

# SMAD4 (MADH4) Full Gene Sequencing

*TO CONFIRM A DIAGNOSIS OF HEREDITARY HEMORRHAGIC TELANGIECTASIA AND/OR JUVENILE POLYPOSIS*

## Disease Overview

- Hereditary Hemorrhagic Telangiectasia (HHT):
  - Characterized by recurrent nosebleeds, telangiectases (mouth, face, hands, GI tract), and arteriovenous malformations (lung, brain, liver, spine).
  - AVMs are usually congenital, while nosebleeds and external telangiectases often do not present until the second or third decade of life.
  - Undetected and untreated lung or brain AVMs are a significant cause of morbidity and mortality and may present prior to the onset of recurrent nosebleeds and/or externally apparent telangiectases.
  - Early screening and treatment for internal AVMs can dramatically improve outcome.
- Juvenile Polyposis Syndrome (JPS):
  - Characterized by multiple hamartomatous polyps predisposing to gastrointestinal cancer.

## Epidemiology

Incidence unknown for combined HHT/JPS, 1/5,000-10,000 for HHT, 1/16,000-100,000 for JPS.

## Genetics

- Autosomal dominant for combined HHT/JPS, HHT and JPS.
- De novo mutations are uncommon in HHT, but relatively common in combined HHT/JPS.
- Mutations in the *SMAD4 (MADH4)* gene have been found in:
  - Patients with combined JP/HHT (100 percent, based on small numbers).
  - Patients with HHT, but without reported symptoms of JP (2-3 percent, based on small numbers).
  - Patients with JPS, but without reported symptoms of HHT (~20 percent).

## Indications for Ordering

- Individuals/families with manifestations of both HHT and JPS.
- Individuals with HHT if no mutation is detected in the *Endoglin (ENG)* and *ACVRL1* genes.
- Individuals with JPS.

## Contraindications for Ordering

- Presymptomatic or diagnostic testing for at-risk family members when a causative HHT mutation has previously been identified in the family. In these cases, mutation-specific analysis should be performed; contact ARUP for details on how to order.
- Prenatal testing. Contact ARUP for details on how to order this testing on a fetal specimen.

## Interpretation

- For optimal test interpretation, provide information regarding patient symptoms and family history of HHT and JPS.
  - A positive result means a gene alteration was detected that is predicted to cause HHT and/or JPS.
  - A negative result does not rule out HHT or JPS, due to the possibility of an undetectable mutation in the *SMAD4 (MADH4)* gene or other causative genes that were not tested. Medical management should rely on clinical findings and family history.
  - An uncertain result means that a gene alteration was detected, but it is not certain whether this variation would cause HHT and/or JPS or is merely a benign genetic variant. Medical management should rely on clinical findings and family history.

## Methodology

- The entire coding region and intron-exon borders of the *SMAD4 (MADH4)* gene are bi-directionally sequenced.

## Limitations

- *BMPRIA* gene mutations are not tested; these cause about 20 percent of JPS.
- *ENG* or *ACVRL1* gene mutations are not tested; these are the most common cause of HHT.
- Gene variants of uncertain significance are common.
- Large deletions/duplications or mutations in intronic or regulatory regions are not detected.

## Related Tests

- Hereditary Hemorrhagic Telangiectasia (HHT), Full Gene Analysis (0051382)
- Hereditary Hemorrhagic Telangiectasia (HHT), Full Gene Sequencing (0051381)
- Hereditary Hemorrhagic Telangiectasia (HHT), Deletion & Duplication (0051348)

## References

1. Gallione CJ, et al. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in *MADH4 (SMAD4)*. *The Lancet* 2004;363:852-859.
2. Gallione CJ, et al. *SMAD4* mutations in unselected HHT patients. *J Med Genet* 2006;43(10):793-7.
3. Prigoda NL, et al. Hereditary haemorrhagic telangiectasia: mutation detection, test sensitivity and novel mutations. *J Med Genet* 2006;43(9):722-8.
4. Howe JR. The prevalence of *MADH4* and *BMPRIA* mutations in juvenile polyposis and absence of *BMPR2*, *BMPR1B*, and *ACVRL1* mutations. *J Med Genet* 2004;41:484-491.

## Test Information

**0051510**      *SMAD4 (MADH4) Full Gene Sequencing*

For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).