Recognizing
The National Bone and Joint Decade 2002–2011

# Questions & Answers about . . .

# Marfan Syndrome

*National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)*
*National Institutes of Health*
*Public Health Service • U.S. Department of Health and Human Services*

## For Your Information

This publication contains information about medications used to treat the health condition discussed here. When this booklet was printed, we included the most up-to-date (accurate) information available. Occasionally, new information on medication is released.

For updates and for any questions about any medications you are taking, please contact the U.S. Food and Drug Administration at 1–888–INFO–FDA (1–888–463–6332, a toll-free call) or visit their Web site at www.fda.gov.



Additional copies of this booklet are available from:

National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIAMS/National Institutes of Health
1 AMS Circle
Bethesda, MD 20892–3675

You can also find this booklet on the NIAMS Web site at www.niams.nih.gov.

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This booklet answers general questions about Marfan syndrome. It describes the characteristics of the disorder, the diagnostic process, and ways to manage symptoms. If you have additional questions after reading this booklet, you may wish to discuss them with your doctor.

## What Is Marfan Syndrome?

Marfan syndrome is a heritable condition that affects the connective tissue. The primary purpose of connective tissue is to hold the body together and provide a framework for growth and development. In Marfan syndrome, the connective tissue is defective and does not act as it should. Because connective tissue is found throughout the body, Marfan syndrome can affect many body systems, including the skeleton, eyes, heart and blood vessels, nervous system, skin, and lungs.

Marfan syndrome affects men, women, and children, and has been found among people of all races and ethnic backgrounds. It is estimated that at least 1 in 5,000 people in the United States have the disorder.

## What Are the Symptoms of Marfan Syndrome?

Marfan syndrome affects different people in different ways. Some people have only mild symptoms, while others are more severely affected. In most cases, the symptoms progress as the person ages. The body systems most often affected by Marfan syndrome are:

- **Skeleton** – People with Marfan syndrome are typically very tall, slender, and loose-jointed. Because Marfan syndrome affects the long bones of the skeleton, a person's arms, legs, fingers, and toes may be disproportionately long in relation to the rest of the body. A person with Marfan syndrome often has a long, narrow face, and the roof of the mouth may be arched, causing the teeth to be crowded. Other skeletal problems include a sternum (breastbone) that is either protruding or indented, curvature of the spine (scoliosis), and flat feet.

- **Eyes** – More than half of all people with Marfan syndrome experience dislocation of one or both lenses of the eye. The lens may be slightly higher or lower than normal, and may be shifted off to one side. The dislocation may be minimal, or it may be pronounced and obvious. One serious complication that may occur with this disorder is retinal detachment. Many people with Marfan syndrome are also nearsighted (myopic), and some can develop early glaucoma (high pressure within the eye) or cataracts (the eye's lens loses its clearness).

- **Heart and blood vessels (cardiovascular system)** – Most people with Marfan syndrome have problems associated with the heart and blood vessels. Because of faulty connective tissue, the wall of the aorta (the large artery that carries blood from the heart to the rest of the body) may be weakened and stretch, a process called aortic dilatation. Aortic dilatation increases the risk that the aorta will tear (aortic dissection) or rupture, causing serious heart problems or sometimes sudden death. Sometimes, defects in heart valves can also cause problems. In some cases, certain valves may leak, creating a "heart murmur," which a doctor can hear with a stethoscope. Small leaks may not result in any symptoms, but larger ones may cause shortness of breath, fatigue, and palpitations (a very fast or irregular heart rate).

- **Nervous system** – The brain and spinal cord are surrounded by fluid contained by a membrane called the dura, which is composed of connective tissue. As someone with Marfan syndrome gets older, the dura often weakens and stretches, then begins to weigh on the vertebrae in the lower spine and wear away the bone surrounding the spinal cord. This is called dural ectasia. These changes may cause only mild discomfort; or they may lead to radiated pain in the abdomen; or to pain, numbness, or weakness in the legs.

- **Skin** – Many people with Marfan syndrome develop stretch marks on their skin, even without any weight change. These stretch marks can occur at any age and pose no health risk. However, people with Marfan syndrome are also at increased risk for developing an abdominal or inguinal hernia, in which a bulge develops that contains part of the intestines.

- **Lungs** – Although connective tissue problems make the tiny air sacs within the lungs less elastic, people with Marfan syndrome generally do not experience noticeable problems with their lungs. If, however, these tiny air sacs become stretched or swollen, the risk of lung collapse may increase. Rarely, people with Marfan syndrome may have sleep-related breathing disorders such as snoring, or sleep apnea (which is characterized by brief periods when breathing stops).

