampling (CVS), which is a procedure performed at 10-11 weeks gestation by transabdominal or trans-cervical removal of placental cells. The second procedure is called amniocentesis, which is a procedure performed at approximately 16-18 weeks gestation by transabdominal removal of amniotic fluid. Either sample can be tested for a gene mutation. The parent's mutation must first be identified before considering these options.
- Children, who are at a 50 percent chance of inheriting Marfan syndrome from an affected parent, may benefit from genetic testing because early clinical evaluation of infants and young children may not allow for confirmation of the diagnosis. Clinical features may emerge as the child ages, at which point the diagnosis can usually be confirmed. A child with a positive genetic test who does not have clinical features should be monitored on an ongoing basis.
- People who have one of the cardinal features of Marfan syndrome, aortic dilatation or dissection or ectopia lentis (dislocated lens), but no other obvious signs of the disorder, may benefit from genetic testing. As the established diagnostic criteria indicates, an FBN1 gene mutation known to be associated with Marfan syndrome in the presence of either of the cardinal features is sufficient to make the diagnosis. Some individuals with isolated ectopia lentis also have mutations in the gene.

- When someone has features of more than one disorder, a genetic test may be informative in considering differential diagnosis and may indicate a specific course of treatment. For example, people with Loeys-Dietz syndrome, a connective tissue disorder caused by mutations in the TGFBR1 or TGFBR2 genes, may have many features of Marfan syndrome. Individuals with Loeys-Dietz syndrome may also display other unique features such as cleft palate or club foot; however, they do not develop lens dislocation. Most importantly, individuals with Loeys-Dietz syndrome tend to have arterial tortuosity (twisting arteries, primarily in head and neck vessels) with a risk of aneurysms throughout the arterial tree. These aneurysms tend to tear or rupture at younger ages and smaller dimensions when compared to those in people with Marfan syndrome. This clinical difference leads to early imaging and the use of different thresholds for surgical intervention. Not all individuals with Loeys-Dietz syndrome have striking craniofacial abnormalities. Individuals with some features of Marfan syndrome who do not have lens dislocation should be evaluated for features of Loeys-Dietz syndrome, and any suspicion should prompt genetic testing. Clinical findings can help determine the order of evaluation of FBN1 and the TGFBR1 and TGFBR2 genes.
- Families with a history of aortic aneurysm or dissection may choose imaging or genetic testing to identify those in the family who may be at risk. Researchers have identified numerous genes that are associated with aortic aneurysm and dissection.

What are the limitations of genetic testing in Marfan syndrome?

There are several limitations in the effective use of genetic tests for Marfan syndrome.

- Although the current tests to identify a mutation in the FBN1 gene are very effective, a limited group of people may require more than the usual testing to identify the alteration. For example, gene sequencing may not find mutations if part or all of one copy of a gene is missing.
- Mutations in the FBN1 gene can cause conditions other than Marfan syndrome (see Table on page 5); therefore, it can be difficult to predict what condition to expect when a mutation is found.
- Family members with the same mutation causing Marfan syndrome can show wide variation in the timing of onset and severity of many of the complications.

What is the cost of genetic testing?

The initial identification of a mutation (through sequence analysis) in the first person in a family is expensive, ranging between \$1,400 and \$2,000, depending on the laboratory. Health insurance plans differ in the coverage of mutation analysis. Once a mutation has been identified, detection of the known familial mutation can be performed reliably in other family members at a greatly reduced cost of approximately \$250-\$400 per person.

As genetic testing becomes more widely utilized, it is possible that costs may come down and more insurance companies will cover it.

Where can I get genetic testing?

Certified laboratories that provide genetic testing for Marfan syndrome as a clinical service are listed on the Gene Clinics Laboratory Directory (genetests.org). Additional laboratories may perform

Conditions That Overlap With Marfan Syndrome			
Condition	Overlap with Marfan Syndrome	Mutation in <i>FBN1</i> ?	Mutations in Other Genes
Beals Syndrome	Mitral valve prolapse; skeletal findings	No	<i>FBN2</i>
Vascular Ehlers-Danlos Syndrome	Skin and skeletal findings; aortic aneurysm/tear (selected types only)	No	<i>COL3A1</i>
Familial Thoracic Aortic Aneurysm and Dissection ¹	Aortic enlargement/tear; variable skeletal findings	Generally not	<i>ACTA2, MYH11, MYLK, PRKG1</i>
Homocystinuria	Mitral valve prolapse; eye lens dislocation; skin and skeletal findings	No	Several
Loeys-Dietz Syndrome ²	Aortic aneurysm/tear; skin and skeletal findings	No	<i>TGFBR1, TGFBR2</i>
Ectopia Lentis Syndrome	Eye lens dislocation; skeletal findings	Yes	<i>ADAMTS4L</i>
MASS Phenotype	Mitral valve prolapse; myopia; borderline aortic enlargement; skin and skeletal findings	At least sometimes	Not known
Shprintzen-Goldberg Syndrome	Aortic enlargement; skin and skeletal findings	Rare	<i>SKI</i>
Stickler Syndrome	Eye features; some skeletal findings	No	<i>COL2A1, COL11A1, COL11A2, COL9A1, COL9A2</i>

1. In addition, the *TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFBR2* genes have been associated with FTAAD and other disorders that have specific outward physical characteristics.

