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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/31/1752
Sex:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Cerebral Cavernous Malformation Panel, Sequencing and Deletion/Duplication

ARUP test code 3002286

Cerebral Cavernous Malformation Specimen	Whole Blood
Cerebral Cavernous Malformation Interp	Positive

RESULT
One pathogenic variant was detected in the KRIT1 gene.

PATHOGENIC VARIANT
Gene: KRIT1 (NM_194456.1)
Nucleic Acid Change: c.1363C>T; Heterozygous
Amino Acid Alteration: p.Gln455Ter
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.1363C>T; p.Gln455Ter, was detected in the KRIT1 gene by massively parallel sequencing. Pathogenic KRIT1 variants are inherited in an autosomal dominant manner, and are associated with cerebral cavernous malformations (MIM: 116860, OMIM(R)). This result is consistent with a diagnosis of familial cerebral cavernous malformation (FCCM). This individual's future 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 KRIT1 (CCM1) c.1363C>T; p.Gln455Ter variant (rs267607203, ClinVar Variation ID: 5721), also known as 742C>T or as the Common Hispanic Mutation, is an established founder variant in Hispanic families of Spanish and Mexican descent affected with cerebral cavernous malformations (Choquet 2014, Sahoo 1999). This variant is only observed on one allele in the Genome Aggregation Database (v2.1.1), 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 to be pathogenic.

RECOMMENDATIONS
Genetic and neurological consultations are indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic KRIT1 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

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

with sufficient confidence in this sample due to technical limitations: None

REFERENCES

Choquet H et al. Association of cardiovascular risk factors with disease severity in cerebral cavernous malformation type 1 subjects with the common Hispanic mutation. Cerebrovasc Dis 2014; 37:57-63. PMID: 24401931.
Sahoo T et al. Mutations in the gene encoding KRIT1, a Krev-1/rap1a binding protein, cause cerebral cavernous malformations (CCM1). Hum Mol Genet 1999; 8(12):2325-2333. PMID: 10545614.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Cerebral Cavernous Malformation Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Cerebral cavernous malformations (CCMs) are vascular malformations occurring in the brain or other CNS locations, which involve closely clustered, enlarged capillary channels without normal intervening brain parenchyma. CCMs do not always cause clinical symptoms, but may result in intracranial hemorrhage, seizures, headaches, or focal neurological deficits without intracranial bleed. Familial CCM (FCCM) is defined by the presence of multiple CCMs, a single CCM and at least one family member with one or more CCM, or a pathogenic heterozygous variant in one of the associated genes (CCM2, KRIT1, or PDCD10).

EPIDEMIOLOGY: CCMs occur in approximately 0.4-0.5 percent of the general population. FCCM is estimated to occur in 1:2,000 to 1:10,000 individuals. Up to 20 percent of all CCMs are familial.

CAUSE: Pathogenic germline variants in CCM2, KRIT1, or PDCD10

INHERITANCE: Autosomal dominant with reduced penetrance

PENETRANCE: Up to 50 percent of individuals with a molecular diagnosis of FCCM remain clinically asymptomatic.

CLINICAL SENSITIVITY: 85-95 percent for FCCM

GENES TESTED: CCM2, KRIT1, PDCD10

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 were 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 FCCM. This test only detects variants within the coding regions and intron-exon boundaries of the targeted 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 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
Cerebral Cavernous Malformation Specimen	25-174-101013	6/23/2025 8:07:00 AM	6/23/2025 8:08:38 AM	6/23/2025 9:01:00 AM
Cerebral Cavernous Malformation Interp	25-174-101013	6/23/2025 8:07:00 AM	6/23/2025 8:08:38 AM	6/23/2025 9:01:00 AM

END OF CHART

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