Loeys-Dietz Syndrome (*TGFBR1* and *TGFBR2*)

Indications for Ordering

- Confirm clinical diagnosis of Loeys-Dietz syndrome (LDS)
- 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

Test Description

Polymerase chain reaction (PCR) and Sanger sequencing of *TGFBR1* and *TGFBR2* genes

- Promoter and coding regions
- Intron/exon boundaries

Tests to Consider

Primary test

Loeys-Dietz Syndrome (*TGFBR1* & *TGFBR2*) Sequencing 2002705

- Confirm clinical diagnosis of LDS

Related tests

Aortopathy Panel, Sequencing and Deletion/Duplication 2006540

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

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

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
- LDS types 1 and 2 form a clinical continuum
  - Subclassifying into either type based on craniofacial finding or skin findings is less meaningful

Risk estimates

- Mean age of death – 26 years due to arterial aneurysms
- Death or uterine rupture from pregnancy in affected individuals – ~50%

Genetics

Genes –*TGFBR1* and *TGFBR2*

Inheritance – autosomal dominant

Penetrance – rare examples of nonpenetrance have been observed

De novo variants – 75% of affected individuals

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – 95% for both *TGFBR1* and *TGFBR2* (Pomianowski, 2013)
- Analytical sensitivity and specificity – 99%

Results

- 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 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

- Loeys BL, Dietz HC. Loeys-Dietz Syndrome. 2008 Feb 28 [Updated 2013 Jul 11]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1133/
- Pomianowski P, Elefteriades JA. The genetics and genomics of thoracic aortic disease. Ann Cardiothorac Surg. 2013;2(3):271-279.
- Van Hemelrijk C, et al. The Loeys-Dietz syndrome: an update for the clinician. Current Opinion in Cardiology. 2010;25(6):546-551.