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, 21 Genes 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

Penetration – rare examples of nonpenetration 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 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