

# LOEYS-DIETZ SYNDROME

Loeys-Dietz syndrome is a genetic disorder of connective tissue. Because connective tissue is found throughout the body, Loeys-Dietz syndrome features can occur in the heart, blood vessels, bones, joints, skin, and internal organs, such as the intestines, spleen, and uterus. Some Loeys-Dietz syndrome features are easy to see. Other features, such as heart and blood vessel problems, need imaging tests to find them.

**There is considerable variability in the symptoms associated with Loeys-Dietz syndrome. Some people can be severely affected, while others only show mild symptoms.**



Disorders that share features with Loeys-Dietz syndrome include Marfan syndrome, vascular Ehlers-Danlos syndrome, and Shprintzen-Goldberg syndrome. There is considerable variability in the symptoms associated with Loeys-Dietz syndrome. Some people can be severely affected, while others only show mild symptoms. Knowing the signs is the key to early and accurate diagnosis and life-saving treatment.

## **How prevalent is Loeys-Dietz syndrome?**

It is not known how many people have Loeys-Dietz syndrome. It is likely there are people who are diagnosed with another connective tissue disorder who actually have Loeys-Dietz syndrome. This is especially likely for some people diagnosed with Marfan syndrome or “atypical” Marfan syndrome. Loeys-Dietz syndrome affects both males and females, and people of all ethnicities.

## What are the characteristics of Loeys-Dietz syndrome?

There are four key features in Loeys-Dietz syndrome:

- Arteries that twist and wind (arterial tortuosity)
- Widely-spaced eyes (hypertelorism)
- Wide or split uvula (the tissue that hangs down in the back of the throat) and/or cleft palate
- Widening or dilation of arteries (aneurysms), which can be observed by imaging techniques. These most often occur in the aortic root (base of the artery leading from the heart), but can be seen in other arteries throughout the body as well.

It is important to note, however, that these features are not observed in all patients and do not definitively lead to a diagnosis of Loeys-Dietz syndrome.

Some Loeys-Dietz syndrome features are also found in Marfan syndrome. These include:

- Enlarged or bulging aorta, the main blood vessel that carries blood from the heart (aortic dilation or aneurysm)
- Tear of the wall of the aorta (aortic dissection)
- “Floppy” mitral valve (mitral valve prolapse)
- Chest that sinks in (pectus excavatum) or sticks out (pectus carinatum)
- Spine that curves to the side (scoliosis) or from the back to the front (kyphosis)
- Flexible joints
- Flat feet
- Swelling, bulging or widening of the spinal sac (dural ectasia)
- Long fingers and toes
- Myopia
- Retinal detachment

Some Loeys-Dietz syndrome features are different from Marfan syndrome features and are very important for making a correct diagnosis. When a person has these particular features, it is important that the doctor think about Loeys-Dietz syndrome. The features that set Loeys-Dietz syndrome apart from Marfan syndrome and many other connective tissue disorders include:

- Arteries that twist and wind (arterial tortuosity)
- Aneurysms and dissections in arteries other than the aorta
- Widely-spaced eyes (hypertelorism)
- Wide or split uvula (the tissue that hangs down in the back of the throat)
- Cleft palate (when the roof of the mouth is split at birth)

- Clubfoot (when the foot is turned inward and upward at birth)
- White of the eye looks blue or gray
- Premature fusion of the bones of the skull (craniosynostosis)
- Heart defects at birth, such as atrial septal defect, patent ductus arteriosus, bicuspid aortic valve
- Features in the skin, such as easy bruising, wide scars, soft skin texture, and translucent skin (when it looks almost see-through)
- Gastrointestinal problems (stomach and intestine problems), such as difficulty absorbing food, chronic (comes and goes but never really goes away) diarrhea, abdominal pain, and/or gastrointestinal bleeding and inflammation
- Food and environmental allergies
- Rupture of the spleen or bowel
- Rupture of the uterus during pregnancy
- Instability or malformation of the spine in the neck (cervical spine instability)
- Poor mineralization of the bones (osteoporosis) that can make the bones more likely to break
- Collection of fluid in the brain (hydrocephalus)
- Part of the brain (cerebellum) with an abnormal shape (Chiari I malformation)

It is also important to note that ectopia lentis (dislocation of the lens of the eye) and prominently long limbs are usually not associated with Loeys-Dietz syndrome.