## What Causes Marfan Syndrome?

Marfan syndrome is caused by a defect, or mutation, in the gene that determines the structure of fibrillin-1, a protein that is an important part of connective tissue. A person with Marfan syndrome is born with the disorder, even though it may not be diagnosed until later in life.

The defective gene that causes Marfan syndrome can be inherited: The child of a person who has Marfan syndrome has a 50 percent chance of inheriting the disease. Sometimes a new gene defect occurs during the formation of sperm or egg cells, making it possible for two parents without the disease to have a child with the disease. But this is rare. Two unaffected parents have only a 1 in 10,000 chance of having a child with Marfan syndrome. Possibly 25 percent of cases are due to a spontaneous mutation at the time of conception.

Although everyone with Marfan syndrome has a defect in the same gene, different mutations are found in different families, and not everyone experiences the same characteristics to the same degree. In other words, the defective gene expresses itself in different ways in different people. This phenomena is known as variable expression. Scientists do not yet understand why variable expression occurs in people with Marfan syndrome.

## How Is Marfan Syndrome Diagnosed?

There is no specific laboratory test, such as a blood test or skin biopsy, to diagnose Marfan syndrome. The doctor and/or geneticist (a doctor with special knowledge about inherited diseases) relies on observation and a complete medical history, including:

- information about any family members who may have the disorder or who had an early, unexplained, heart-related death

- a thorough physical examination, including an evaluation of the skeletal frame for the ratio of arm/leg size to trunk size

- an eye examination, including a "slit lamp" evaluation

- heart tests such as an echocardiogram (a test that uses ultrasound waves to examine the heart and aorta).

The doctor may diagnose Marfan syndrome if the patient has a family history of the disease, and if there are specific problems in at least two of the body systems known to be affected. For a patient with no family history of the disease, at least three body systems must be affected before a diagnosis is made. Moreover, two of the systems must show clear signs that are relatively specific for Marfan syndrome.

In some cases, a genetic analysis may be useful in making a diagnosis of Marfan syndrome, but such analyses are often time consuming and may not provide any additional helpful information. Family members of a person diagnosed with Marfan syndrome should not assume they are not affected if there is no knowledge that the disorder existed in previous generations of the family. After a clinical diagnosis of a family member, a genetic study might identify the specific mutation for which a test can be performed to determine if other family members are affected.

Recently, doctors discovered a connective tissue disorder known as Loeys-Dietz syndrome, which has several characteristics that overlap with those of Marfan syndrome. When making a diagnosis, it is important to distinguish between the two disorders: Loeys-Dietz is more likely to cause fatal aortic aneurysms, and treatment for the two is different. A diagnostic test for Loeys-Dietz syndrome is available.

## What Types of Doctors Treat Marfan Syndrome?

Because a number of body systems may be affected, a person with Marfan syndrome should be cared for by several different types of doctors. A general practitioner or pediatrician may oversee routine health care and refer the patient to specialists such as a cardiologist (a doctor who specializes in heart disorders), an orthopaedist (a doctor who specializes in bones), or an ophthalmologist (a doctor who specializes in eye disorders), as needed. Some people with Marfan syndrome also go to a geneticist.

## What Treatment Options Are Available?

There is no cure for Marfan syndrome. To develop one, scientists may have to identify and change the specific gene responsible for the disorder before birth. However, a range of treatment options can minimize and sometimes prevent complications. The appropriate specialists will develop an individualized treatment program; the approach the doctors use depends on which systems have been affected.

- **Skeletal** – Annual evaluations are important to detect any changes in the spine or sternum. This is particularly important in times of rapid growth, such as adolescence. A serious malformation not only can be disfiguring, but also can prevent the heart and lungs from functioning properly. In some cases, an orthopaedic brace or surgery may be recommended to limit damage and disfigurement.

- **Eyes** – Early, regular eye examinations are essential for identifying and correcting any vision problems associated with Marfan syndrome. In most cases, eyeglasses or contact lenses can correct the problem, although surgery may be necessary in some cases.

- **Heart and blood vessels** – Regular checkups and echocardiograms help the doctor evaluate the size of the aorta and the way the heart is working. The earlier a potential problem is identified and treated, the lower the risk of life-threatening complications. Those with heart problems are encouraged to wear a medical alert bracelet and to go to the emergency room if they experience chest, back, or abdominal pain. Some heart-valve problems can be managed with drugs such as beta-blockers, which may help decrease stress on the aorta. In other cases, surgery to replace a valve or repair the aorta may be necessary.

