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*****Example Report*****

Patient Age/Gender: 40 years Male
Printed: 20-Dec-18 11:18:57

Procedure	Result	Units	Ref Interval	Accession	Collected	Received	Reported/ Verified
CMAVM Specimen	Whole Blood			18-354-900079	20-Dec-18 10:57:00	20-Dec-18 10:57:00	20-Dec-18 11:14:50
CMAVM Interpretation	**Positive *f**			18-354-900079	20-Dec-18 10:57:00	20-Dec-18 10:57:00	20-Dec-18 11:14:50

20-Dec-18 10:57:00 CMAVM Interpretation:
TEST PERFORMED - 3001132
TEST DESCRIPTION - Capillary Malformation-Arteriovenous Malformation (EPHB4 and RASA1) Sequencing and (RASA1) Deletion/Duplication
INDICATION FOR TEST - Confirm Diagnosis

RESULT
One pathogenic variant was detected in the RASA1 gene.

DNA VARIANT
Classification: Pathogenic
Gene: RASA1
Nucleic Acid Change: c.431_438delCCCCTTTG; Heterozygous
Amino Acid Alteration: p.Pro144fs

INTERPRETATION
One pathogenic variant, c.431_438delCCCCTTTG; p.Pro144fs, was detected in the RASA1 gene by sequencing. This result is consistent with a diagnosis of a RASA1-related disorder, including capillary malformation-arteriovenous malformation syndrome type 1 (CM-AVM1); clinical manifestations are variable. This individual's offspring have a 50 percent chance of inheriting the causative variant.

No pathogenic variants were detected in the EPHB4 gene by sequencing. No pathogenic variants were detected in the RASA1 gene by deletion/duplication analysis.

Evidence for variant classification: The RASA1 c.431_438delCCCCTTTG; p.Pro144fs variant, to our knowledge, is not reported in the medical literature or gene specific databases. This variant causes a frameshift by deleting 8 nucleotides, so it is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, the p.Pro144fs 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 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Reference Sequence: GenBank # NM_004444.4 (EPHB4), # NM_002890.1 (RASA1)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Benign variants are not included in this report but are available upon request.

This result has been reviewed and approved by Pinar Bayrak-Toydemir, M.D., Ph.D.

20-Dec-18 10:57:00 CMAVM Interpretation:
BACKGROUND INFORMATION: Capillary Malformation-Arteriovenous Malformation (EPHB4 and RASA1) Sequencing and (RASA1) Deletion/Duplication
CHARACTERISTICS: Multifocal, randomly distributed, capillary malformations (CM) of the skin that may be associated with a fast-flow lesion, such as arteriovenous malformations (AVM) or arteriovenous fistula. Fast-flow lesions in the skin, muscle, bone, or central nervous system can cause life-threatening complications such as bleeding, congestive heart failure, or neurological consequences. Capillary malformation-arteriovenous malformation syndrome type 1 (CM-AVM1) is caused by RASA1 pathogenic variants; capillary malformation-arteriovenous malformation syndrome type 2 (CM-AVM2) is caused by EBHB4 pathogenic variants.
INCIDENCE: Estimated at 1 in 20,000 for CM-AVM1 and 1 in 12,000 for CM-AVM2.

INHERITANCE: Autosomal dominant; approximately one-third of RASA1 pathogenic variants are de novo.
PENETRANCE: 90-95 percent.
CAUSE: Pathogenic RASA1 and EPHB4 variants.
CLINICAL SENSITIVITY: Not well-established, but at least 65 percent.
METHODOLOGY: Bidirectional sequencing of all coding regions and intron-exon boundaries of the EPHB4 and RASA1 genes; Multiplex Ligation-dependent Probe Amplification (MLPA) to detect large RASA1 deletions/duplications.
ANALYTICAL SPECIFICITY AND SENSITIVITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region variants and deep intronic variants will not be detected. Large deletions/duplications will not be detected in EPHB4. The breakpoints of large RASA1 deletions/duplications will not be determined.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS