Loeys-Dietz syndrome

Loeys-Dietz syndrome is a disorder that affects the connective tissue in many parts of the body. Connective tissue provides strength and flexibility to structures such as bones, ligaments, muscles, and blood vessels.

There are five types of Loeys-Dietz syndrome, labelled types I through V, which are distinguished by their genetic cause. Regardless of the type, signs and symptoms of Loeys-Dietz syndrome can become apparent anytime from childhood through adulthood, and the severity is variable.

Loeys-Dietz syndrome is characterized by enlargement of the aorta, which is the large blood vessel that distributes blood from the heart to the rest of the body. The aorta can weaken and stretch, causing a bulge in the blood vessel wall (an aneurysm). Stretching of the aorta may also lead to a sudden tearing of the layers in the aorta wall (aortic dissection). People with Loeys-Dietz syndrome can also have aneurysms or dissections in arteries throughout the body and have arteries with abnormal twists and turns (arterial tortuosity).

Individuals with Loeys-Dietz syndrome often have skeletal problems including premature fusion of the skull bones (craniosynostosis), an abnormal side-to-side curvature of the spine (scoliosis), either a sunken chest (pectus excavatum) or a protruding chest (pectus carinatum), an inward- and upward-turning foot (clubfoot), flat feet (pes planus), or elongated limbs with joint deformities called contractures that restrict the movement of certain joints. A membrane called the dura, which surrounds the brain and spinal cord, can be abnormally enlarged (dural ectasia). In individuals with Loeys-Dietz syndrome, dural ectasia typically does not cause health problems. Malformation or instability of the spinal bones (vertebrae) in the neck is a common feature of Loeys-Dietz syndrome and can lead to injuries to the spinal cord. Some affected individuals have joint inflammation (osteoarthritis) that commonly affects the knees and the joints of the hands, wrists, and spine.

People with Loeys-Dietz syndrome may bruise easily and develop abnormal scars after wound healing. The skin is frequently described as translucent, often with stretch marks (striae) and visible underlying veins. Some individuals with Loeys-Dietz syndrome develop an abnormal accumulation of air in the chest cavity that can result in the collapse of a lung (spontaneous pneumothorax) or a protrusion of organs through gaps in muscles (hernias). Other characteristic features include widely spaced eyes (hypertelorism), eyes that do not point in the same direction (strabismus), a split in the soft flap of tissue that hangs from the back of the mouth (bifid uvula), and an opening in the roof of the mouth (cleft palate).

Individuals with Loeys-Dietz syndrome frequently develop immune system-related problems such as food allergies, asthma, or inflammatory disorders such as eczema or inflammatory bowel disease.

Frequency

The prevalence of Loeys-Dietz syndrome is unknown. Loeys-Dietz syndrome types I and II appear to be the most common forms.

Genetic Changes

The five types of Loeys-Dietz syndrome are distinguished by their genetic cause: *TGFBR1* gene mutations cause type I, *TGFBR2* gene mutations cause type II, *SMAD3* gene mutations cause type III, *TGFB2* gene mutations cause type IV, and *TGFB3* gene mutations cause type V. These five genes play roles in a cell signaling pathway called the transforming growth factor beta (TGF-β) pathway, which directs the functions of the body's cells during growth and development. This pathway also regulates the formation of the extracellular matrix, an intricate lattice of proteins and other molecules that forms in the spaces between cells and is important for tissue strength and repair.

Mutations in the *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, or *TGFB3* gene result in the production of a protein with reduced function. Even though the protein is less active, signaling within the TGF-β pathway occurs at an even greater intensity than normal in tissues throughout the body. Researchers speculate that the activity of other proteins in this signaling pathway is increased to compensate for the protein whose function is reduced; however, the exact mechanism responsible for the increase in signaling is unclear. The overactive TGF-β pathway disrupts the development of the extracellular matrix and various body systems, leading to the signs and symptoms of Loeys-Dietz syndrome.

Inheritance Pattern

Loeys-Dietz syndrome has an autosomal dominant pattern of inheritance, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

In about 75 percent of cases, this disorder results from a new gene mutation and occurs in people with no history of the disorder in their family. In other cases, an affected person inherits the mutation from one affected parent.

Other Names for This Condition

- LDS
- Loeys-Dietz aortic aneurysm syndrome

Diagnosis & Management

Formal Diagnostic Criteria

- Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwöger M, Haverich A, Iung B, Manolis AJ, Meijboom F, Nienaber CA, Roffi M, Rousseau H, Sechtem U, Sirnes PA, Allmen RS, Vrints CJ; ESC Committee for Practice Guidelines. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2014 Nov 1;35(41):2873-926. doi: 10.1093/eurheartj/ehu281. Epub 2014 Aug 29. Erratum in: Eur Heart J. 2015 Nov 1;36(41):2779.
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Formal Treatment/Management Guidelines

- Canadian Cardiovascular Society Position Statement on the Management of Thoracic Aortic Disease
  http://www.onlinecjc.ca/article/S0828-282X(14)00112-3/pdf
- Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwöger M, Haverich A, Iung B, Manolis AJ, Meijboom F, Nienaber CA, Roffi M, Rousseau H, Sechtem U, Sirnes PA, Allmen RS, Vrints CJ; ESC Committee for Practice Guidelines. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2014 Nov 1;35(41):2873-926. doi: 10.1093/eurheartj/ehu281. Epub 2014 Aug 29. Erratum in: Eur Heart J. 2015 Nov 1;36(41):2779.
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- National Guideline Clearinghouse: Aortic Valve and Ascending Aorta Guidelines for Management and Quality Measures
  https://www.guideline.gov/summaries/summary/47278/aortic-valve-and-ascending-aorta-guidelines-for-management-and-quality-measures?q=loeys