Surgery should be performed before the aorta reaches a size that puts it at high risk for tear or rupture. Because blood clots can form around artificial heart valves, people who have a valve replaced must take the blood-thinning drug warfarin (Coumadin)[1] for the rest of their lives. They must also take extreme care to prevent endocarditis (inflammation of the lining of the heart cavity and valves). Dentists should be alerted to this risk; they are likely to recommend that the patient be prescribed protective medicines before they perform dental work.

Because warfarin carries a risk of some serious side effects, including excessive bleeding, and because it is dangerous to unborn babies, doctors are increasingly opting for a newer aortic root replacement procedure that enables people to keep their own valves. The procedure involves removing and replacing the enlarged part of the aorta with a Dacron tube, and resuspending the natural valve into the tube so that the tube supports the valve. The procedure is often performed at an earlier stage than traditional valve replacement. It may also be offered to women with aortic enlargement who are considering becoming pregnant, because it can prevent the rapid aortic growth and possible tearing that sometimes occur during pregnancy.

[1] Brand names included in this booklet are provided as examples only, and their inclusion does not mean that these products are endorsed by the National Institutes of Health or any other Government agency. Also, if a particular brand name is not mentioned, this does not mean or imply that the product is unsatisfactory.

- **Nervous system** – If dural ectasia (swelling of the covering of the spinal cord) develops, medication may help minimize any associated pain.

- **Lungs** – It is especially important that people with Marfan syndrome not smoke, as they are already at increased risk for lung damage. Any problems with breathing during sleep should be assessed by a doctor.

Pregnancy poses a particular concern due to the stress on the body, particularly the heart. A pregnancy should be undertaken only under conditions specified by obstetricians and other specialists familiar with Marfan syndrome. The pregnancy should be monitored as a high-risk condition. Women with an aortic measurement of 4 centimeters or greater may want to discuss the possibility of a valve-sparing aortic root replacement with their doctors before becoming pregnant. Women with Marfan syndrome may also seek genetic counseling concerning the likelihood that they will pass the disease on to their children.

While eating a balanced diet is important for maintaining a healthy lifestyle, no vitamin or dietary supplement has been shown to help slow, cure, or prevent Marfan syndrome.

For most people with Marfan syndrome, engaging in moderate aerobic exercise is important for promoting skeletal and cardiovascular health and a sense of well-being. However, because of the risk of aortic dissection, people with the syndrome should not engage in contact sports, competitive athletics, or isometric exercise.

## What Are Some of the Emotional and Psychological Effects of Marfan Syndrome?

Being diagnosed and learning to live with a genetic disorder can cause social, emotional, and financial stress. It often requires a great deal of adjustment in outlook and lifestyle. A person who is an adult when Marfan syndrome is diagnosed may feel angry or afraid. There may also be concerns about passing the disorder to future generations or about its physical, emotional, and financial implications.

The parents and siblings of a child diagnosed with Marfan syndrome may feel sadness, anger, and guilt. It is important for parents to know that nothing that they did caused the fibrillin-1 gene to mutate. Parents may be concerned about the genetic implications for siblings or have questions about the risk to future children.

Some children with Marfan syndrome are advised to restrict their activities. This may require a lifestyle adjustment that is hard for a child to understand or accept.

For both children and adults, appropriate medical care, accurate information, and social support make it easier to live with the disease. Genetic counseling may also be helpful for understanding the disease and its potential impact on future generations.

While Marfan syndrome is a lifelong disorder, the outlook has improved in recent years. As early as the 1970s, the life expectancy of a person with Marfan syndrome was two-thirds that of a person without the disease; however, with improvements in recognition and treatment, people with Marfan syndrome now have a life expectancy similar to that of the average person.

## What Research Is Being Conducted to Help People With Marfan Syndrome?

Numerous studies are underway that should lead to a better understanding of Marfan syndrome and its treatment. They include a plan to identify the factors responsible for the cardiovascular manifestations of Marfan syndrome, a study to better understand the process that leads to skeletal manifestations, and studies to clarify the role of a chemical messenger called transforming growth factor-beta (TGF-β) in the disorder.

Scientists are conducting research on Marfan syndrome from a variety of perspectives. One approach is to better understand what happens once the genetic defect or mutation occurs. How does it change the way connective tissue develops and functions in the body? Why are people with Marfan syndrome affected differently? Scientists are searching for the answers to these questions both by studying the genes themselves and by studying large family groups affected by the disease. Mouse models that carry mutations in the fib-

rillin-1 gene may help scientists better understand the disorder. Animal studies that can provide preliminary information for gene therapy are also underway.

Other scientists are focusing on ways to treat some of the complications that arise in people with Marfan syndrome. Clinical studies are being conducted to evaluate the usefulness of certain medications in preventing or reducing problems with the aorta.

