

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

Physician: Doctor, Example

Patient: Patient, Example

DOB: 10/23/1938
Gender: Female
Patient Identifiers: 01234567890ABCD, 012345
Visit Number (FIN): 01234567890ABCD
Collection Date: 00/00/0000 00:00

Cerebral Cavernous Malformation Panel, Sequencing and Deletion/Duplication

ARUP test code 3002286

Cerebral Cavernous Malformation Specimen whole Blood

Cerebral Cavernous Malformation Interp

Negative

RESULT

No pathogenic variants were detected in any of the genes tested.

INTERPRETATION

No pathogenic variants were identified by massively parallel sequencing of the coding regions and exon-intron boundaries of the genes tested. No large exonic deletions and duplications were identified in the genes tested. This result decreases the likelihood of, but does not exclude, a heritable form of cerebral cavernous malformation. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

RECOMMENDATIONS

Medical screening and management should rely on clinical findings and family history. Genetic consultation is recommended. Consideration may be given to additional analysis for single exon deletions via a different methodology, as this assay has reduced analytical sensitivity for these variants.

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 limitations; reportable variants are confirmed by Sanger sequencing:

NONE

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).

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

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

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

INHERITANCE: Autosomal dominant with reduced penetrance

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

CLINICAL SENSITIVITY: 85-95% for FCCM

GENES TESTED: CCM2*, KRIT1, PDCD10

*One or more exons are not covered by deletion/duplication analysis for this gene; see limitations section below.

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.

Single exon deletions/duplications will not be called for the following exons:

CCM2 (NM_001363458) 7; CCM2 (NM_001363459) 6

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or

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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
Cerebral Cavernous Malformation Specimen	22-286-400194	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Cerebral Cavernous Malformation Interp	22-286-400194	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

Unless otherwise indicated, testing performed at: