

Hereditary Hemorrhagic Telangiectasia Type 2 (HHT2) / Osler-Weber-Rendu Disease via *ACVRL1/ALK1* Gene Sequencing (Test #862)

Brief Description of Clinical Features: Hereditary Hemorrhagic Telangiectasia (HHT, OMIM 187300) is a disease of vascular dysplasia. HHT is characterized by the presence of arteriovenous malformations (AVMs) that involve direct connections between arteries and veins with no intervening capillary bed. AVMs can be located throughout the body and have a greater tendency towards rupture than normal blood vessels; this is often visible as telangiectases (small red or purple spots) on the lips, hands, or face of HHT patients. Recurrent nosebleeds are the most common symptom of HHT. About 20-25% of patients develop GI bleeding later in life that may lead to severe anemia (Abdalla et al. *J Med Genet* 40:494-502, 2003). Hepatic AVMs are found in up to 32% of patients and are often asymptomatic, but can cause cirrhosis and affect cardiac output (Plauchu et al. *Am J Med Genet* 32:291, 1989; Garcia-Tsao et al. *New Eng J Med* 343:931, 2000). Cerebral AVMs (5-20% of patients) and Pulmonary AVMs (30-50% of patients) are usually present at birth and may cause headaches, seizures, ischemia, hypoxemia, and hemothorax (see Shovlin and Letarte *Thorax* 54:714-729, 1999). The penetrance of HHT varies depending upon type (see below), and symptoms usually present by age 16 (Porteous et al. *J Med Genet* 29:527, 1992). The severity of HHT can vary widely even within families and can go unnoticed in affected individuals.

Genetics: HHT is an autosomal dominant disorder caused by mutations in genes encoding proteins that modulate the normally inhibitory transforming growth factor (TGF)- β signaling pathway during cell proliferation and differentiation. The incidence of HHT is ~ 1:5-8,000 and affects men, women and all ethnic groups (Govani and Shovlin *Eur J Hum Genet* 17:860, 2009). Mutations in the *ACVRL1/ALK1* gene (OMIM 601284) account for ~ 40% of cases (HHT2; OMIM 600376). *ACVRL1/ALK1* encodes activin receptor like kinase 1 (ALK1) which is a type I receptor in endothelial cells that binds (TGF)- β when coexpressed with a type II receptor (Johnson et al. *Nat Genet* 13:189, 1996). HHT2 generally has a lower penetrance, milder phenotype, later onset of disease, and a higher occurrence of hepatic AVMs, but lower occurrence of pulmonary or cerebral AVMs than HHT1 (Letteboer et al. *J Med Genet* 43:371-377, 2006). Over 300 causative mutations have been identified throughout the *ACVRL1* gene and include primarily missense/nonsense mutations. Large whole or multi-exon deletions and splicing mutations are rare (Prigoda et al. *J Med Genet* 43:722, 2006). No predominant mutation has been identified.

Description of This Particular Test: This test involves bidirectional DNA sequencing of the 9 coding exons of the *ACVRL1* gene plus ~50 bp of flanking non-coding DNA on either side of each exon. We will also sequence any single exon (Test #100, \$190) in family members of patients with known mutations, or to confirm research results.

Reference Sequences: Genomic: NC_000012.11 mRNA: NM_000020.2 Protein: NP_000011.2 (CCDS 31804.1)

Indications for Test: Individuals with frequent nosebleeds, telangiectases, or any degree of GI, pulmonary, or cerebral bleeding.

Sensitivity of Test: Mutations in the *ACVRL1* gene are found in ~ 40% of HHT patients.

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

Specimen Requirements: See page 4 of Requisition Form

Price: Sequencing of *ACVRL1* \$ 690

CPT Codes							
Test	83890 x1	83891 x1	83898 x10	83904 x10	83894 x1	83912 x1	Total
<i>ACVRL1</i>	\$ 30	\$ 40	\$200	\$300	\$ 30	\$ 90	\$690

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

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