Juvenile Polyposis Syndrome (JPS)  
Including BMPR1A and SMAD4 Gene Analysis

Mendelian Inheritance in Man Number: 174900 (juvenile polyposis syndrome); 175050 (juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome); 601299 (BMPR1A gene); 600993 (SMAD4 gene)

Clinical features:
Juvenile polyps are hamartomatous lesions in the gastrointestinal (GI) tract with a distinct histological appearance of normal epithelium with cystic glands embedded in hyperplastic stroma and inflammatory infiltrate. Juvenile polyps are typically benign, but in individuals with juvenile polyposis syndrome (JPS), there is greater than a 50% risk for malignant transformation. JPS is defined by either the presence of more than five juvenile polyps in the colorectum, or multiple juvenile polyps throughout the GI tract, or any number of juvenile polyps and a positive family history. Clinical features associated with other hamartomatous polyposis syndromes (i.e. PTEN-related disorders, Gorlin syndrome) are not present in JPS.

Pathogenic variants in both the BMPR1A and SMAD4 genes are known to be causative of JPS. Gastric polyps are more frequently observed in patients with SMAD4 pathogenic variants, while pathogenic SMAD4 variants are also associated with a juvenile polyposis syndrome-hereditary hemorrhagic telangiectasia (JPS-HHT) phenotype. The genotype alone cannot predict the phenotype as the same SMAD4 mutations have been reported in patients with isolated JPS as well as JPS-HHT.

A contiguous gene deletion syndrome including the BMPR1A gene and the neighboring PTEN gene on chromosome 10q has been reported in association with juvenile polyposis of infancy, characterized by its early onset and presence of polyps throughout the GI tract. Additionally, macrocephaly, facial dysmorphism, and hypotonia have been observed in these patients.

Inheritance pattern:
Autosomal dominant with high penetrance by the fourth decade of life. Approximately 25% of the mutations identified are de novo.

Genetics:
JPS is known to be caused by germline mutations in the BMPR1A and SMAD4 genes. The BMPR1A gene, on chromosome 10q23.3, is a member of the transforming growth factor β (TGFβ) receptor superfamily. It encodes the bone morphogenic-protein receptor, a serine-threonine kinase, and acts as a tumor suppressor gene upstream of the SMAD4 pathway. The SMAD4 gene, located on chromosome 18q21.1, is a cytoplasmic mediator in the TGFβ signaling pathway. SMAD4 is involved in signal transduction of the TGFβ superfamily by transcriptional activation of target genes. Like the BMPR1A gene, the SMAD4 gene functions as a tumor suppressor.

Reasons for referral:
- Confirmation of a clinical diagnosis
- Differentiation of JPS from other hereditary hamartomatous polyposis syndromes (PTEN-related disorders, Gorlin syndrome)
- Identification of family members at-risk for juvenile polyposis
- To determine an appropriate surveillance and treatment protocol
- Genetic counseling and recurrence risk assessment
- Prenatal diagnosis in families with a known mutation

Test method:
Variant analysis for the BMPR1A and SMAD4 genes is offered as a tiered (reflex testing) test. JPS Tier 1 analysis includes full sequence analysis of the coding region of the SMAD4 gene (exons 2-12) and concurrent deletion/duplication testing for both the SMAD4 and BMPR1A genes. JPS Tier 2 analysis includes full sequence analysis of the complete coding region of the BMPR1A gene (exons 3-13). Pathogenic variants found in the first individual in a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or other appropriate method.
**Variant spectrum**

Nonsense, frameshift, missense, and splice-site variants have been reported in the BMPR1A and SMAD4 genes; pathogenic variants all lead to loss of function in the resultant protein. Partial as well as whole gene deletions have been observed.

**Test sensitivity**

The likelihood of identifying a mutation in either the BMPR1A or SMAD4 genes in an individual with JPS is approximately 49% by sequence and deletion/duplication analysis; 22-25% of mutations are identified in the BMPR1 gene and 26-35% of mutations are identified in the SMAD4 gene, respectively\(^9,16\). The majority of mutations are identified by sequence analysis (11-16% BMPR1A and ~22% in SMAD4) compared to deletion/duplication analysis (4-11% BMPR1A and 4-8% SMAD4)\(^9,16\). Approximately 79% of individuals with JPS-HHT will have a mutation in the SMAD4 gene; approximately 1-2% of patients with only the HHT phenotype are expected to have a mutation in the SMAD4 gene\(^5\).

As performed at GeneDx, JPS Tier 1 analysis is expected to identify a pathogenic variant in approximately 36% of individuals with JPS and JPS Tier 2 analysis is expected to identify a pathogenic variant in up to 16% of individuals with JPS.

**Specimen Requirements and Shipping/Handling:**

- **Blood:** A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- **Buccal Brushes:** We cannot accept buccal brush specimens for this test.
- **Prenatal Diagnosis:** For prenatal testing for a known mutation in the BMPR1A and SMAD4 genes please refer to the specimen requirements table on our website at: http://www.genedx.com/test-catalog/prenatal/. Ship specimen overnight at ambient temperature, using a cool pack in hot weather.

**Required Forms:**

- Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions

For test codes, prices, CPT codes, and turn-around-times, please refer to the “Juvenile Polyposis Syndrome” page on our website: www.genedx.com

**References cited:**