Genetic Testing

- Arslan-Kirchner M, Epplen JT, Faivre L, Jondeau G, Schmidtke J, De Paepe A, Loeys B. Clinical utility gene card for: Loeys-Dietz syndrome (TGFBR1/2) and related phenotypes. Eur J Hum Genet. 2011 Oct;19(10). doi: 10.1038/ejhg.2011.68.
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  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3190257/
- Genetic Testing Registry: Loeys-Dietz syndrome
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C2697932/
- Genetic Testing Registry: Loeys-Dietz syndrome 1
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C2697933/
- Genetic Testing Registry: Loeys-Dietz syndrome 2
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C2674876/
- Genetic Testing Registry: Loeys-Dietz syndrome 3
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C3151087/
- Genetic Testing Registry: Loeys-Dietz syndrome 4
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C3553762/
- Genetic Testing Registry: Loeys-Dietz syndrome 5
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C3810012/

Other Diagnosis and Management Resources

- GeneReview: Loeys-Dietz Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1133
- Johns Hopkins Medicine: Diagnosis of Craniosynostosis
  http://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/pediatric_neurosurgery/conditions/craniosynostosis/diagnosis.html
- MedlinePlus Encyclopedia: Aortic Dissection
  https://medlineplus.gov/ency/article/000181.htm
- National Heart Lung and Blood Institute: How Is an Aneurysm Treated?
  https://www.nhlbi.nih.gov/health/health-topics/topics/arm/treatment

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html

- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Aortic Dissection
  https://medlineplus.gov/ency/article/000181.htm
- Encyclopedia: Aortic Dissection (image)
  https://medlineplus.gov/ency/imagepages/18073.htm
- Health Topic: Aortic Aneurysm
  https://medlineplus.gov/aorticaneurysm.html
- Health Topic: Connective Tissue Disorders
  https://medlineplus.gov/connectivetissuedisorders.html
- Health Topic: Osteoarthritis
  https://medlineplus.gov/osteoarthritis.html

Genetic and Rare Diseases Information Center

- Loeys-Dietz syndrome
  https://rarediseases.info.nih.gov/diseases/10788/loeys-dietz-syndrome

Additional NIH Resources

- National Institute of Arthritis and Musculoskeletal and Skin Diseases: Handout on Health: Osteoarthritis
  https://www.niams.nih.gov/health_info/osteoarthritis/

Educational Resources

- Barnes Jewish Hospital
  http://www.barnesjewish.org/Medical-Services/Heart-Vascular/Thoracic-Aortic-Disease/Loeys-Dietz-Aneurysm-Syndrome
- Boston Children's Hospital
  http://www.childrenshospital.org/conditions-and-treatments/conditions/l/loeys-dietz-syndrome
- Centers for Disease Control and Prevention: Aortic Aneurysm Fact Sheet
  https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_aortic_aneurysm.htm

- Cleveland Clinic: Aortic Aneurysm
  http://my.clevelandclinic.org/health/articles/aortic-aneurysm
- Cleveland Clinic: Scoliosis
  http://my.clevelandclinic.org/health/articles/scoliosis
- Disease InfoSearch: Loeys-Dietz Syndrome
  http://www.diseaseinfosearch.org/Loeys-Dietz+Syndrome/4288
- JAMA Patient Page: Aortic Aneurysms
  http://jamanetwork.com/journals/jama/fullarticle/184864
- Johns Hopkins Medicine: Loeys-Dietz Syndrome
  http://www.hopkinsmedicine.org/heart_vascular_institute/conditions_treatments/conditions/loeys_dietz.html
- MalaCards: loeys-dietz syndrome
  http://www.malacards.org/card/loeys_dietz_syndrome
- March of Dimes: Clubfoot
  http://www.marchofdimes.org/baby/clubfoot.aspx
- Merck Manual Home Edition for Patients and Caregivers: Aortic Dissection
  http://www.merckmanuals.com/home/heart-and-blood-vessel-disorders/aneurysms-and-aortic-dissection/aortic-dissection
- My46 Trait Profile
  https://www.my46.org/trait-document?trait=Loeys-Dietz%20syndrome&type=profile
- Orphanet: Loeys-Dietz syndrome
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=60030

Patient Support and Advocacy Resources

- American Heart Association
  http://www.heart.org/HEARTORG/
- Cleft Palate Foundation
  http://www.cleftline.org/
- The Marfan Foundation: Loeys-Dietz Syndrome
  http://www.marfan.org/loeys-dietz

GeneReviews

- Loeys-Dietz Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1133

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22Loeys-Dietz+syndrome%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Loeys-Dietz+Syndrome%5BMAJR%5D%29+AND+%28Loeys-Dietz+syndrome%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

OMIM

- LOEYS-DIETZ SYNDROME 1
  http://omim.org/entry/609192
- LOEYS-DIETZ SYNDROME 2
  http://omim.org/entry/610168
- LOEYS-DIETZ SYNDROME 3
  http://omim.org/entry/613795
- LOEYS-DIETZ SYNDROME 4
  http://omim.org/entry/614816
- LOEYS-DIETZ SYNDROME 5
  http://omim.org/entry/615582

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