Loeys-Dietz Syndrome Core Panel, Sequencing

Loeys-Dietz syndrome (LDS) is a connective tissue disorder causing a wide range of vascular, skeletal, craniofacial, cutaneous, allergic/inflammatory, gastrointestinal, and ocular abnormalities. Pathogenic variants in the *TGFBR1* and *TGFBR2* genes cause most cases of LDS. Quality of life may be significantly affected depending on the type and severity of symptoms, and average life expectancy is decreased due to the risk of arterial aneurysms. The most critical aspect of medical management and screening for individuals with LDS is cardiovascular evaluation in order to monitor risks of aneurysms, dissections, and ruptures. Significant variation in clinical features is common, even among family members with LDS.

Disease Overview

Incidence

Unknown

Symptoms

Vascular	• Aortic dilatation or dissection • Dissections or aneurysms in other arteries • Arterial aneurysm and tortuosity
Musculoskeletal	• Scoliosis • Arachnodactyly • Talipes equinovarus • Joint laxity or contracture • Pectus excavatum or carinatum • Cervical spine malformation and/or instability • Osteoarthritis
Craniofacial	• Hypertelorism • Craniosynostosis • Cleft palate/bifid uvula
Cutaneous	• Translucent, velvety skin, with noticeable veins • Dystrophic scars • Easy bruising • Striae

Tests to Consider

Loeys-Dietz Syndrome Core Panel, Sequencing 3003947

Method: Massively Parallel Sequencing

- Preferred test to diagnose LDS in individuals who meet diagnostic criteria.
- Use to determine if at-risk family members have a *TGFBR1* or *TGFBR2* gene variant when familial variant is unknown and affected relatives are not available for testing.

Familial Targeted Sequencing 3005867

Method: Massively Parallel Sequencing

- Testing for a known familial sequence variant by sequencing gene of interest. A copy of the family member's test result documenting the familial gene variant is REQUIRED.
- To determine if the variant(s) of interest are detectable by this assay, contact an ARUP genetic counselor at 800-242-2787.

Related Tests

Aortopathy Panel, Sequencing and Deletion/Duplication 2006540

Method: Massively Parallel Sequencing

- Preferred panel for individuals with clinical phenotype of aortic or vascular aneurysm, dissection, or rupture if no single specific diagnosis is strongly suspected.

Marfan Syndrome (FBN1) Sequencing and Deletion/Duplication 3004102

Method: Massively Parallel Sequencing

Preferred test to diagnose Marfan syndrome in individuals who meet diagnostic criteria.

Allergic/inflammatory disease	• Seasonal allergies • Asthma • Food allergies • Eosinophilic esophagitis/gastritis • Eczema • Inflammatory bowel disease
Ocular	• Blue sclerae

Diagnostic Criteria

A diagnosis can be established in an individual with no family history of LDS when a pathogenic variant causative for LDS is identified in *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2*, and there is either:

- Aortic root enlargement with a z-score of at least 2.0, type A dissection.

OR

- A combination of craniofacial, skeletal, cutaneous, and vascular findings characteristic of LDS.

In asymptomatic individuals with a positive family history, a diagnosis of LDS can be made based on molecular genetic testing alone.

Genetics

Causative Genes

TGFBR1, *TGFBR2*, *TGFB2*, *TGFB3*, *SMAD2*, and *SMAD3*

Inheritance

Autosomal dominant; 75% of cases are due to de novo variants

Penetrance

Nearly complete

Test Interpretation

Sensitivity/Specificity

Up to 75-85% by sequencing of *TGFBR1* and *TGFBR2*[1]

Analytical Sensitivity/Specificity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Result	Result Description	Interpretive Data
Positive	Pathogenic variant detected	Confirms a diagnosis of LDS in a symptomatic individual
Negative	No variant detected	Reduces risk, but does not exclude a diagnosis of LDS in a symptomatic individual
Inconclusive	Sequence variant of unknown clinical significance may be detected	Uncertain whether variant is causative for LDS

Limitations

- A negative result does not exclude a diagnosis of Loeys-Dietz syndrome or other related disorders.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of *TGFBR1* and *TGFBR2*
  - Regulatory region and deep intronic variants
  - Noncoding transcripts
  - Large deletions/duplications in any of the tested genes
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

References

1. Loeys BL, Dietz HC. Loeys-Dietz syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2021. [Last updated: Mar 2018; Accessed: Jun 2021]

Additional Resources

Pomianowski P, Elefteriades JA. The genetics and genomics of thoracic aortic disease. *Ann Cardiothorac Surg*. 2013;2(3):271-279.

Van Hemelrijk C, Renard M, Loeys B. The Loeys-Dietz syndrome: an update for the clinician. *Curr Opin Cardiol*. 2010;25(6):546-551.

Related Information

Aortopathy Panel, Sequencing and Deletion/Duplication
Marfan Syndrome (FBN1) Sequencing and Deletion/Duplication

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
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