### What causes Loeys-Dietz syndrome?

Loeys-Dietz syndrome (type 1-5) is caused by a genetic mutation in one of five genes that encode for the receptors and other molecules in the transforming growth factor-beta (TGF- $\beta$ ) pathway. These genes are:

- LDS-1 — transforming growth factor beta-receptor 1 (TGF $\beta$ R1)
- LDS-2 — transforming growth factor beta-receptor 2 (TGF $\beta$ R2)
- LDS-3 — mothers against decapentaplegic homolog (SMAD-3)
- LDS-4 — transforming growth factor beta-2 ligand (TGF $\beta$ 2)
- LDS-5 — transforming growth factor beta-3 ligand (TGF $\beta$ 3)

When any of these genes has a mutation, growth and development of the body's connective tissue and other body systems is disrupted, leading to the signs and symptoms of Loeys-Dietz syndrome. Marfan syndrome is different from Loeys-Dietz syndrome in that the gene mutation which causes Marfan syndrome is in fibrillin-1 (FBN-1), a protein within the connective tissue in the body. However, there are many common features between the two syndromes.

**How is Loeys-Dietz syndrome inherited?**

People can inherit Loeys-Dietz syndrome; that is, it is passed down from a parent who has Loeys-Dietz syndrome. Others have a spontaneous mutation; that is, they are the first in the family to have Loeys-Dietz syndrome.

**How is Loeys-Dietz syndrome diagnosed?**

A medical geneticist is usually most knowledgeable about recognizing and diagnosing Loeys-Dietz syndrome. To make the diagnosis, the medical geneticist reviews the patient's family health history, conducts a physical exam, and performs special tests which can include:

- Echocardiogram. This test looks at the heart, its valves, and the aorta (artery that carries blood from the heart) close to the heart.
- Either a computerized tomography (CT) or magnetic resonance (MR) angiogram (study of the blood vessels) with 3-D reconstruction, from the top of the head to the top of the legs. The CT or MR can find twisted blood vessels and aneurysms in blood vessels in the body.
- Genetic testing that can find the genetic changes (mutations) in the genes known to cause Loeys-Dietz syndrome. Genetic testing is most helpful for people who have Loeys-Dietz syndrome features not usually seen in other connective tissue disorders. A doctor must order this testing. To find laboratories that conduct Loeys-Dietz syndrome genetic testing, go to the website for Gene Tests at [genetests.org](http://genetests.org).

When genetic testing finds a change in one of the genes, the person most likely has Loeys-Dietz syndrome and needs special medical care and counseling. They may also need to find out if others in their family also have Loeys-Dietz syndrome.

When genetic testing does not find a mutation, it is still possible a person has Loeys-Dietz syndrome or a different connective tissue disorder. They should ask their doctor if they need to be evaluated for other conditions or if additional testing or medical care is recommended.

Although Loeys-Dietz syndrome is diagnosed most often in children, there has been a growing number of diagnoses in adults.

People who are in any of the following groups should talk with their doctor about the possibility of Loeys-Dietz syndrome:

- Those with a diagnosis of Marfan syndrome or "atypical" Marfan syndrome who also have any Loeys-Dietz syndrome specific features.
- Those who have several Marfan syndrome features, but who do not have a clear diagnosis, and who have any Loeys-Dietz syndrome features.
- Those with Marfan syndrome features who have family members with Loeys-Dietz syndrome features.
- Those who have multiple features associated with the diagnosis of Loeys-Dietz syndrome.

**Why is it important to have a correct diagnosis?**

People with Loeyes-Dietz syndrome features need to see a doctor who knows about Loeyes-Dietz syndrome to confirm if they have the disorder. Medical problems can be managed, but a person needs a correct diagnosis and proper medical care and counseling as soon as possible.

Most importantly, life-threatening aneurysms in Loeyes-Dietz syndrome are more likely to tear and rupture at smaller sizes than in people who have Marfan syndrome or other connective tissue disorders. In Loeyes-Dietz syndrome, tears and ruptures can also happen at younger ages and in different parts of the body than in Marfan syndrome. For these reasons, surgery to repair aneurysms is often done earlier in Loeyes-Dietz syndrome.

**How is Loeyes-Dietz syndrome managed?****Heart & Blood Vessels**

Monitoring of the aorta and other arteries:

- An echocardiogram to check the valves of the heart and the part of the aorta closest to the heart at least once a year.
- Either a CT or MRI angiogram—with contrast—of the head, neck, chest, abdomen (stomach area), and pelvis (lower stomach area just above the legs) on a regular basis. The scans detect aneurysms and/or dissections (tears) in any of the arteries in the head, neck, chest, abdomen, and pelvis. How often depends upon the initial findings (results of the first scan), as well as the size of any aneurysms that are found, and how fast they are growing. Larger and faster growing aneurysms need more frequent monitoring.

Medications:

- Medications that lower heart rate and/or blood pressure might help prevent bulging or tearing of blood vessels. Doctors often use medications called beta blockers to treat Loeyes-Dietz syndrome for this purpose. Some blood pressure medications called angiotension receptor blockers (ARBs) may also help treat Loeyes-Dietz syndrome in other ways. More research is needed to learn about how and whether ARBs can treat Loeyes-Dietz syndrome effectively. In the meantime, some doctors prescribe an ARB called losartan to treat Loeyes-Dietz syndrome. Losartan is FDA-approved for lowering blood pressure, and the risks of using it appear low while the potential benefits appear high.

