SMAD4

Background: Hereditary hemorrhagic telangiectasia (HHT, OMIM 187300), also called Osler-Weber-Rendu disease, is a blood vessel disorder characterized by abnormal, direct connections between arteries and veins. Telangiectases, small abnormal blood vessels, which appear as red spots are often found on the lips, tongue, fingers, intestines, or nose. Larger abnormal blood vessels called arteriovenous malformations (AVMs) can occur in the internal organs, most commonly the lung, liver, spine, gastrointestinal tract, and brain. Bleeding telangiectases in the nose or intestines can be either a minor annoyance or a major medical problem, sometimes requiring transfusions.

Juvenile Polyposis Syndrome (JPS, OMIM 174900, 175050) is an autosomal dominant disease in which individuals are predisposed to hamartomatous polyps and gastrointestinal cancer. In patients with JPS, 20% have been shown to have a mutation in SMAD4.

Some individuals with the combined HHT and JPS carry a mutation in the SMAD4 gene. Approximately 2-3% of individuals with a clinical diagnosis of HHT but no juvenile polyposis have reportedly been found to have a mutation in SMAD4 gene.

Eligibility: Patients who meet the established clinical criteria for HHT (at least 2 of the following): spontaneous and recurrent nosebleeds (epistaxis); multiple mucocutaneous telangiectases at characteristic sites, including lips, oral cavity, fingers, and nose; visceral arteriovenous malformation (AVM) of the lung, brain or spine; a family history of a first-degree relative with a clinical diagnosis of HHT; and a history of GI bleeding.

Patients who meet the diagnostic criteria for Juvenile Polyposis Syndrome (JPS) (5 or more hamartomatous gastrointestinal polyps or any number of polyps in addition to a family history of polyposis).

Once a family member has had a mutation identified, relatives are eligible for site specific testing.

Assay: Direct mutation analysis by full sequencing of SMAD4.

Sensitivity: Approximately 20% of individuals affected with JPS have mutations in the SMAD4 gene. (Reference: The Rate of Germline Mutations and Large Deletions of SMAD4 and BMPR1A in juvenile polyposis. Clinic Genet, 75:79-85, 2009).

Approximately 2-3% of HHT patients who are negative for ENG or ALK1 mutations may have a SMAD4 mutation. (Reference: SMAD4 Mutations Found in Unselected HHT Patients. J. Med.Genet. 43:793-7, 2006).

Full sequencing identifies the mutation >99% of the time. Mutations in non-coding sequences, insertions, deletions or other rearrangements will not be detected by sequencing.

Turnaround: 8-10 weeks for full sequencing
2-3 weeks for familial mutation
7-10 days for prenatal diagnosis of known mutation

Fees: $600 for full sequencing
$360 for known familial mutation
$460 for prenatal diagnosis (cost includes MCC studies)

CPT codes: Full sequencing: 81406
Familial mutation: 81403
Prenatal diagnosis: 81403, 81265