2. Also, changes in the *SMAD3* and *TGFBR2* genes have been implicated in causing syndromes which have similarities to Loeys-Dietz syndrome.

genetic testing. It is recommended that a medical professional experienced with the diagnosis of Marfan syndrome coordinate testing. In some circumstances, testing may also be available as part of a research study.

What is the Genetic Information Nondiscrimination Act and how may it impact my family?

In the past, people have hesitated pursuing genetic testing because they were concerned that the information may result in discrimination, such as being refused health insurance or employment. The Genetic Information Nondiscrimination Act (GINA) took effect in November 2009, protecting every American against genetic discrimination in both health insurance and employment. Specifically, GINA strictly prohibits the following:

In healthcare:

- Health insurers may not require individuals to provide their genetic information or the genetic information of a family member to the insurer for eligibility, coverage, underwriting, or premium-setting decisions. However, a health insurer may request that an individual provide genetic information if coverage of a particular claim may be appropriate only if a genetic risk is known.

- Health insurers may not use genetic information either collected with intent or incidentally to make enrollment or coverage decisions.
- Health insurers may not request or require that an individual or an individual's family member undergo a genetic test.
- In the Medicare supplemental policy and in individual health insurance markets, genetic information cannot be used as a pre-existing condition.

In employment:

- An employer may not use genetic information in making decisions regarding hiring, promotion, terms or conditions, privileges of employment, compensation, or termination.
- An employer, employment agency, labor organization, or training program may not limit, segregate, or classify an employee or member, or deprive that employee or member of employment opportunities on the basis of genetic information.
- An employer, employment agency, labor organization, or training program may not request, require, or purchase genetic information about an individual or a family member of the individual, except in rare cases.
- An employment agency, labor organization, or training program may not fail or refuse to refer an individual for employment on the basis of genetic information; nor may the agency, labor organization, or training program attempt to cause an employer to discriminate against an individual on the basis of genetic information.
- An employer, labor organization, or joint labor-management committee may not use genetic information to make decisions regarding admission to or employment in any program for apprenticeship or training and retraining, including on-the-job training.
- A labor organization may not exclude or expel from membership, or otherwise discriminate against, an individual because of genetic information.

Summary

The diagnosis of Marfan syndrome is established by clinical criteria to include the observation of specific physical features and family history. Genetic testing can provide additional useful information to the comprehensive clinical evaluation for the diagnosis of Marfan syndrome or certain related disorders.

Improperly applied or interpreted genetic tests can be misleading and even dangerous. For example, an individual with nonspecific connective tissue findings and absent or borderline aortic enlargement might equate the failure to find an FBN1 gene mutation with a clean bill of health. In fact, this individual may have Marfan syndrome with a missed FBN1 gene mutation or may have another disorder that puts them at risk of an aortic enlargement and tear that is unrelated to mutations in the FBN1 gene. In either case, the absence of clinical follow-up is life-threatening.

In most people with Marfan syndrome, the diagnosis can be established by clinical evaluation alone. Individual features of Marfan syndrome can be adequately treated in the absence of a specific diagnosis. There are no "hidden" features of Marfan syndrome that cannot be recognized and ad-

dressed after a comprehensive clinical evaluation that includes routine and noninvasive diagnostic tests.

Genetic testing can be useful for preimplantation diagnosis (PGD), prenatal diagnosis, and confirmation of the diagnosis in families with other members at risk.

With the exception of establishing the diagnosis of another specific connective tissue disorder, such as Loeys-Dietz syndrome, genetic testing cannot exclude the presence of Marfan syndrome or another serious connective tissue disorder, offer definitive information regarding outcome, or alter treatment of the physical problems that brought the individual to clinical attention.

The rationale and accurate application of these methods requires individualized assessment and counseling by medical professionals who are familiar with Marfan syndrome and are aware of the uses and limitations of genetic testing.

Do you have questions? Would you like more information?

- Call our help center, 800-862-7326, ext. 126 to speak with a nurse who can answer your questions and send you additional information.
- Visit our website at marfan.org. You can print information that interests you and ask questions online.
- See the online Gene Clinics Laboratory Directory; visit genetests.org and select the Laboratory Directory link.
- Learn more at genereviews.org. GeneReviews are expert-authored, peer-reviewed, current disease descriptions that apply genetic testing to the diagnosis, management, and genetic counseling of patients and families with specific inherited conditions.