

Loeys-Dietz Syndrome (*TGFBR1* and *TGFBR2*) Sequencing and Deletion/Duplication

TO CONFIRM A CLINICAL DIAGNOSIS OF LOEYS-DIETZ SYNDROME IN A SYMPTOMATIC INDIVIDUAL OR AT-RISK FAMILY MEMBER

Disease Overview

- Loeys-Dietz syndrome (LDS) is characterized by the following vascular, skeletal, skin, and craniofacial findings:
 - Vascular: thoracic, cerebral, and abdominal arterial aneurysms and/or dissections.
 - Skeletal: scoliosis, arachnodactyly, talipes equinovarus, joint laxity, pectus excavatum, and carinatum.
 - Craniofacial: hypertelorism, craniosynostosis, and cleft palate/ bifid uvula.
 - Cutaneous: translucent, velvety skin, widened/poorly formed scars, and easy bruising.
- LDS is subclassified as either type 1 or type 2 based on whether affected individuals have craniofacial findings (75 percent of cases) or skin findings (25 percent of cases). Since it is now known that LDS types 1 and 2 form a clinical continuum, the subclassifications are less meaningful.
- Diagnosis of LDS is important, as affected individuals benefit from frequent echocardiography to monitor the size of the ascending aorta, evaluations by an orthopedist for severe or progressive scoliosis or cervical spine instability, and avoidance of contact or competitive sports and isometric exercise.
- Mean age of death is 26.1 years due to arterial aneurysms. The risk of death or uterine rupture from pregnancy in affected individuals is ~50 percent.

Epidemiology

Incidence is unknown but does not appear to differ between genders or ethnicities.

Genetics

- Autosomal dominant transmission with near 100 percent penetrance.
- De novo mutations are present in 75 percent of those affected.
- Only mutations in two genes, transforming growth factor beta receptor genes 1 and 2 (*TGFBR1* and *TGFBR2*), are known to be causative.
- 95 percent of mutations causing LDS can be identified by sequencing both *TGFBR1* and *TGFBR2*.
- 75 percent of such mutations occur in *TGFBR2* and 25 percent in *TGFBR1*.
- No phenotypic differences can be observed between individuals with mutations in either gene.
- To date, no individuals affected with LDS have been shown to have a large *TGFBR* gene deletion.

Indications for Ordering

- To confirm a clinical diagnosis of LDS.
- To determine if at-risk family members have a *TGFBR1* or *TGFBR2* mutation when the familial mutation is unknown and affected relatives are not available for testing.

Contraindications

Testing for individuals with a previously identified familial *TGFBR* mutation. To test individuals for a specific mutation, it is more cost-effective to order [Familial Mutation, Targeted Sequencing \(ARUP test #2001961\)](#) and provide a copy of the lab report detailing the familial mutation.

Interpretation

- Identification of a known pathogenic *TGFBR1* or *TGFBR2* mutation in a symptomatic individual confirms a diagnosis of LDS.
- Lack of an identifiable *TGFBR1* or *TGFBR2* mutation in a clinically affected individual decreases, but does not exclude, a diagnosis of LDS. Medical management should rely on clinical findings and family history.
- TGFBR1* or *TGFBR2* sequence variants of unknown clinical significance may be detected by sequencing or deletion/duplication testing.

Methodology

- Bidirectional sequencing of the *TGFBR1* and *TGFBR2* coding regions, intron-exon borders, and promoter; multiplex ligation-dependent probe amplification (MLPA) of the entire *TGFBR1* and *TGFBR2* coding region.
- The clinical sensitivity of sequencing both *TGFBR1* and *TGFBR2* is 95 percent for LDS. Analytical sensitivity and specificity of sequencing are 99 percent.
- The clinical sensitivity for MLPA for large deletions/duplications in *TGFBR1* and *TGFBR2* is unknown. Analytical sensitivity and specificity of MLPA are 90 and 98 percent, respectively.

Limitations

- Deep intronic mutations and some regulatory region mutations are not detected.
- Rare diagnostic errors may occur due to primer- or probe-site mutations.
- Breakpoints of large deletions/duplications detected in *TGFBR1* or *TGFBR2* will not be determined.

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Related Tests

- Loeys-Dietz Syndrome (*TGFBR1&TGFBR2*) Sequencing ([2002705](#))
- Loeys-Dietz Syndrome (*TGFBR1&TGFBR2*) Deletion/Duplication ([2002697](#))

References

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4. Loeys BL, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. *Nat Genet* 2005;37:275–81.
5. Yetman AT, et al. Importance of the clinical recognition of Loeys-Dietz syndrome in the neonatal period. *Pediatrics* 2007;119: e1199–202.

Test Information

2002701 **Loeys-Dietz Syndrome (*TGFBR1&TGFBR2*) Sequencing and Deletion/Duplication**

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.