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

Patient Age/Gender: 35 years Female
Printed: 20-Dec-18 11:18:38

Procedure	Result	Units	Ref Interval	Accession	Collected	Received	Reported/ Verified
CMAVM EPHB4 FGS Specimen	Whole Blood			18-354-900081	20-Dec-18 10:58:00	20-Dec-18 11:09:00	20-Dec-18 11:12:05
CMAVM EPHB4 FGS Interpretation	**Positive *f**			18-354-900081	20-Dec-18 10:58:00	20-Dec-18 11:09:00	20-Dec-18 11:12:05

20-Dec-18 10:58:00 CMAVM EPHB4 FGS Interpretation:
TEST PERFORMED - 3001129
TEST DESCRIPTION - EPHB4-Related Disorders (EPHB4) Sequencing
INDICATION FOR TEST - Confirm Diagnosis

RESULT
One pathogenic variant was detected in the EPHB4 gene.

DNA VARIANT
Classification: Pathogenic
Gene: EPHB4
Nucleic Acid Change: c.1180C>T; Heterozygous
Amino Acid Alteration: p.Arg394Ter

INTERPRETATION
One pathogenic variant, c.1180C>T; p.Arg394Ter, was detected in the EPHB4 gene by sequencing. This result is consistent with a diagnosis of an EPHB4-related disorder, such as capillary malformation-arteriovenous malformation type 2 (CM-AVM2) syndrome; clinical manifestations are variable. This individual's offspring have a 50 percent chance of inheriting the causative variant.

Evidence for variant classification: The EPHB4 c.1180C>T; p.Arg394Ter variant, to our knowledge, is not reported in the medical literature or gene specific databases. This variant is also absent from general population databases (1000 Genomes Project, Exome Variant Server, and Genome Aggregation Database), indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Though the EPHB4 c.1180C>T; p.Arg394Ter variant has not been reported, one study reported downstream truncating variants in EPHB4 in patients with capillary malformation-arteriovenous malformation (Amyere 2017). Based on available information, this 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)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Benign variants are not included in this report but are available upon request.

REFERENCES
Amyere M et al. Germline Loss-of-Function Mutations in EPHB4 Cause a Second Form of Capillary Malformation-Arteriovenous Malformation (CM-AVM2) Deregulating RAS-MAPK Signaling. Circulation. 2017 Sep 12;136(11):1037-1048.

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

20-Dec-18 10:58:00 CMAVM EPHB4 FGS Interpretation:
BACKGROUND INFORMATION: Capillary Malformation-Arteriovenous Malformation (CM-AVM)
CHARACTERISTICS: Multifocal, randomly distributed, capillary malformations (CM) 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 EPHB4 pathogenic variants.

INCIDENCE: Estimated at 1 in 20,000 for CM-AVM1 and 1 in 12,000 for CM-AVM2.
INHERITANCE: Autosomal dominant.
PENETRANCE: 90-95 percent.
CAUSE: Pathogenic EPHB4 or RASA1 gene variants.
GENE TESTED: EPHB4 only.
CLINICAL SENSITIVITY: Not well established, at least 15 percent.
METHODOLOGY: Bidirectional sequencing of all coding regions and intron-exon boundaries of the EPHB4 gene.
ANALYTICAL SPECIFICITY AND SENSITIVITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region variants, deep intronic variants, and large deletions/duplications will not be detected. Variants in genes other than EPHB4 are not detected.

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