

FAMILIAL AORTOPATHY

GENETIC TESTING



What are familial aortopathies?

An aortopathy is an abnormal change in the aorta. The aorta is the largest artery in the body. Oxygen-rich blood leaves the heart through the aorta, which extends into the chest (thorax) and then splits into the ascending aorta, which sends blood to the vessels of the neck and head, and the descending aorta, which sends blood to vessels that deliver it to the rest of the body.

Thoracic aortic aneurysm and aortic dissection (TAAD) is one type of aortopathy. It causes the aorta to expand (dilate) over time, causing weak areas to form in the wall of the aorta. The presence of these weak areas can lead to¹⁻⁴:

- Bulges in the wall of the aorta (thoracic aortic aneurysms).
- Tears in the layers of muscle and tissue that make up the wall of the aorta (aortic dissections).

TAAD increases the risk that the aorta will break open (rupture), which can cause life-threatening bleeding inside the chest.

- About 20% of the time, TAAD affects 2 or more closely related family members.^{4,6,7} These familial TAADs tend to progress rapidly than those that are not familial.⁶
- Aortopathies, including TAAD, may develop in people who have certain inherited health conditions, including Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and vascular-type Ehlers-Danlos syndromes (vt-EDS).¹⁻⁴

Depending on the underlying cause of an aortopathy, treatment may include drugs that lower blood pressure, which may slow aortic dilation and/or surgery to prevent aortic dissection.¹⁻⁵ Lifestyle changes may also help reduce the risk of life-threatening events.¹⁻⁴

What causes familial aortopathies?

Familial TAAD is caused by abnormal changes in certain genes. The same is true for MFS, LDS, and vt-EDS, which can lead to aortopathies. Genes are found in every cell

in your body. They carry the instructions for making proteins that control how each of your cells work. Genes can undergo abnormal changes (called mutations) that may cause cells to stop working the way they should. Gene mutations may result in health conditions, and they may be passed from parent to child (inherited).

- Mutations in several different genes have been linked with familial TAAD. In some cases, it is understood that the mutations affect the ability of arteries to maintain their shape, allowing them to become stretched and weak.⁷ More mutations that cause familial TAAD are likely to be discovered in the future, because the mutations that have been identified so far only account for about 20% of all cases.⁴
- Many gene mutations that cause MFS, LDS, and vt-EDS have been identified. The mutations affect the properties of connective tissue, which gives structure and support to blood vessels like the aorta, as well as other body tissues. When connective tissue is defective, the wall of the aorta is weakened.

How are familial aortopathies inherited?

Normally, each of your cells carries 2 copies of all your genes. You inherit 1 copy of a gene from each of your parents. Familial TAAD is usually inherited in an autosomal dominant manner, as are MFS, LDS, and vt-EDS.¹⁻⁴ This means a child only needs to inherit 1 copy of a gene mutation (from 1 parent) to be affected with one of those conditions.

In some cases MFS, vt-EDS, and LDS are caused by *de novo* mutations.¹⁻³ This means the mutations that cause these disorders occur for the first time in an affected child instead of being passed from parent to child.

How are familial aortopathies diagnosed?

An aortopathy can be diagnosed based on the presence of dilation and/or tears in the tissue layers of the aorta wall.⁴ These defects can be found by doing imaging studies of the heart, such as a CT scan, MRI, echocardiogram, or angiography.

Your doctor may have reason to believe you have familial TAAD if⁴:

- Other members of your family have TAAD or other thoracic aorta defects.

- You have an aortopathy, but you do not have any of the other signs and symptoms of either Marfan syndrome, Loeys-Dietz syndrome, or vascular-type Ehlers-Danlos syndrome.

Your doctor may recommend a genetic test called gene sequencing to confirm a diagnosis of familial TAAD.

What is gene sequencing for familial aortopathies?

Gene sequencing for familial aortopathies is a procedure that reads the instructions (DNA) that make up the genes known to play a role in the development of these disorders. This test, which is performed on a sample of blood, is a way to identify the presence of altered genes in a person's cells, which can help a doctor^{1-4,8}:

- Confirm a diagnosis of familial TAAD or a diagnosis of MFS, LDS, or vt-EDS.
- Identify close relatives of an affected person who have a TAAD gene mutation and may benefit from regular monitoring of the health of their aorta, lifestyle changes, and drug and/or surgical treatment.
- In some cases, predict the severity of the aortopathy based on the exact mutation found.

What possible results of gene sequencing can be reported, and what might they mean?

- **Negative:** No mutations were found in the genes tested. A negative result may reduce the chance that a person is affected with a familial aortopathy but cannot completely rule it out.
- **Positive:** A mutation was found in 1 or more of the genes tested, confirming the diagnosis of a familial aortopathy.

- **Variant of unknown significance:** A mutation was found in the genes tested that either has not been reported before or previous reports are conflicting. Therefore, it is unclear if the mutation is the cause of the person's signs and symptoms. Genetic testing of family members may provide more information. If all affected family members have the same mutation, then it is likely to be linked to the inherited disorder. If some affected family members do not have the mutation, it is less likely to be linked to the disorder.

Gene sequencing test results should be combined with clinical findings and reviewed by a health professional who specializes in medical genetics.

Where can I find more information?

If you have questions or want more information about genetic testing for familial aortopathy, ask your doctor or genetic counselor. You may search for a genetic counselor in your area using an online address book provided by the National Society of Genetic Counselors at www.nsgc.org.

Other information resources include:

- Ehlers-Danlos National Foundation
Telephone: 703-506-2892
Home page: www.ednf.org
- Genetics Home Reference
Home page: <http://ghr.nlm.nih.gov>
- Loeys-Dietz Syndrome Foundation
Home page: www.loeysdietz.org
- National Marfan Foundation
Telephone: 800-8-MARFAN (800-862-7326)
Home page: www.marfan.org

Note: This material is provided for general information purposes only. It is not intended as a substitute for medical advice and/or consultation with a physician or technical expert.

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