Cerebral Cavernous Malformation Panel, Sequencing and Deletion/Duplication

Cerebral cavernous malformations (CCMs), or cavernomas, are vascular malformations occurring in the brain or other central nervous system (CNS) locations that 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. CCMs represent 5-15% of all cerebral vascular malformations and may be sporadic or familial. 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*). Molecular testing can be useful to confirm a diagnosis of FCCM.

Tests to Consider

Cerebral Cavernous Malformation Panel, Sequencing and Deletion/Duplication 3002286

Method: Massively Parallel Sequencing / Genomic Microarray (Oligo-based Array)

Use to confirm diagnosis of FCCM in individual with suggestive findings

Vascular Malformations Panel, Sequencing and Deletion/Duplication 2007384

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

- Preferred DNA test to confirm clinical diagnosis of a hereditary vascular malformation disorder if no specific vascular malformation syndrome is strongly suspected
- For test-specific information, see the Vascular Malformations Panel, Sequencing and Deletion/Duplication Test Fact Sheet

See Related Tests

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%).
- CCMs may increase in number over time; lesions may also decrease or increase in size over time.
- Cutaneous vascular lesions (9%) or retinal vascular lesions (5%) may be present in FCCM.
- CCM disease presentation often first occurs in the second to fifth decade of life, but may occur at any age.
- 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.

Etiology

Pathogenic germline variant in *CCM2, KRIT1* (CCM1), or *PDCD10* (CCM3)

Penetrance

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

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.[1]

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
- *CCM2* deletion of exons 2-10: identified in up to 22% of affected individuals in U.S. populations
- *CCM2* c.30+5_30+6delGCinsTT: identified in unrelated Ashkenazi Jewish kindreds

Test Description

Clinical Sensitivity

85-95% for FCCM[2]

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.

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
  - Noncoding transcripts
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Deletions/duplications less than 1kb in the targeted genes
  - Low-level somatic variants

Analytical Sensitivity

The analytical sensitivity of this test is approximately 99% for single nucleotide variants (SNVs) and greater than 93% 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.

Table of 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. Zafar A, Quadri SA, Farooqui M, et al. Familial Cerebral Cavernous Malformations. Stroke. 2019;50(5):1294-1301. PubMed

2. Morrison L, Akers A. Cerebral Cavernous Malformation, Familial. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2020. [Last Update: Aug 2016; Accessed: Feb 2020]

Related Tests

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

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