Cerebral Cavernous Malformation Panel, Sequencing and Deletion/Duplication

Cerebral cavernous malformations (CCMs) are vascular malformations occurring in the brain or other central nervous system 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 CCMs, or a pathogenic heterozygous variant in one of the associated genes (*CCM2*, *KRIT1*, or *PDCD10*).

Featured ARUP Testing

Cerebral Cavernous Malformation Panel, Sequencing and Deletion/Duplication 3002286

Method: Massively Parallel Sequencing

Use to confirm a diagnosis of familial cerebral cavernous malformation (FCCM) in an individual with suggestive findings

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Disease Overview

Symptoms

- CCM may result in intracranial hemorrhage (25-32%), and symptoms such as seizures (40-70%), headaches (10-30%), or focal neurological deficits without intracranial bleed (25-50%).[1]
- CCMs may increase in number over time; lesions may also decrease or increase in size over time.[1]
- Cutaneous vascular lesions (9%) or retinal vascular lesions (5%) may be present in FCCM.[1]
- CCM disease presentation often first occurs in the second to fifth decade of life, but may occur at any age.[1]
- FCCM resulting from *PDCD10* variants may result in a more severe disease course and manifest at younger ages, compared to causative *KRIT1* or *CCM2* variants.[1]

Genetics

See Genes Tested table

Etiology

Pathogenic germline variant in *CCM2, KRIT1*, or *PDCD10* genes

Penetrance

Up to 50% of individuals with a molecular diagnosis of FCCM remain clinically asymptomatic.[1]

Epidemiology

Based on autopsy studies, 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 and up to 20% of all CCMs are familial.[2]

Inheritance

Autosomal dominant with reduced penetrance; the frequency of de novo variants is unknown.

Pathogenic Founder Variants

- *KRIT1* c.1363C>T; p.Gln455Ter: common in individuals with ancestry from northern Mexico and the Southwestern United States[1]
- *CCM2* deletion of exons 2-10: identified in up to 22% of affected individuals in U.S. populations[1]
- *CCM2* c.30+5_30+6delGCinsTT: identified in unrelated Ashkenazi Jewish kindreds[1]

Test Interpretation

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as NGS) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Clinical Sensitivity

- 85-95% for FCCM[1]
- The majority of identifiable pathogenic variants in *CCM2*, *KRIT1*, and *PDCD10* are sequence variants. Large deletions and duplications account for 20-25% of identifiable pathogenic variants in these genes.

Analytic Sensitivity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [Single exon]	>99.9
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; PPA, positive percent agreement; NPA, negative percent agreement; SNVs, single nucleotide variants

Results

Result	Variant(s) Detected	Clinical Significance
Positive	One *CCM2*, *KRIT1*, or *PDCD10* pathogenic variant detected	Consistent with a diagnosis of FCCM; individual may or may not develop clinical symptoms
Negative	No *CCM2*, *KRIT1*, or *PDCD10* pathogenic variants detected	Diagnosis of FCCM is unlikely but not excluded
Uncertain	*CCM2*, *KRIT1*, or *PDCD10* variant of unknown clinical significance detected	It is unknown whether variant is benign or pathogenic

Limitations

- A negative result does not exclude a diagnosis of FCCM.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted genes
  - Regulatory region and deep intronic variants
  - Breakpoints of large deletions/duplications
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Large duplications less than 3 exons in size
  - Single exon deletions/duplications in the following exons:

    - *CCM2* (NM_001363458) 7
    - *CCM2* (NM_001363459) 6
  - Noncoding transcripts
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

Genes Tested

Gene Symbol	Aliases	MIM #	Disorders	Inheritance
CCM2	C70rf22, MGC4607, OSM	607929	CCM2	AD
KRIT1	CCM1, CAM	604214	CCM1	AD
PDCD10	CCM3, TFAR15	609118	CCM3	AD

AD, autosomal dominant

References

1. Morrison L, Akers A. Cerebral cavernous malformation, familial. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2022. [Last Update: Aug 2016; Accessed: Feb 2022]

2. Zafar A, Quadri SA, Farooqui M, et al. Familial cerebral cavernous malformations. *Stroke*. 2019;50(5):1294-1301.

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