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

Penetration – 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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