Loeys-Dietz Syndrome (TGFBR1 and TGFBR2)

Variants in the *TGFBR1* and *TGFBR2* genes cause Loeys-Dietz syndrome (LDS). LDS affects connective tissue throughout the body, causing a wide range of vascular, skeletal, craniofacial, cutaneous, allergic/inflammatory, gastrointestinal, and ocular abnormalities. Quality of life may be significantly affected depending on the type and severity of symptoms. Life expectancy is typically shortened due to aortic or vascular aneurysms.

Indications for Ordering

- Confirm clinical diagnosis of LDS
- Determine if at-risk family members have a *TGFBR1* or *TGFBR2* gene variant when
  - Familial variant is unknown
  - Affected relatives are not available for testing

Disease Overview

Incidence

Unknown; seen in all ethnicities

Symptoms

Vascular	• Aortic dilation or dissection • Arterial aneurysm and tortuosity
Musculoskeletal	• Scoliosis • Arachnodactyly • Talipes equinovarus • Joint laxity or contracture • Pectus excavatum or carinatum • Cervical spine malformation and/or instability
Craniofacial	• Hypertelorism • Craniosynostosis • Cleft palate/bifid uvula
Cutaneous	• Translucent, velvety skin • Widened/poorly formed scars • Easy bruising • Striae

- Mean age of death: 26 years due to arterial aneurysms
- Death or uterine rupture from pregnancy in affected individuals: ~50%
- Various clinical presentations have previously been labeled as LDS types 1, 2, and 3
  - LDS now recognized as a clinical continuum; affected individuals can have various combinations of phenotypic features
- Diagnosis of LDS is based on clinical findings and/or by identifying a heterozygous pathogenic variant in *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2*

Tests to Consider

Loeys-Dietz Syndrome (TGFBR1 and TGFBR2) Sequencing 2002705

Method: Polymerase Chain Reaction/Sequencing

Confirm clinical diagnosis of LDS

Related Tests

Aortopathy Panel, Sequencing and Deletion/Duplication 2006540

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

- Preferred panel for individuals with clinical phenotype of aortic or vascular aneurysm, dissection, or rupture if no single specific diagnosis is strongly suspected
- See Aortopathy Panel, Sequencing and Deletion/Duplication Test Fact Sheet for more information

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

Useful when a pathogenic familial variant identifiable by sequencing is known

Genetics

Genes

TGFBR1 and *TGFBR2*

Inheritance

Autosomal dominant

Penetrance

Rare examples of nonpenetrance have been observed

De novo Variants

Approximately 75% of affected individuals

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity: up to 85% for both *TGFBR1* and *TGFBR2*[1]
- Analytical sensitivity/specificity: 99%

Results

Result	Result Description	Interpretive Data
Positive	Pathogenic variant detected in *TGFBR1* or *TGFBR2* gene	Confirms a diagnosis of LDS in a symptomatic individual
Negative	No variant detected in *TGFBR1* or *TGFBR2* gene	Reduces risk, but does not exclude a diagnosis of LDS in a symptomatic individual
Inconclusive	*TGFBR1* or *TGFBR2* sequence variants of unknown clinical significance may be detected	

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not detected
  - Regulatory region and deep intronic variants
  - Large deletions/ duplications of *TGFBR1* and *TGFBR2*
  - Variants in genes other than *TGFBR1* and *TGFBR2*

References

1. Meester JAN, Verstraeten A, Schepers D, et al. Differences in manifestations of Marfan syndrome, Ehlers-Danlos syndrome, and Loeys-Dietz syndrome. Ann Cardiothorac Surg. 2017;6(6):582-594. PubMed

Additional Resources

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

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

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