Regular but gentle exercise:

- Most people with Loeyes-Dietz syndrome can and should be physically active, but they should not exercise to the point of becoming exhausted. As a general rule, while exercising, a person with Loeyes-Dietz syndrome should be able to comfortably talk with another person without needing to take breaths in the middle of short sentences.
- Walking, gentle hiking, bike riding, and swimming are safe ways to stay physically active.
- They should not do exercises such as weight lifting, push-ups, chin-ups, sit-ups, and other exercises that strain muscles.

- They should avoid contact sports, such as football and basketball, or any other activity in which there is a high risk of a sharp blow to the head or chest.
- Based upon the size of blood vessels or instability of the neck, some people with Loeys-Dietz syndrome need to be even more careful and gentle when exercising.

Most people with Loeys-Dietz syndrome can be helped by planned vascular surgery. This means having surgery to remove aneurysms before they cause a life-threatening dissection (tear) or rupture. This is a very important part of Loeys-Dietz syndrome care.

- Doctors use the size of an aneurysm, how fast the aneurysm is growing, where the aneurysm is located, and/or family history of early dissection or rupture to decide when it is time to perform vascular surgery.
- The most common vascular surgery is replacement of the aortic root (the part of the aorta closest to the heart).
- Vascular surgery is generally very successful in people with Loeys-Dietz syndrome.
- Keep in mind that replacement of the aortic root is also done in people with other connective tissue disorders, especially Marfan syndrome. However, using Marfan guidelines to decide when to do surgery in a person with Loeys-Dietz syndrome can be dangerous, because aneurysms in people with Loeys-Dietz syndrome can tear or rupture at smaller sizes and at younger ages.

### **Bones & Joints**

People with Loeys-Dietz syndrome need special care of the bones and joints.

X-rays of the cervical spine (neck) are used to look for problems in the neck. These problems include:

- abnormal vertebrae (bones of the spine)
- subluxation (incomplete dislocation) of the vertebrae in the neck
- unstable vertebrae in the neck

When the x-rays show any of these features, talk to an orthopedist (a doctor who cares for bones and joints) or a neurosurgeon (a doctor who operates on the brain and spine) about the problem and what should be done to take care of it. In some cases, the doctor will recommend cervical spine fusion (surgery to join together the bones in the neck).

Before people with Loeys-Dietz syndrome have any kind of surgery, they should have an x-ray of the neck to check for cervical spine instability (any unstable vertebrae in the neck). This x-ray study is important because cervical spine instability can affect intubation procedures (how the doctor places the tube in the throat used for breathing during an operation). Additionally, people with cervical spine instability should not have spinal manipulation by a chiropractor.

Non-surgical care of the bones and joints may include:

- checking for scoliosis (curving of the spine) and frequent monitoring of the size of any curve to see if surgery to straighten the spine is needed
- bracing for scoliosis

- orthotics (special shoe inserts) for loose ankle joints or misshaped feet
- harnesses or braces for loose or dislocated joints
- checking for poor mineralization of the bones (osteoporosis) that can make the bones more likely to break

Surgery used to manage problems in the bones and joints includes:

- Surgery for scoliosis. Only some people with Loeys-Dietz syndrome need scoliosis surgery. The guidelines for the surgery are similar for people with Loeys-Dietz syndrome and Marfan syndrome.
- Surgery to repair either a chest that sinks in (pectus excavatum) or sticks out (pectus carinatum). This is done when a person wants a more normal looking chest. Only in rare cases is surgery needed on the chest bone to improve heart or lung function or for another medical reason.

#### **Allergies and Gastrointestinal Issues**

Environmental and food allergies are increased in people with Loeys-Dietz syndrome and may require a consultation with an allergist or gastroenterologist. Allergic reactions may present as rhinitis or sinusitis, eczema, or hives. Gastrointestinal complaints can include the feeling of food getting stuck in your throat, diarrhea, abdominal pain, or difficulty gaining weight. Some people have severe inflammatory disease of the esophagus or intestines that may need stricter intervention, such as medications or feeding tubes to help with caloric intake.

#### **What is the life expectancy for someone with Loeys-Dietz syndrome?**

More experience is necessary to accurately predict life expectancy for people with Loeys-Dietz syndrome. Many patients are first being diagnosed with this condition at an older age. Recent progress in the diagnosis, medical, and surgical management of Loeys-Dietz syndrome is improving both the length and quality of life for people with the condition.

#### **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](http://marfan.org). You can print information that interests you and ask questions online.