Juvenile Polyposis *BMPR1A* Sequencing and Deletion/Duplication

Indications for Ordering

Confirm a diagnosis of JPS syndrome in symptomatic individuals

Contraindications for Ordering

- Do not use for presymptomatic or diagnostic testing when a causative *BMPR1A* variant has previously been identified in the family
- *BMPR1A* testing should not be ordered for HHT
  - Gene is not causative for HHT or JPS/HHT

Test Description

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

Tests to Consider

Primary Tests

Juvenile Polyposis Syndrome (*BMPR1A*) Sequencing and Deletion/Duplication 2004992

- Diagnostic and predictive testing for JPS

Related Tests

Familial Mutation, Targeted Sequencing 2001961

- Useful for confirming a diagnosis when a pathogenic sequence variant has been identified in family member
- A copy of the family member's lab report documenting the familial variant is REQUIRED

Deletion/Duplication Analysis by MLPA 3003144

- Useful for confirming a diagnosis when a pathogenic deletion/duplication variant has been identified in family member
- A copy of the family member's lab report documenting the familial variant is REQUIRED

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

Gene: *BMPR1A*

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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
  - *BMPR1A* variants are causative for ~50% of JPS
    - 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)
- Analytical sensitivity/specificity for sequencing and MLPA for *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

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