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Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
Gender:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Juvenile Polyposis (SMAD4) Sequencing and Deletion/Duplication

ARUP test code 2001971

SMAD4 FGA Specimen	Whole Blood

JPS (SMAD4) Seq and Del/Dup Interp

Positive *

TEST PERFORMED - 2001971
TEST DESCRIPTION - Juvenile Polyposis (SMAD4) Sequencing and Deletion/Duplication
INDICATION FOR TEST -Not Provided

RESULT
One pathogenic variant was detected in the SMAD4 gene.

DNA VARIANT
Classification: Pathogenic
Gene: SMAD4
Nucleic Acid Change: c.1081C>T; Heterozygous
Amino Acid Alteration: p.Arg361Cys

INTERPRETATION
One pathogenic variant, c.1081C>T; p.Arg361Cys, was detected in the SMAD4 gene by sequencing. This result is consistent with a diagnosis of juvenile polyposis syndrome (JPS); clinical manifestations are variable. This individual's offspring have a 50 percent chance of inheriting the causative variant. No variants were detected by deletion/duplication analysis.

Evidence for variant classification: The SMAD4 c.1081C>T; p.Arg361Cys variant (rs80338963) is reported in the literature in multiple individuals affected with hereditary hemorrhagic telangiectasia (HHT) or juvenile polyposis syndrome (JPS) (Aretz 2007, Gallione 2006, Gallione 2010, Houlston 1998, Woodford-Richens 2001). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. The arginine at amino acid 361 is highly conserved, and functional analyses suggest that this variant exhibits deficient homo-oligomerization and deficient binding to other partner proteins (Shi 1997), which may result in instability and degradation (Woodford-Richens 2001). Additionally, other amino acid substitutions at this codon (Gly, His, Leu, Ser) have been reported in individuals with HHT or JPS and are considered disease-causing (Aretz 2007, Gallione 2010, Howe 2004). Based on available information, the p.Arg361Cys variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic variant

H=High, L=Low, *=Abnormal, C=Critical

(Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Reference Sequence: GenBank # NM_005359.4 (SMAD4)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not included in this report.

REFERENCES
Aretz S et al. High proportion of large genomic deletions and a genotype phenotype update in 80 unrelated families with juvenile polyposis syndrome. J Med Genet. 2007 Nov;44(11):702-9.

Gallione C et al. Overlapping spectra of SMAD4 mutations in juvenile polyposis (JP) and JP-HHT syndrome. Am J Med Genet A. 2010 Feb;152A(2):333-9.

Gallione CJ et al. SMAD4 mutations found in unselected HHT patients. J Med Genet. 2006 Oct;43(10):793-7.

Houlston et al. Mutations in DPC4 (SMAD4) cause juvenile polyposis syndrome, but only account for a minority of cases. Hum Mol Genet. 1998 Nov;7(12):1907-12.

Howe JR et al. The prevalence of MADH4 and BMPR1A mutations in juvenile polyposis and absence of BMPR2, BMPR1B, and ACVR1 mutations. J Med Genet. 2004 Jul;41(7):484-91.

Shi Y et al. A structural basis for mutational inactivation of the tumour suppressor Smad4. Nature. 1997 Jul 3;388(6637):87-93.

Woodford-Richens KL et al. Comprehensive analysis of SMAD4 mutations and protein expression in juvenile polyposis: evidence for a distinct genetic pathway and polyp morphology in SMAD4 mutation carriers. Am J Pathol. 2001 Oct;159(4):1293-300.

This result has been reviewed and approved by Rong Mao, M.D.

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BACKGROUND INFORMATION: Juvenile Polyposis (SMAD4)
Sequencing and Deletion/Duplication
CHARACTERISTICS OF JUVENILE POLYPOSIS SYNDROME (JPS): Gastrointestinal (GI) bleeding, multiple hamartomatous polyps in the GI tract, increased risk for GI carcinoma.
CHARACTERISTICS OF JP/HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT): Recurrent nosebleeds, telangiectases (mouth, face, hands, GI tract), arteriovenous malformations (lung, brain, liver, spine) and hamartomatous polyps in the GI tract.
INCIDENCE: 1 in 16,000 to 1 in 100,000 for JPS; unknown for JP/HHT.
INHERITANCE: Autosomal dominant; de novo mutations occur in 25 percent of JPS.
PENETRANCE: Suspected to be greater than 90 percent for JPS.
CAUSE FOR JPS: Mutations in SMAD4, BMPR1A, and other unknown genes.
CAUSE FOR JP/HHT: Mutations in SMAD4.
CLINICAL SENSITIVITY: Approximately 25 percent for JPS; unknown for JP/HHT.
METHODOLOGY: Bidirectional sequencing of the entire SMAD4 coding region and intron-exon boundaries. Multiplex ligation-dependent probe amplification (MLPA) to detect large SMAD4 coding region delections/duplictions.
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Breakpoints for large deletions/duplications will not be determined. This assay is not designed to detect somatic variants associated with malignancy. Interpretation of this test result may be impacted if the patient has had an allogeneic stem cell transplantation.
Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
SMAD4 FGA Specimen	19-308-107374	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
JPS (SMAD4) Seq and Del/Dup Interp	19-308-107374	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical