



Loeys-Dietz syndrome

Loeys-Dietz syndrome is a condition of connective tissue that most commonly affects the heart and skeletal systems. It is mainly caused by mutations in TGF-Beta genes which make proteins that promote growth and development of the body's tissues.

Characteristics of Loeys-Dietz syndrome

Loeys-Dietz syndrome (LDS) is a disorder of connective tissue. Connective tissue helps provide strength and flexibility to the body and is found in many different parts of the body. As a result, individuals with LDS may have features in different body systems. The most commonly affected systems are the heart (cardiovascular), face and skull (craniofacial), and bones (skeletal). The signs and symptoms of all types of LDS can be seen in children and adults and some individuals may have intellectual disability. There are several types of LDS, each of which have specific features as well as some features in common.

Types 1 and 2 are the most common forms of LDS. Both conditions have cardiovascular features including dilation (enlargement or stretching) or aneurysm (ballooning) of the aorta. Dilation or aneurysm of the aorta can lead to more serious complications including aortic dissection (tearing of the aortic wall) if not monitored. Individuals with LDS may have additional congenital heart defects and other heart problems such as arterial tortuosity (arteries that are twisted and have many unusual turns). Aneurysms or dissections can also occur in these abnormal arteries, not just the aorta. Individuals with LDS type 1 may also have characteristic facial features such as wide spaced eyes, a wide or bifid uvula (a split or fork in the tissue that dangles in the back of the throat between the tonsils), an opening in the roof of the mouth (cleft palate), craniosynostosis (premature closure of the bones in the skull), and a large head size. Other skeletal features an individual might have include curvature of the spine (scoliosis), problems in the neck bones (cervical spine), chest abnormalities such as a protrusion of the chest bone (pectus carinatum) or a sunken chest bone (pectus excavatum), contractures or joint limitations in the hands and feet, flexible joints, and flat or club feet. They can also have gastrointestinal or digestive problems and sometimes the white part of the eye (sclera) is a greyish or bluish color. Individuals with LDS types 1 and 2 may bruise easily and have atrophic or abnormal scarring. Individuals with type 2 LDS may have the skeletal or craniofacial features to a lesser degree than individuals with type 1, or not at all. People with LDS type 2 tend to have soft, velvety skin that is sometimes described as translucent, or almost see-through.

LDS type 3, also called aneurysm-osteoarthritis syndrome, is less common than types 1 or 2. Individuals with LDS type 3 may have enlargement of the aorta as well as the arterial tortuosity, skeletal, craniofacial, and skin characteristics just as individuals with types 1 and 2. They may also have joint pain, most commonly in the knees, hands, wrists, and spine. These individuals may have additional problems with bones such as osteoporosis, or poor mineralization of the bone.

Diagnosis/Testing

Most individuals with LDS have a change or mutation in one of the genes within the TGF-Beta pathway. These genes include TGF Beta Receptors 1 and 2 (TGFB1, TGFB2) and TGF Beta 2 (TGFB2). The genes in this pathway play a role in cell signaling that promote growth and development of the body's tissues. In LDS type 3, changes or mutations the SMAD3 gene, also part of the TGF Beta receptor protein complex, also cause the condition.

Management/Surveillance

Management of LDS typically involves care from many different specialists or multidisciplinary care. Cardiovascular evaluation includes routine ultrasounds of the heart (echocardiograms) as well as imaging of the top half of the body (i.e., CTA or MRA image from the head through the pelvis). Full vascular imaging should be performed when someone is first diagnosed and repeated at least every 18-24 months. Frequently, exercise restrictions and blood-pressure lowering medications are used to reduce stress on the aorta and arteries. When the aorta widens or dilates to the point that it may require surgery, aortic root replacement surgery is indicated to reduce the risk of aortic dissection. Vascular surgery is often necessary for aneurysms or dissections in other portions of the body as well. Women with LDS who become pregnant should be followed carefully for arterial problems.

X-rays of the neck in the flexion and extension position should be performed at diagnosis and surgical intervention is needed in rare cases. Cervical spine abnormalities should be investigated before any type of surgery requiring intubation. Routine management for craniosynostosis, cleft palate, heart defects, scoliosis, and foot deformities should occur. If there are symptoms of allergies, asthma, failure-to-thrive, or other gastrointestinal problems, affected individuals should be referred to an allergist and/or gastroenterologist.

Mode of inheritance

LDS is inherited in an autosomal dominant pattern. This means inheriting one gene mutation is enough for an individual to be affected and show signs of LDS. The mutation can be inherited from an affected parent or it can occur brand new (de novo) in an affected child. Most of the time (approximately 75%), the condition occurs de novo in an affected child.

Risk to family members

The risk to family members depends on whether or not the individual with LDS has a parent affected with LDS. If a parent also has LDS, the risk of having a child with LDS is 50% with each pregnancy. If a parent does not have LDS, the risk of other siblings being affected is very low.

Special considerations

In LDS, dissection of the aorta can occur earlier or at dimensions not thought to be dangerous in other aneurysm syndromes, such as Marfan syndrome (see trait profile) or Familial Thoracic Aortic Aneurysm syndrome (see trait profile).

Resources

Loeys-Dietz Syndrome Foundation

<http://www.loeysdietz.org>

Thoracic Aortic Disease (TAD) Coalition

<http://TADCoalition.org>

Genetics Home Reference: Loeys-Dietz syndrome

<http://ghr.nlm.nih.gov/condition/loeys-dietz-syndrome>

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Created by: Gretchen Oswald, MS, CGC, Karin M. Dent, MS, LCGC

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Edited by: Seema Jamal, MSc, LCGC