Juvenile Polyposis *SMAD4* and *BMPR1A* Sequencing and Deletion/Duplication

Indications for Ordering

SMAD4 Sequencing and Deletion/Duplication
- Confirm a diagnosis of juvenile polyposis syndrome (JPS) or JPS/ hereditary hemorrhagic telangiectasia (HHT) syndrome in symptomatic individuals
- Confirm a diagnosis of HHT in symptomatic individuals if no variant was previously detected in the *ENG* and *ACVRL1* genes by sequencing and deletion/duplication

BMPR1A Sequencing and Deletion/Duplication
- Confirm a diagnosis of JPS syndrome in symptomatic individuals

Contraindications for ordering
- Do not use for presymptomatic or diagnostic testing when a causative *BMPR1A* or *SMAD4* variant has previously been identified in the family
  - To test individuals for a specific variant, use the more cost-effective Familial Mutation, Targeted Sequencing test and provide a copy of the lab report detailing the familial variant
- *BMPR1A* testing should not be ordered for HHT
  - Gene is not causative for HHT or JPS/HHT
- Do not use for prenatal testing

Test Description

- Polymerase chain reaction/bidirectional sequencing of the entire *SMAD4* and *BMPR1A* coding regions and intron/exon borders
- Multiplex ligation-dependent probe amplification for large deletion/duplication analysis

Tests to Consider

Primary tests

Juvenile Polyposis (*SMAD4*) Sequencing and Deletion/Duplication 2001971
- Diagnostic and predictive testing for JPS or JPS/HHT

Juvenile Polyposis Syndrome (*BMPR1A*) Sequencing and Deletion/Duplication 2004992
- Diagnostic and predictive testing for JPS

Related tests

Juvenile Polyposis (*SMAD4*) Sequencing 0051510
- Diagnostic and predictive testing for JPS or JPS/HHT

Juvenile Polyposis Syndrome (*BMPR1A*) Sequencing 2004988
- Diagnostic and predictive testing for JPS

Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Prevalence
- JPS – 1/16,000-100,000
- JPS/HHT – unknown

Symptoms

JPS
- Multiple juvenile (hamartomatous) polyps in the stomach, small intestine, colon, and rectum
  - "Juvenile" – refers to particular type of hamartomatous polyp, not age of onset
- Onset varies from childhood to middle age
  - By age 20, most affected individuals have some polyps
- Gastrointestinal (GI) tract cancer risk estimates
  - ~20% by 35 years
  - Approaches 70% by 60 years

HHT
- Recurrent nosebleeds
- Telangiectases (mouth, face, hands, GI tract)
- Brain, lung, and liver arteriovenous malformations
  - Brain arteriovenous malformations are congenital and are at risk to bleed during infancy and early childhood

JPS/HHT
- Characterized by manifestation of both JPS and HHT

Diagnostic issues

DNA testing recommended for individuals with at-risk relatives
- In infancy for JPS/HHT
- By 15 years for JPS

Screening and medical management issues

- Screening/detection
  - Individuals with a variant in either gene should begin GI tract screening by 15 years
    - CBC
    - Colonoscopy (lower endoscopy)
    - Upper endoscopy
  - Screening should begin earlier if rectal bleeding, anemia, abdominal pain, constipation, or diarrhea occur
- Disease management
  - Usually involves routine endoscopy with removal of polyps to reduce risk of bleeding, obstruction, and cancer
  - Occasionally, large numbers of polyps may necessitate removal of a portion of the stomach or intestine

Genetics

Genes – *SMAD4*, *BMPR1A*

Inheritance – autosomal dominant for JPS and JPS/HHT syndrome

Penetrance – germline JPS variants predicted to be >90% for polyp development

De novo variants – 25% of JPS cases

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity
  - *SMAD4* or *BMPR1A* variants are causative for ~50% of JPS
    - 28% of individuals with JPS have *SMAD4* variants
      - 21% detectable by sequencing (Aretz, 2007; Calva-Cerqueira, 2009; van Hattem, 2008)
      - 7% detectable by large deletion/duplication analysis (Aretz, 2007; Calva-Cerqueira, 2009; van Hattem, 2008)
  - 20-25% of patients with JPS have *BMPR1A* variants (Howe, 2004; Sayed, 2002)
    - ~18% detectable by sequencing (Aretz, 2007; Calva-Cerqueira, 2009; Calva-Cerqueira, 2010; van Hattem, 2008)
    - ~4% detectable by large deletion/duplication analysis (Aretz, 2007; Calva-Cerqueira, 2009; van Hattem, 2008)
  - JPS/HHT syndrome
    - Nearly 100% of individuals have a variant in *SMAD4*
      - ~95% detectable by sequencing
      - ~5% detectable by large deletion/duplication analysis
  - *SMAD4* variants are causative for ~1-3% of HHT (Prigoda, 2006)
- Analytical sensitivity/specificity for sequencing and MLPA for *SMAD4* and *BMPR1A* – 99%

Results

- Positive – pathogenic variant detected
  - Predicted to cause JPS, JPS/HHT, or HHT
- Negative – no pathogenic variant detected
  - Does not rule out JPS, JPS/HHT, or HHT due to possibility of undetectable *SMAD4* or *BMPR1A* variants
  - Medical management of patient should rely on clinical findings and family history
- Uncertain
  - Gene variant detected, but whether variant is benign or pathogenic is unclear
  - Medical management of patient should rely on clinical findings and family history
- Juvenile Polyposis Patient History Form documenting patient symptoms and family history of both JPS and HHT is required with specimen submission for optimal test interpretation

Limitations

- Not determined or evaluated
  - Regulatory region or deep intronic variants
  - Breakpoints of large deletions/duplications
  - Variants in genes other than *SMAD4* or *BMPR1A*
- Large deletions/duplications of exons 7 and 8 in *BMPR1A* gene may not be detected
- Diagnostic errors can occur due to rare sequence variations

References

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