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Tracy I. George, MD, Chief Medical Officer

Patient Report

Client: UU University Division Validation
50 N. Medical Drive
Salt Lake City, UT 84132-
USA

Provider: 1 -TEST,

Patient: **OME, CMAVM CERT2**
DOB:
Gender: Unknown
Patient Identifiers: 558165
Visit Number (FIN): 581319
Client Supplied ID:

Specimen Collected: 23-Dec-20 10:10

CMAVM NGS, DelDup **|Received: 23-Dec-20 10:10** **Report/Verified: 23-Dec-20 15:01**

	Result	Units	Reference Interval
CMAVM Specimen	See Note		
CMAVM Interp	Positive f1 i1		

Result Footnote

f1: CMAVM Interp

INDICATION FOR TESTING
Confirm a diagnosis of capillary malformation-arteriovenous malformation (CM-AVM).

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 individual’s offspring have a 50 percent chance of inheriting the pathogenic variant.

No additional pathogenic variants were identified in the EPHB4 or RASA1 genes by massively parallel sequencing or by deletion/duplication analysis of the RASA1 gene. Please refer to the background information included in this report for 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 Mutation, Targeted Sequencing, ARUP test code 2001961).

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H=High, i=Test Information, L=Low, t=Interpretive Text, @=Performing Lab

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Result Footnote

f1: CMAVM Interp
COMMENTS
Likely benign and benign variants are not included in this report.

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 Mar;51(3):409-411.

This result has been reviewed and approved by [redacted]

Test Information

i1: CMAVM Interp
BACKGROUND INFORMATION: Capillary Malformation-Arteriovenous Malformation (CM-AVM) Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Multifocal, randomly distributed, capillary malformations (CM) of the skin 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. 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 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 33 percent of pathogenic variants in RASA1 and 20 percent in EPHB4. Somatic mosaicism has been reported.
PENETRANCE: 90-99 percent%
CLINICAL SENSITIVITY: Not well established but at least 65 percent.
GENES TESTED: EPHB4** (NM_004444), RASA1 (NM_002890)
** - Deletion/duplication detection is not available for this gene.
METHODOLOGY: Multiplex ligation-dependent probe amplification (MLPA) of the RASA1 gene. Capture of all coding exons and exon-intron junctions of the EPHB4 and RASA1 genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.
ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity for MLPA is greater than 99 percent. The analytical sensitivity of sequencing is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for

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insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. 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. Large deletions/duplications in EPHB4 are not assessed. Regulatory region variants and deep intronic variants will not be identified and breakpoints of large deletions/duplications will not be determined. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level mosaic or somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding 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 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.