Loeys-Dietz syndrome (LDS) is a recently described genetic syndrome, caused by mutations in the TGFBR2 and TGFBR1 genes. LDS is characterized by vascular findings and skeletal manifestations. The TGFBR1 gene codes for a member of the serine/threonine protein kinase family and the TGF-beta receptor subfamily. Mutations in the TGFBR1 gene can affect multiple organ systems. Clinical findings frequently include skeletal, vascular, craniofacial and cutaneous abnormalities. The TGFBR1 gene contains 9 exons and is located at chromosome 9q33-34.

Up to 25% of individuals with a clinical diagnosis of LDS have TGFBR1 mutations. Approximately 75% of individuals with a known or suspected diagnosis of LDS who did not have mutations in TGFBR1 had mutations in TGFBR2. TGFBR1 and TGFBR2 mutations are inherited in an autosomal dominant manner with a variable clinical expression. Approximately 75% of individuals with LDS have an affected parent, and 25% have a de novo mutation. TGFBR1 and TGFBR2 are the only two genes known to cause LDS.

Mutations in TGFBR1 have also been identified in patients with a clinical diagnosis of Ehlers-Danlos syndrome (vascular type), Marfan syndrome and familial thoracic aortic aneurysm. There is significant phenotypic overlap among these conditions and it is possible that upon further clinical evaluation, these patients actually meet diagnostic criteria for LDS.

**Indication**
TGFB1 testing is utilized to confirm a diagnosis of LDS in patients with clinically evident disease. Genetic testing also allows for early identification and diagnosis of individuals at greatest risk prior to the expression of typical clinical manifestations and can be used for prenatal diagnosis. If a mutation is identified in an asymptomatic individual, regular and routine outpatient follow up is indicated. If clinically unaffected members of a family with an identified mutation for LDS are found not to carry that mutation, they can be definitely diagnosed as unaffected and reassured that neither they nor their children will be at higher risk compared to the general population to develop symptoms related to LDS. A negative test result in an individual with a known familial mutation also eliminates the need for routine follow up.
Methodology:

All 9 exons of the TGFBR1 gene, as well as the exon/intron boundaries and a portion of untranslated regions of the gene will be amplified by PCR. Genomic DNA sequences from both forward and reverse directions are obtained by automatic fluorescent detection using an ABI PRISM® 3730 DNA Analyzer. Sequence variants different from National Center for Biotechnology Information GenBank reference will be evaluated for genetic significance. If a mutation is identified, a known familial mutation analysis will be available for additional family members.

Sensitivity & Accuracy:

Greater than 98.5% of the mutations in exon 1-9 of TGFBR1 are detectable by sequence based methods. Sequencing does not detect deletions or duplications. Mutations in TGFBR1 account for approximately 25% of cases of Loeys-Dietz syndrome. Greater than 90% of mutations in exon 1-9 of TGFBR1 are detectable by sequence based methods. Sequencing does not detect deletions or duplications.

References:


Specimen:

Peripheral blood in EDTA tube
Adult: 5-10mL
Child: 3-5mL
Infant: 1-3mL
For other specimen types, please contact Amy Shikany at 513-803-3317

Turnaround Time:

Full Mutation Analysis 2-4 weeks
Known Mutation Analysis 1-2 weeks

CPT Codes:

Full Gene Sequencing 81405
Additional Family Members 81403