Activin A receptor and type II-like 1 (ACVRL1), also known as Activin receptor-like kinase 1 (ALK-1), is a type I cell-surface receptor for the TGF-beta superfamily of ligands. It shares with other type I receptors a high degree of similarity in serine-threonine kinase subdomains, a glycine- and serine-rich region (called the GS domain) preceding the kinase domain and a short C-terminal tail. The ACVRL1 gene is a 10-exon gene with nine coding exons spanning 15kb of genomic distance that was mapped to chromosome 12q11-14. ACVRL1 gene expression is highly restricted to the endothelial cells. ALK-1 and another TGF-beta type I receptor, ALK-5, regulate angiogenesis by controlling TGF-beta signal transduction, and ALK-5 is required for ALK-1 signaling. ALK-1 protein shares similar domain structures with other closely related ALK or activin receptor-like kinase proteins that form a subfamily of receptor serine/threonine kinases, it has been suggested to be implicated in the blood vessel development and repair. Mutations in this gene are associated with both hemorrhagic telangiectasia type 2 (HHT2), also known as Rendu-Osler-Weber syndrome 2 (ORW2), and pulmonary arterial hypertension (PAH). HHT2 is an autosomal dominant multisystemic vascular dysplasia.

The John Welsh Cardiovascular Diagnostic Laboratory offers molecular genetic testing for ACVRL1 mutations. Individuals are tested by DNA sequencing of the coding exons of the ACVRL1 gene. We strongly recommend initial testing of a clearly affected individual, if available, in order to provide the greatest test sensitivity and clearest interpretation of results for subsequent family members. Genetic counseling is recommended for all individuals.

REASONS FOR REFERRAL

Molecular confirmation of the diagnosis of pulmonary arterial hypertension (PAH) and hemorrhagic telangiectasia type 2 (HHT2).

METHODOLOGY

Genomic DNA is analyzed for ACVRL1 mutations by DNA sequencing of the coding exons of the ACVRL1 gene, as well as the exon/intron junctions and a portion of the 3' untranslated region. Patient DNA is sequenced in both the forward and reverse orientations. If a mutation is identified, additional family members are analyzed only for the familial mutation by automatic fluorescent DNA sequencing.

SERVICE FEES

<table>
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<tr>
<th>Index Case (Male or Female)</th>
<th>Direct and Institutional Billing</th>
<th>CPT Codes</th>
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<tr>
<td></td>
<td>$700 per sample</td>
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<tr>
<td>Additional Family Members</td>
<td>$300 per sample; known familial mutation only</td>
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SENSITIVITY

DNA Sequencing Analysis: Approximately 99 percent detection of mutations in the coding exons of ACVRL1.

SPECIMEN REQUIREMENTS

Blood (preferred): EDTA (purple-top) tubes: Adult: 5 cc  Child: 5 cc  Infant: 2-3 cc
Tissue: Frozen (preferred), RNAlater
Other Body Fluids and Formalin-fixed, Paraffin-embedded Tissue: Call to inquire