City of Hope

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Assay Summary

BMPR1A Gene Mutation Analyses

Juvenile polyposis syndrome (JPS) and hereditary mixed polyposis syndrome 2 (HMPS2)

Synopsis

The *BMPR1A* gene (MIM#:601299) encodes the Bone morphogenetic protein receptor type *IA*, a member of the transmembrane serine/threonine kinase family. This family mediates signaling initiated by the TGF-β superfamily, which is involved in the regulation of cellular proliferation of the intestinal lining.[1]
Germline mutations in *BMPR1A* have been identified in 20% of the cases of JPS,[4,5] a condition with reported incidence of 1:16,000-1:100,000.[6] Another 20% of JPS cases have been attributed to *SMAD4,*[1] a gene that codes for a common intracellular mediator of the TGF-β signaling pathways,[2,3] for which we also offer clinical testing.
BMPR1A and *SMAD4* mutations may correlate with polyps with different histological profiles.[1] Regardless of the causal gene, patients with JPS are susceptible to developing gastrointestinal (GI) hamartomatous polyps as early as in infancy, which, if left untreated, may result in bleeding and anemia.[6] Even more importantly, 9%-50% of the families with JPS develop GI cancers, most commonly cancer of the colon, and less often, of the stomach, upper GI and pancreas.[7] By age 35, the incidence of colorectal cancer in the patients with JPS is 17%-22%, approaching 68% by age 60 years.[7] Patients with JPS and a *SMAD4* mutation are more likely to have a family history of upper-GI polyps than are patients with mutations in *BMPR1A* or patients with no known mutations.[6]
BMPR1A mutations also cause HMPS2, which presents with atypical juvenile polyps and predisposition to colonic adenomas and carcinomas.[8] HMPS2, like JPS, shows autosomal dominant inheritance.
About a quarter of the families with positive history of JPS have *de novo* mutations.[6] Approximately 18% of the *BMPR1A* mutations are detectable by sequencing and a further 6% by multiple ligation-based probe amplification assay in patients who are negative for point mutations.[6] Tumor tissues from mutation-positive cases typically also show loss of heterozygosity in *BMPR1A.*[9] Of over 70 pathogenic mutations identified so far, about half are missense or nonsense mutations.[10] Most of these mutations affect the protein kinase domain or, less often, the cysteine-rich extracellular domain.[6] While the penetrance seems virtually complete, variability of expression is considerable, even within families.[6] To date, germline mosaicism has not been reported for JPS.[6]

Indications for testing

1. Individuals meeting diagnostic criteria for JPS
2. Individuals meeting diagnostic criteria for HMPS2
3. Blood relatives of individuals with an identified mutation in BMPR1A. Because surveillance for JPS is recommended as early as at age 15, presymptomatic genetic testing for at-risk relatives in their first two decades of life may be appropriate

Methodology

Sequence analysis: Coding exons and associated intron junctions are captured and enriched using custom Agilent SureSelect technology. Next-generation sequencing is performed on Illumina MiSeq. Additional

Sanger sequencing is performed for any regions with insufficient depth of coverage or for verification of suspect variant calls. Targeted testing for known familial mutation is performed by Sanger sequencing.

***BMPR1A* MLPA analysis**: We have incorporated the SALSA MLPA (multiplex ligation-dependent probe amplification) kit that is a rapid, high throughput technique for copy number quantification, specifically testing for large deletions/duplications of exons 1-13 of the *BMPR1A* gene. This assay should be considered for patients where full gene sequencing did not detect a mutation in the *BMPR1A* gene.

Limitations

For mutation analysis, the method will not detect mutations located in regions of the genes that are not analyzed (selected non-coding exon regions, intron regions other than the splice junctions, and upstream and downstream regions). Some sequence alterations that may be detected (such as those causing missense or synonymous changes) will be of unknown clinical significance. Interpretation of test results should be in the context of the patient's ethnicity, clinical and family histories, and other laboratory test results.

Specimen Requirements

Blood samples: 2 tubes with a total of 6 ccs in ACD (yellow top) or EDTA (lavender top) tubes.
Keep at ambient temperature and ship by overnight courier. Samples must be received in our laboratory within 72 hours of draw.

Note:

i) for infants, a minimum of 3 ccs is sufficient
ii) we accept DNA; at least 10 micrograms is required

Test Request Form (TRF)

a) A completed CMDL TRF is required for each specimen. Please submit the completed TRF with the specimen. Complete testing and billing information must be provided before the specimen is processed.
b) **General Cancer Patient Information Form**: Include a completed General Cancer Patient Information for the proband and a complete pedigree.

Order Codes	*CPT Codes*	*TAT*
BMPR1A-SEQ (BMPR1A gene, full gene sequencing by NGS)	81479, G0452	3 wks
BMPR1A-CAS (BMPR1A gene, targeted mutation analysis, known mutation)	81479, G0452	2 wks
BMPR1A_SMAD4-DEL (BMPR1A and SMAD4 genes, MLPA analysis)	81479, 81405, G0452	3 wks
BMPR1A_SMAD4-DEL-CAS (BMPR1A and SMAD4 genes, MLPA analysis, known deletions/duplications)	81479, 81405, G0452	3 wks

References

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6. Larsen, H.J., et al. 1993. GeneReviews: Juvenile polyposis syndrome.
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NOTE: This test is performed pursuant to a license agreement with Roche Molecular Systems, Inc.