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Patient Report

Patient Age/Gender: 75 years Male

Specimen Collected: 14-Apr-20 14:05

Cerebral Cavernous Malformation |Received: 14-Apr-20 14:05 Report/Verified: 14-Apr-20 17:19

	Result	Units	Reference Interval
Cerebral Cavernous Malformation Specimen	DNA		
Cerebral Cavernous Malformation Interp	Positive f1 i1		

Result Footnote

f1: Cerebral Cavernous Malformation Interp

INDICATION FOR TESTING
Confirm diagnosis.

RESULT
One pathogenic variant was detected in the CCM2 gene.

PATHOGENIC VARIANT
Gene: CCM2 (NM_031443.3)
Nucleic Acid Change: c.71delG; Heterozygous
Amino Acid Alteration: p.Gly24fs
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.71delG; p.Gly24fs, was detected in the CCM2 gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic variants in CCM2 are associated with autosomal dominant cerebral cavernous malformation (MIM: 603284). This result is consistent with a diagnosis of familial cerebral cavernous malformation (FCCM). Offspring of this individual have a 50 percent chance of inheriting the pathogenic variant.

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing or deletion/duplication analysis. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification:
The CCM2 c.71delG, p.Gly24fs variant has not been reported in the medical literature, listed in gene-specific variant databases, nor observed in the general population databases (1000 Genomes Project, Exome Variant Server, Genome Aggregation Database). The variant introduces a frameshift, and is predicted to result in a truncated protein or an absent transcript. Based on the above information, the variant is classified as 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 CCM2 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Likely benign and benign variants are not included in this report.

Test Information

i1: Cerebral Cavernous Malformation Interp

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

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

Test Information

i1: Cerebral Cavernous Malformation Interp

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 (KRIT1, CCM2, 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 (CCM1), or PDCD10 (CCM3).

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: Targeted 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 confirm reported variants. A custom tiled comparative genomic hybridization array (aCGH) was used to detect large deletions or duplications in the indicated subset of genes. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for 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 FCCM. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified and breakpoints of large deletions/duplications will not be determined. Single exon deletions/duplications or deletions/duplications less than 1kb may not be detected. Deletions/duplications/insertions of any size may not be detected by

Test Information

i1: Cerebral Cavernous Malformation Interp

massively parallel sequencing. Diagnostic errors can occur due to rare sequence variations. 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.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS