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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	5/4/2011
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Vascular Malformations Panel, Sequencing and Deletion/Duplication

ARUP test code 2007384

Vascular Malformations Panel Specimen: Whole Blood

Vascular Malformations Panel Interp: Positive

RESULT
One likely pathogenic variant was detected in the EPHB4 gene.

LIKELY PATHOGENIC VARIANT
Gene: EPHB4 (NM_004444.5)
Nucleic Acid Change: c.1638del; Heterozygous
Amino Acid Alteration: p.Val547TrpfsTer57
Inheritance: Autosomal Dominant

INTERPRETATION
One likely pathogenic variant, c.1638del; p.Val547TrpfsTer57, was detected in the EPHB4 gene by massively parallel sequencing. Pathogenic germline variants in EPHB4 are inherited in an autosomal dominant manner and are associated with capillary malformation-arteriovenous malformation 2 (CM-AVM2; MIM: 618196) and lymphatic malformation 7 (MIM: 617300, OMIM(R)). This result is consistent with a diagnosis of vascular malformation. This individual's offspring have a 50 percent chance of inheriting the likely pathogenic variant.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification:
The EPHB4 c.1638del; p.Val547TrpfsTer57 variant, to our knowledge, is not reported in the medical literature or gene specific databases. This variant is also absent from the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. This variant causes a frameshift by deleting a single nucleotide, so it is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be likely 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 likely pathogenic EPHB4 variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical

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

limitations:
ACVRL1(NM_000020.3) intron 9
FAT4(NM_024582.5) intron 5

REFERENCES
OMIM(R) Copyright (C) 1996 - Present year, Johns Hopkins University All rights reserved.

This result has been reviewed and approved by [redacted]
BACKGROUND INFORMATION: Vascular Malformations Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Pathogenic variants in vascular malformation genes lead to defects of blood vessels, causing fast-flow or slow-flow lesions, shunting, swelling, or skin findings. For some disorders, this may lead to potentially life-threatening hemorrhage, stroke, or heart failure.

EPIDEMIOLOGY: The prevalence of hereditary hemorrhagic telangiectasia (HHT) is estimated to be 1 in 5,000 to 1 in 10,000; familial cerebral cavernous malformation (CCM) is 1 in 2,000 to 1 in 10,000; RASA1-CM-AVM is approximately 1 in 20,000; EPHB4-CM-AVM is approximately 1 in 12,000; PTEN hamartoma tumor syndrome is 1 in 200,000; and AKT1-related proteus syndrome is less than 1 in 1,000,000.

INHERITANCE: Autosomal dominant and/or autosomal recessive, depending on the causative gene

PENETRANCE: All conditions exhibit age-related penetrance.

GENES TESTED: ACVRL1, AKT1, BMPR2, CCBE1, CCM2*, EIF2AK4, ELMO2, ENG*, EPHB4, FAT4, FLT4*, FOXC2, GATA2, GDF2, GJC2*, GLMN*, KCNK3, KRIT1, PDCD10, PIEZO1*, PTEN*, RASA1, SMAD4, SMAD9, SOX18*, STAMBP*, TEK, VEGFC

* - One or more exons are not covered by sequencing and/or deletion/duplication analysis for the indicated gene; see limitations section below.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes (including the 5' UTR of ENG, a region of ACVRL1 intron 9 encompassing the CT-rich variant hotspot region, and selected PTEN promoter variants), followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a heritable vascular malformation disorder. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes, unless otherwise noted in the methodology section above. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be

identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) variants, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
CCM2(NM_001363458) exon(s) 7
CCM2(NM_001363459) exon(s) 6
FLT4(NM_001354989) exon(s) 30
GJC2(NM_020435) partial exon(s) 2(Chr1:228346380-228346419)
PTEN(NM_000314) exon(s) 9
PTEN(NM_001304717) exon(s) 10
PTEN(NM_001304718) exon(s) 9
SOX18(NM_018419) partial exon(s) 1(Chr20:62680707-62680791)
STAMBP(NM_001353969) exon(s) 10
STAMBP(NM_001353970) exon(s) 11
STAMBP(NM_001353976) exon(s) 10

Single exon deletions/duplications will not be called for the following exons:
CCM2(NM_001363458) 7; CCM2(NM_001363459) 6; ENG(NM_001114753) 1; ENG(NM_000118) 1; FLT4(NM_001354989) 30; GLMN(NM_053274) 16; GLMN(NM_001319683) 15; PIEZO1(NM_001142864) 1,25,47; PTEN(NM_000314) 9; PTEN(NM_001304717) 1,10; PTEN(NM_001304718) 9; STAMBP(NM_001353969) 10; STAMBP(NM_001353970) 11; STAMBP(NM_001353976) 10

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Vascular Malformations Panel Specimen	24-335-400019	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Vascular Malformations Panel Interp	24-335-400019	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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