For example, research has shown that the blood pressure medication losartan prevents aortic aneurysms in a mouse model of Marfan syndrome. New studies receiving funding from the **National Heart, Lung and Blood Institute** are now underway to determine whether the drug has the same beneficial effect in people.

## Where Can People Find More Information About Marfan Syndrome?

- **National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)**
  National Institutes of Health
  1 AMS Circle
  Bethesda, MD 20892–3675
  Phone: 301–495–4484 or
  877–22–NIAMS (226–4267) (free of charge)
  TTY: 301–565–2966
  Fax: 301–718–6366
  E-mail: niamsinfo@mail.nih.gov
  www.niams.nih.gov

NIAMS provides information about various forms of arthritis and other rheumatic diseases; as well as other bone, muscle, joint, and skin diseases. It distributes patient and professional education materials and refers people to other sources of information. Additional information and updates can also be found on the NIAMS Web site.

- **National Human Genome Research Institute (NHGRI)**
  National Institutes of Health
  9000 Rockville Pike
  Bethesda, MD 20892–2152
  Phone: 301–402–0911
  Fax: 301–402–2218

NHGRI conducts studies involving various aspects of Marfan syndrome. To find out if there is a study for which you might qualify, call or e-mail NHGRI using the contact information below, or visit www.clinicaltrials.gov

Phone: 800–411–1222 (free of charge) (for information about entering a clinical study)
E-mail: prpl@mail.cc.nih.gov

- **NHGRI Genetic and Rare Diseases Information Center**
  P.O. Box 8126
  Gaithersburg, MD 20898–8126
  Phone: 888–205–2311 (free of charge, Monday - Friday, noon to 6:00 p.m. Eastern Time)
  International Phone: 1–301–519–3194
  TTY: 888–205–3223 (free of charge)
  E-mail: gardinfo@nih.gov
  Fax: 240–632–9164
  *By phone, call Monday to Friday, noon to 6 p.m. Eastern Time. By e-mail, fax, or mail, allow 5 to 10 working days for response.*

The Genetic and Rare Diseases Information Center (GARD) employs experienced information specialists to answer questions in English and Spanish from the general public, including patients and their families, health care professionals, and biomedical researchers. It was established by the National Human Genome Research Institute (NHGRI) and the NIH Office of Rare Diseases (ORD).

- **National Marfan Foundation**
  22 Manhasset Avenue
  Port Washington, NY 11050–2023
  Phone: 516–883–8712 or
  800–8–MARFAN (862–7326) (free of charge)
  Fax: 516–883–8040
  E-mail: staff@marfan.org
  www.marfan.org

This organization helps people who have Marfan syndrome and related connective tissue disorders. It provides information and materials about the disorder and about how to seek appropriate medical care. It supports research and promotes public awareness of Marfan syndrome. The foundation can also provide the names of doctors who diagnose and treat Marfan syndrome.

- **National Organization of Rare Disorders (NORD)**
  55 Kenosia Avenue
  P.O. Box 1968
  Danbury, CT 06813–1968
  Phone: 203–744–0100 or
  800–999–6673 (free of charge, voicemail only)
  Fax: 203–798–2291
  E-mail: orphan@rarediseases.org
  www.rarediseases.org

NORD is a federation of voluntary health organizations that help people with rare "orphan" diseases. NORD is committed to identifying, treating, and curing rare disorders through programs of education, advocacy, research, and service. NORD offers basic information about Marfan syn-

drome on its Web site, as well as a downloadable report, and links to organizations worldwide that help people with various aspects of Marfan syndrome.

- **March of Dimes Birth Defects Foundation**
  1275 Mamaroneck Avenue
  White Plains, NY 10605–5201
  Phone: 914–428–7100 or
  888–663–4637 (free of charge)
  E-mail: Askus@marchofdimes.com
  www.marchofdimes.com

The foundation's mission is to improve the health of babies by preventing birth defects, premature birth, and infant mortality through research, community services, education, and advocacy. It offers fact sheets and other information on numerous genetic and congenital defects, including Marfan syndrome.

- **American Heart Association**
  7272 Greenville Avenue
  Dallas, TX 75231–5129
  Phone: 800–AHA–USA1 (242–8721) (free of charge)
  E-mail: inquiries@heart.org
  www.americanheart.org

The American Heart Association has a fact sheet on its Web site that describes the blood-vessel and heart-valve complications of Marfan syndrome. It is also a source of information on precautions doctors and other health professionals must use in treating patients who have heart problems associated with Marfan syndrome.

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