

Juvenile Polyposis: (*SMAD4*) Sequencing and Deletion/Duplication, (*BMPRI1A*) Sequencing and Deletion/Duplication

TO CONFIRM A DIAGNOSIS OF JUVENILE POLYPOSIS SYNDROME (JPS), HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT), OR COMBINED (JP/HHT) SYNDROME

Disease Overview

- JPS is characterized by multiple juvenile (hamartomatous) polyps in the stomach, small intestine, colon, and rectum. The term “juvenile” refers the particular type of hamartomatous polyp, not the age of onset.
- Affected individuals may have a few to hundreds of polyps, and onset varies from childhood to middle age. By age 20, most affected individuals have some polyps.
- The risk of colon cancer with JPS is about 20 percent by age 35 and approaches 70 percent by age 60. The risk for other cancers (e.g., stomach, upper GI tract, and pancreas) is also increased.
- Management of JPS usually involves routine colonoscopy with polypectomy to reduce the risk of bleeding, obstruction, and cancer; occasionally, large numbers of polyps may necessitate removal of the stomach or large intestine.
- At-risk individuals should begin screening by CBC, colonoscopy, and upper endoscopy by age 15. Screening should begin earlier if rectal bleeding, anemia, abdominal pain, constipation, or diarrhea occur.
- HHT is characterized by recurrent nosebleeds, telangiectases (mouth, face, hands, GI tract), and solid organ arteriovenous malformations.
- JP/HHT syndrome is characterized by manifestations of both JPS and HHT.
- If the familial mutation causing any of the above syndromes is known, then DNA testing is recommended in infancy for HHT and JP/HHT or by age 15 for JPS for at-risk relatives.

Epidemiology

Prevalence of JPS is one in 16,000–100,000; prevalence is unknown for JP/HHT syndrome.

Genetics

- Autosomal dominant for JPS, JP/HHT syndrome, and HHT.
- Approximately 25 percent of JPS cases occur due to de novo mutations.

- Penetrance of germline JPS mutations is predicted to be higher than 90 percent for polyp development.
- Mutations in either the *SMAD4* or *BMPRI1A* genes are causative for approximately 50 percent of JPS.
 - Approximately 28 percent of individuals with JPS have *SMAD4* gene mutations; 21 percent are detectable by sequencing and 7 percent by large deletion/duplication testing.
 - Additionally, 24 percent of patients with JPS have *BMPRI1A* mutations, with 18 percent detectable by sequencing and 6 percent identified by large deletion/duplication testing.
- Mutations in *ACVRL1* and *ENG* are causative for at least 85 percent of HHT. *SMAD4* mutations may be responsible for an additional 5–10 percent
- JP/HHT syndrome has only been associated with *SMAD4* gene mutations.

Indications for Ordering

- SMAD4* Sequencing and Deletion/Duplication
 - To confirm a diagnosis of JPS or JP/HHT syndrome in symptomatic individuals.
 - To confirm a diagnosis of HHT in symptomatic individuals if no mutation was previously detected in the *ENG* and *ACVRL1* genes by sequencing and deletion/duplication analysis.
- BMPRI1A* Sequencing and Deletion/Duplication
 - To confirm a diagnosis of JPS syndrome in symptomatic individuals.

Contraindications for Ordering

- Presymptomatic or diagnostic testing when a causative *BMPRI1A* or *SMAD4* mutation has previously been identified in the family. To test individuals for a specific mutation, it is more cost-effective to order Familial Mutation, Targeted Sequencing (ARUP test code 2001961) and provide a copy of the lab report detailing the familial mutation.
- BMPRI1A* testing should not be ordered for HHT, as this gene is not causative for that condition or JP/HHT.
- Prenatal testing.

Interpretation

- For optimal test interpretation, a completed Juvenile Polyposis Patient History Form documenting the patient symptoms and family history of both JPS and HHT is required with sample submission.
- A positive result means a pathogenic gene mutation predicted to cause JPS, JP/HHT syndrome, or HHT was detected.
- A negative result does not rule out JPS, JP/HHT, or HHT due to the possibility of an undetectable *SMAD4* or *BMPRIA* mutation or a mutation in another causative gene(s) not tested. Medical management should rely on clinical findings and family history.
- An uncertain result means that a DNA variant was detected, but it is not known whether this variant is benign or pathogenic. Medical management should rely on clinical findings and family history.

Methodology

- Bidirectional sequencing of the entire *SMAD4* and *BMPRIA* coding regions and intron-exon borders; multiplex ligation-dependent probe amplification (MLPA) for large deletion/duplication analysis.
- Analytic sensitivity and specificity for sequencing are 99 percent.
- Analytic sensitivity and specificity for MLPA are 99 percent and 90 percent, respectively.
- Clinical sensitivity for *SMAD4* sequencing and deletion/duplication is approximately 28 percent for JPS and 5–10 percent for HHT.
- Clinical sensitivity for *BMPRIA* sequencing and deletion/duplication testing is approximately 24 percent for JPS.

Limitations

- Breakpoints of large *SMAD4* or *BMPRIA* deletions/duplications will not be determined.
- *SMAD4* and *BMPRIA* deep intronic or promoter mutations will not be detected.
- Rare diagnostic errors may occur due to primer- or probe-site mutations.
- Genes, other than *SMAD4* or *BMPRIA*, are not tested.

Related Tests

- Juvenile Polyposis (*SMAD4*) Sequencing (0051510): Sensitivity for JPS is 21 percent, 5–10 percent for HHT, and unknown for JP/HHT syndrome.
- Juvenile Polyposis (*SMAD4*) Deletion/Duplication (2001976): Sensitivity for JPS is 7 percent and unknown for HHT and JP/HHT.
- Hereditary Hemorrhagic Telangiectasia (*ACVRL1* and *ENG*) Sequencing and Deletion/Duplication (0051382): Sensitivity is 85 percent for HHT; recommended first test for individuals with symptoms of HHT only.
- Juvenile Polyposis (*BMPRIA*) Sequencing (2004988): sensitivity for JPS is 18 percent.
- Juvenile Polyposis (*BMPRIA*) Deletion/Duplication (2004984): sensitivity for JPS is 6 percent.

References

1. Gallione CJ, et al. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). *Lancet* 2004;363:852–59.
2. Gallione CJ, et al. SMAD4 mutations in unselected HHT patients. *J Med Genet* 2006;43(10):793–7.
3. Howe JR. The prevalence of MADH4 and BMPR1A mutations in juvenile polyposis and absence of BMPR2, BMPR1B, and ACVRL1 mutations. *J Med Genet* 2004;41:484–91.
4. Aretz, S, et al. High proportion of large genomic deletions and a genotype phenotype update in 80 unrelated families with juvenile polyposis syndrome. *J Med Genet* 2007;44:702–9.
5. 6. Van Hattem WA, et al., Large genomic deletions of SMAD4, BMPR1A and PTEN in Juvenile Polyposis. *Gut* 2008;57(5):623–7.

Test Information

2004992 **Juvenile Polyposis (*BMPRIA*) Sequencing and Deletion/Duplication**
2001971 **Juvenile Polyposis (*SMAD4*) Sequencing and Deletion/Duplication**

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.