BMPR1A and *SMAD4* Gene Analysis in Juvenile Polyposis Syndrome

Disorder Also Known As: Juvenile intestinal polyposis, JPS, JIP

Clinical Features:
Juvenile Polyposis Syndrome (JPS), an autosomal dominant condition predisposing to juvenile polyps in the colorectum, stomach, and small intestine. The term "juvenile" refers to pathological features of the polyp rather than the age of onset of the condition. The phenotype of JPS is often variable among affected members of the same family; therefore, genotype-phenotype correlations are not reliable. Polyp burden varies from a few polyps to over 100, and while most affected individuals have evidence of polyps by age 20, age of onset ranges from the first decade of life to beyond the fourth decade. Most juvenile polyps are benign, but it is possible for them to become malignant. The lifetime risk of gastrointestinal cancer in patients with JPS has been reported to be between 9% and 50%.[1] Specifically, the lifetime risk for colorectal cancer has been estimated to be about 40%, and the gastric cancer risk is estimated to be about 21% in individuals with gastric polyps.[1,2] Cancers of the small bowel and pancreas have also been reported in individuals with JPS.[1,3] Additionally, congenital abnormalities have been described in approximately 15-20% of individuals with JPS.[4]

Family studies have identified *BMPR1A* pathogenic variants in families with Hereditary Mixed Polyposis Syndrome (HMPS), a condition that is associated with the development of juvenile, hyperplastic, and/or mixed polyps,[5,6] as well as in individuals with hereditary non-polyposis colorectal cancer with microsatellite stable tumors.[7–9]

It has been found that *SMAD4* pathogenic variant carriers have higher incidences of gastric polyposis and/or gastric cancer than the JPS population overall.[10,11] A majority of individuals with a germline *SMAD4* pathogenic variant have a combined phenotype of JPS and Hereditary Hemorrhagic Telangiectasia (HHT), a condition characterized by visceral arteriovenous malformations, mucocutaneous telangiectases, recurrent nosebleeds (epistaxis), and intracranial bleeding.[12,13] Connective tissue disorders including aortopathies have been reported in approximately 20-38% of patients with a germline *SMAD4* pathogenic.[13,14]

Inheritance Pattern:
JPS is inherited in an autosomal dominant manner. Approximately 25% of the variants identified are *de novo* (new).[15]

Test Methods:
Using genomic DNA from the submitted specimen, the coding regions and splice junctions of *BMPR1A* and *SMAD4* are PCR amplified and capillary sequencing is performed. Bi directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing or another appropriate method is used to confirm all variants with clinical or uncertain significance. If present, apparently homozygous variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. All sequence alterations are described

according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Concurrent deletion/duplication testing is performed using either exon-level array CGH or MLPA. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat aCGH analysis. The array is designed to detect most single-exon deletions and duplications. Array CGH alterations are reported according to the International System for Human Cytogenetic Nomenclature (ISCN) guidelines. Benign and likely benign variants, if present, are not reported but are available upon request.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of *BMPR1A* and *SMAD4* depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of JPS as outlined above. The likelihood of identifying a variant in either the *BMPR1A* or *SMAD4* genes in an individual with JPS is approximately 45-60% by sequence and deletion/duplication analysis; 22-25% of variants are identified in the *BMPRA1* gene and 22-35% of variants are identified in the *SMAD4* gene.[16–18] The majority of identifiable variants are found by sequence analysis (81-92% of identifiable *BMPR1A* variants and 74-91% of identifiable *SMAD4* variants) compared to deletion/duplication analysis (8-19% of identifiable *BMPR1A* variants and 9-26% of identifiable *SMAD4* variants).[16–18] 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.[15]

DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while array CGH, or MLPA will detect exon-level deletions and duplications. These methods are expected to be greater than 99% sensitive in detecting pathogenic variants identifiable by sequencing or CNV technology.

References:

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