ARUP LABORATORIES
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Tracy I. George, MD, Chief Medical Officer

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

Physician: Doctor, Example

Patient: Patient, Example

DOB	11/2/2011
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Capillary Malformation-Arteriovenous Malformation 2 (EPHB4) Sequencing

ARUP test code 3001129

CMAVM EPHB4 FGS Specimen	Whole Blood

CMAVM EPHB4 FGS Interpretation

Negative

TEST PERFORMED - 3001129
TEST DESCRIPTION - EPHB4-Related Disorders (EPHB4) Sequencing
INDICATION FOR TEST - Confirm Diagnosis

RESULT
No pathogenic variants were detected in the EPHB4 gene.

INTERPRETATION
According to information provided to ARUP, this individual has multiple capillary malformations. No pathogenic EPHB4 gene variants were detected by sequencing of all coding regions and intron-exon boundaries. This result decreases the likelihood, but does not exclude a diagnosis of EPHB4-related disorders such as capillary malformation-arteriovenous malformation type 2 (CM-AVM2) syndrome or other EPHB4-related vascular malformations. Please refer to the background information included in this report for the clinical sensitivity and limitations of this test.

RECOMMENDATIONS
Medical screening and management should rely on clinical findings and family history. Genetic consultation is recommended. Prior testing for this patient with ARUP's Vascular Malformations Panel, Sequencing and Deletion/Duplication in 2018 did not reveal any pathogenic variants (see ARUP accession 18-333-400288). However, if there is still strong clinical suspicion for a hereditary vascular malformations disorder, consideration may be given to re-ordering this panel, as it now includes analysis of additional genes that were not tested previously (see ARUP test code 2007384).

COMMENTS
Reference Sequence: GenBank # NM_004444.4 (EPHB4)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not reported.

This result has been reviewed and approved by Steven Steinberg, Ph.D.

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

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
CMAVM EPHB4 FGS Specimen	20-140-400358	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
CMAVM EPHB4 FGS Interpretation	20-140-400358	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