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

**Clinical Features:**

Juvenile polyps are hamartomatous lesions in the gastrointestinal (GI) tract with a distinct histological appearance of normal epithlium 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 a 9-68% risk for malignant transformation.[3] 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.

Variants in both the BMPR1A and SMAD4 genes are known to be causative of JPS. There are no strong genotype-phenotype correlations, although gastric polyps are more frequently observed in patients with SMAD4 gene variants. Variants in the SMAD4 gene are also associated with a juvenile polyposis syndrome-hereditary hemorrhagic telangiectasia (JPS-HHT) phenotype. Once again, the genotype alone can not predict the phenotype as the same SMAD4 variants have been reported in patients with isolated JPS as well as JPS-HHT. [2]

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, digital clubbing, and hypotonia have been observed in these patients. Prognosis is generally poor.

**Genetics**

JPS is autosomal dominant with age-dependent penetrance. Approximately 25% of the variants identified are de novo. JPS is known to be caused by germline variants 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 forms a complex with phosphorylated, receptor-regulated SMAD2 and SMAD3 (not known to be associated with JPS) and relocates from the cytoplasm of the cell to the nucleus, where it helps to regulate the transcription of genes involved in the cell cycle and transcriptional regulation. Like the BMPR1A gene, the SMAD4 gene functions as a tumor suppressor.

Nonsense, frameshift, missense, splice-site, and large deletions have been reported in the BMPR1A and SMAD4 genes. Pathogenic variants all lead to loss of function in the resultant protein. Partial and whole gene deletions have been observed. Note that juvenile polyposis of infancy is due to a contiguous gene deletion of the BMPR1A gene and the neighboring PTEN gene.

**Test Methods:**

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). 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.

**Test Sensitivity:**

The likelihood of identifying a variant in either the BMPR1A or SMAD4 genes in an individual with JPS is approximately 49% by sequence and deletion/duplication analysis; 22-25% of variants are identified in the BMPRA1 gene and 26-35% of variants are identified in the SMAD4 gene.[1,4] The majority of variants are identified by sequence analysis (11-16% BMPR1A and ~22% in SMAD4) compared to deletion/duplication analysis (4-11% BMPR1A and 4-8% SMAD4).[1,4] Approximately 79% of individuals with JPS-HHT will have a variant in the SMAD4 gene; approximately 1-2% of patients with only the HHT phenotype are expected to have a variant in the SMAD4 gene. [2]

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

**References:**

1. Aretz et al., (2007) J Med Genet 44:702-709.
2. Gallione et al., (2010) Am J Med Genet Part A 152A:333-339.
3. Howe et al., (1998) Science 280:1086-1088.
4. Van Hattem et al., (2008) Gut 57:623-627.