Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: arup, arup

Patient: Test, CMAVM NGS Pos

DOB
Sex: Male
Patient Identifiers: 44265
Visit Number (FIN): 44592
Collection Date: 11/15/2022 11:22

Capillary Malformation-Arteriovenous Malformation (CM-AVM) Panel, Sequencing and Deletion/Duplication

ARUP test code 3003634

CMAVM Specimen	Whole Blood
CMAVM Interp	Positive

RESULT
One pathogenic variant was detected in the RASA1 gene.

PATHOGENIC VARIANT
Gene: RASA1 (NM_002890.2)
Nucleic Acid Change: c.2035C>T; heterozygous
Amino Acid Alteration: p.Arg679Ter
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.2035C>T; p.Arg679Ter, was detected in the RASA1 gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic RASA1 variants are inherited in an autosomal dominant manner and are associated with capillary malformation-arteriovenous malformation 1 (CM-AVM1; MIM: 608354). This result is consistent with a diagnosis of a RASA1-related disorder; clinical manifestations are variable. This individuals offspring have a 50 percent chance of inheriting the 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 RASA1 c.2035C>T; p.Arg679Ter variant (rs1554049394) is reported in the literature in multiple individuals affected with capillary malformation-arteriovenous malformation (CM-AVM) (Lacalm, 2018; Revencu, 2013; Wooderchak-Donahue, 2018). This variant is absent from general population databases (Exome Variant Server, 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. Based on available information, this variant is considered 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 pathogenic RASA1 variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Likely benign and benign variants are not reported.

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

Variants in the following region(s) may not be detected with sufficient confidence in this sample due to technical limitations:
NONE

REFERENCES
Lacalm A, et al. Prenatal diagnosis of cerebral and extracerebral high-flow lesions revealing familial capillary malformation-arteriovenous malformation (CM-AVM) syndrome. Ultrasound Obstet Gynecol. 2018;51(3):409-411.

Revencu N, et al. RASA1 mutations and associated phenotypes in 68 families with capillary malformation-arteriovenous malformation. Hum Mutat. 2013;34(12):1632-1641.

Wooderchak-Donahue WL, et al. Expanding the clinical and molecular findings in RASA1 capillary malformation-arteriovenous malformation. Eur J Hum Genet. 2018;26(10):1521-1536.

This result has been reviewed and approved by Pinar Bayrak-Toydemir, MD, PhD

BACKGROUND INFORMATION: Capillary Malformation-Arteriovenous Malformation (CM-AVM) Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Multifocal, randomly distributed, capillary malformations (CMs) of the skin that may be associated with a fast-flow lesion, such as arteriovenous malformations (AVMs) 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. Type 1 (CM-AVM1) is caused by pathogenic variants in the RASA1 gene; CM-AVM type 2 (CM-AVM2) is caused by pathogenic variants in the EPHB4 gene.

EPIDEMIOLOGY: Prevalence is estimated at 1 in 20,000 for CM-AVM1 and 1 in 12,000 for CM-AVM2.

CAUSE: Pathogenic germline variants in the EPHB4 or RASA1 genes

INHERITANCE: Autosomal dominant. De novo variants account for approximately 30 percent of pathogenic variants in RASA1 and 20 percent in EPHB4. Somatic mosaicism has been reported.

PENETRANCE: 90-99%

CLINICAL SENSITIVITY: Not well established, but at least 60 percent

GENES TESTED: EPHB4 (NM_004444); RASA1 (NM_002890)

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, 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/SPECIFICITY: 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 diagnosis of CM-AVM syndrome. This test only detects variants within the coding regions and intron-exon boundaries of the EPHB4 and RASA1 genes. 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) mutations, 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.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. 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
CMAVM Specimen	22-319-106023	11/15/2022 11:22:00 AM	11/15/2022 11:22:23 AM	11/15/2022 11:25:00 AM
CMAVM Interp	22-319-106023	11/15/2022 11:22:00 AM	11/15/2022 11:22:23 AM	11/15/2022 11:25:00 AM

END OF CHART

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