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** | 10/22/1986 |
| **Gender:** | Female |
| **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 | **Positive** | * |

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

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.1423-6G>A; Heterozygous

INTERPRETATION
One pathogenic variant, c.1423-6G>A, 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.1423-6G>A variant (rs762817852) is reported in the literature in individuals affected with capillary malformation-arteriovenous malformation 2, including one de novo occurence (Amyere 2017, Wooderchak-Donahue 2019). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. This is an intronic variant in a weakly conserved nucleotide, but computational analyses (Alamut v.2.11) predict that this variant may impact splicing by creating a novel cryptic acceptor splice site. Functional analyses demonstrate mRNA with an insertion of 4 nucleotides of intronic sequence resulting in a frameshift (p.Gly475Thrfs*39) (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.
Likely benign and benign variants are not included in this report.

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.
Wooderchak-Donahue WL et al. Phenotype of CM-AVM2 caused by variants in EPHB4: how much overlap with hereditary hemorrhagic telangiectasia (HHT)? Genet Med. 2019 Sep;21(9):2007-2014.

This result has been reviewed and approved by Yuan Ji, Ph.D.

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 | 20-038-402045 | 00/00/0000 00:00 | 00/00/0000 00:00 | 00/00/0000 00:00 |
| CMAVM EPHB4 FGS Interpretation | 20-038-402045 | 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**