

Loeys-Dietz Syndrome via *TGFBR2* Gene Sequencing (Test #397)

Brief Description of Clinical Features: Loeys-Dietz syndrome (LDS) is characterized by two major clinical features: vascular findings (cerebral, thoracic, and abdominal arterial aneurysms and/or dissections) and skeletal manifestations (pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, talipes equinovarus). Additional variable features include craniofacial abnormalities (ocular hypertelorism, bifid uvula/cleft palate and craniosynostosis) and cutaneous findings (translucent skin, easy bruising and dystrophic scars) (Loeys et al. Nat Genet 37:275-281, 2005). Two clinical entities of LDS have been described (types 1 and 2), which represent a continuum of clinical features. Approximately 75% of patients with LDS type 1 have craniofacial manifestations, while approximately 25% of patients with LDS type 2 have cutaneous manifestations (Loeys et al. 2005; Loeys et al. N Eng J Med 355:788-798, 2006). LDS is usually characterized by aggressive arterial aneurysms (mean age at death 26.1 years) and high incidence of pregnancy-related complications including death and uterine rupture (Loeys et al. 2005). Of particular note, clinical features of LDS overlap with Marfan syndrome (OMIM 154700) (Loeys et al. 2005).

Genetics: LDS is inherited in an autosomal dominant manner. Mutations in the *TGFBR2* gene cause LDS type 1B (LSD1B; OMIM 610168) and type 2B (LSD2B; OMIM 610380) (Mizuguchi et al. Nat Genet 36:855-60, 2004; Loeys et al. 2005). The *TGFBR2* gene encodes a Transforming Growth Factor β (TGF β) receptor. This receptor binds a family of multipotential cytokines that are involved in cellular proliferation, migration and death (Loeys et al. 2005). A mix of missense, nonsense and deletion mutations has been reported in the *TGFBR2* gene (Loeys et al. 2005; Loeys et al. 2006; Sthenur et al. Hum Mutat 29:E284-E295, 2008).

Description of this Particular Test: This test involves bidirectional DNA sequencing of all coding exons (1, 3-8) of the *TGFBR2* gene along with ~50 bases of non coding flanking DNA on each side. As indicated, we will also perform sequencing of any single exon in this gene for family members of patients with known mutations and to confirm research results (\$190 charge).

Reference Sequences: Genomic: NC_000003.11 mRNA: NM_003242.5 Protein: NP_003233.4 (CCDS 2648.1)

Indications for Test: Candidates for this test are patients with symptoms consistent with Loeys-Dietz syndrome and family members of patients who have known *TGFBR2* mutations.

Sensitivity of Test: The prevalence of Loeys-Dietz syndrome is currently unknown. Approximately 25% of LDS cases have an affected parent, while the remaining ~75% of LDS cases as the result of a *de novo* mutations in the *TGFBR1* or *TGFBR2* genes (Loeys et al. 2006).

Turnaround Time: Maximum of 40 days, although many tests are completed in 2 – 3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Prices: Sequencing of *TGFBR2* gene \$ 710

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x11	83898 \$ 190	Sequencing x11	83904 \$ 280
Separation x1	83894 \$ 50	Interpretation/Report x1	83912 \$ 120

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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