Cincinnati Children's
Heart Institute

Heart Institute Diagnostic Lab
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Shipping Instructions

Please enclose a test requisition form with sample. All information must be complete before sample can be processed. Samples may be shipped at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship To:

Cincinnati Children's
Hospital Medical Center
Attn: Heart Institute Diagnostic Lab
240 Albert Sabin Way,
Room S4.381
Cincinnati, OH 45229-3039

TGFBR1 - Loeys-Dietz syndrome Testing

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[1]. 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[2]. 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

TGFBR1 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:

1. Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, Holm T, Meyers J, Leitch CC, Katsanis N, Sharifi N, Xu FL, Myers LA, Spevak PJ, Cameron DE, De Backer J, Hellemans J, Chen Y, Davis EC, Webb CL, Kress W, Coucke P, Rifkin DB, De Paepe AM, Dietz HC. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in *TGFBR1* or *TGFBR2*. *Nature Genetics*. 2005;37:275-281.

2. Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, De Backer JF, Oswald GL, Symoens S, Manouvrier S, Roberts AE, Faravelli F, Greco MA, Pyeritz RE, Milewicz DM, Coucke PJ, Cameron DE, Braverman AC, Byers PH, De Paepe AM, Dietz HC. Aneurysm syndromes caused by mutations in the TGF-Beta receptor. *New England Journal of Medicne*. 2006;355:788-798.

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