

# Cerebral Cavernous Malformation (CCM1, CCM2, and CCM3) Sequencing and Deletion/Duplication

*TO CONFIRM DIAGNOSIS IN SYMPTOMATIC INDIVIDUALS OR IDENTIFY A FAMILIAL MUTATION*

## Disease Overview

- Cerebral cavernous malformation (CCM) is a blood vessel disorder characterized by cavernous malformations in the brain.
- Headaches, seizures, and neurological deficits secondary to intracranial bleeding can occur. However, approximately 25 percent of individuals with CCM remain asymptomatic.
- Malformations can increase in number, size, and appearance (by MRI) over time in the familial form of the disease.
- Hyperkeratotic cutaneous capillary-venous malformations (HCCVMs) occur in a small percentage of affected individuals.

## Epidemiology/Incidence

- Incidence is ~0.1–0.5 percent for all CCM.
- CCM can be sporadic or familial.
- Familial CCM occurs in 1:2,000–1:10,000 individuals.
- The familial form is estimated to represent ~50 percent of CCM cases in Hispanic-Americans and ~10–20 percent in Caucasians.

## Genetics

- Autosomal dominant for familial form; reduced penetrance based on both clinical symptoms and brain imaging studies.
- Three causative genes have been identified to date: *KRIT1* (*CCM1*), *CCM2/MGC4607* (*CCM2*), and *PDCD10* (*CCM3*). A mutation in one of these three genes causes approximately 80 percent of familial CCM.
- Evidence suggests the existence of at least one additional causative gene not yet discovered.
- A founder mutation (*KRIT1* c. 1363C>T) is responsible for the majority of CCM in Hispanic-Americans of Mexican descent.
- HCCVMs are associated with mutations in *KRIT1*.

## Indications for Ordering

- To identify a causative mutation in an individual with multiple cavernous malformations of the brain.
- To identify a causative mutation in familial CCM.

## Contraindications

- Causative CCM mutation has previously been identified in the family. In this case, familial mutation analysis (targeted sequencing) should be ordered; contact ARUP for details on how to order.
- Prenatal testing. Contact ARUP for details on how to order this testing on a fetal specimen.

## Interpretation

- For optimal test interpretation, provide information regarding patient symptoms/manifestations and family history of CCM.
- A positive result means a gene mutation was detected that is predicted to cause CCM.
- A negative result does not rule out CCM due to the possibility of an undetectable mutation in the gene(s) tested or other causative genes that were not tested. In this case, medical management should rely on clinical findings and family history.
- An uncertain result means that a gene alteration was detected, but it is not certain whether it is pathogenic (i.e., would cause CCM) or merely a benign genetic variant. Medical management should rely on clinical findings and family history in this case.

## Limitations

- Genes associated with CCM, other than *KRIT1* (*CCM1*), *CCM2/MGC4607* (*CCM2*), and *PDCD10* (*CCM3*) will not be tested.
- Deep intronic mutations and some regulatory region mutations are not detected.
- Gene mutations of uncertain significance can be identified by sequencing
- Breakpoints of large deletions/duplications detected will not be determined.
- Rare diagnostic errors may occur due to primer- or probe-site mutations.

## Methodology

- *CCM1* sequencing is performed first on all samples. If results do not explain the clinical scenario, deletion/duplication testing for *CCM1*, *CCM2*, and *CCM3* will be performed. If these results do not explain the clinical scenario, *CCM2* sequencing will be performed. If these results do not explain the clinical scenario, *CCM3* sequencing will be performed.
- Upon request, the components of the reflex testing described above can be performed separately. (See related tests.)
- PCR followed by bidirectional sequencing of the entire coding region and intron-exon borders of one or more of the CCM genes.
- Multiplex ligation-dependent probe amplification (MLPA) is performed for large deletion/duplication analysis of the CCM genes.
- The clinical sensitivity of sequencing for familial CCM when all three genes are tested is approximately 60 percent (*CCM1*:40 percent; *CCM2*:15 percent; *CCM3*:5–10 percent). Analytic sensitivity and specificity of sequencing are 99 percent.
- The clinical sensitivity of MLPA is 20–25 percent for the *CCM1*, *CCM2*, and *CCM3* genes combined. Analytic sensitivity and specificity of MLPA are 90 and 99 percent, respectively.

### Related Tests

- Cerebral Cavernous Malformation (CCM1) Sequencing (2003152)
- Cerebral Cavernous Malformation (CCM2) Sequencing (2003156)
- Cerebral Cavernous Malformation (CCM3) Sequencing (2003160)
- Cerebral Cavernous Malformation (CCM1, CCM2, and CCM3) Deletion/Duplication (2003172)
- Familial Mutation, Targeted Sequencing (2001961)

### References

1. Bergametti F, et al. Mutation within the programmed cell death 10 gene cause cerebral cavernous malformations. *Am J Med Genet* 2005;76:42–51.

2. Eerola I, et al. KRIT1 is mutated in hyperkeratotic cutaneous capillary-venous malformation associated with cerebral capillary malformation. *Hum Mol Gen* 2000;9(9):1351–5.
3. Felbor U, et al. Large germline deletions and duplications in isolated cerebral cavernous malformation patients. *Neurogenetics* 2007;8:149–53.
4. Gunel M, et al. A founder mutation as a cause of cerebral cavernous malformation in hispanic americans. *N Eng J Med* 1996;334(15):946–51.
5. Labauge P, et al. Prospective follow-up of 33 asymptomatic patients with familial cerebral cavernous malformations. *Neurology* 2001;57:1825–8.

## Test Information

2003164

**Cerebral Cavernous Malformation (CCM1) Sequencing with Reflex to (CCM1, CCM2, and CCM3) Deletion/Duplication with Reflex to (CCM2) Sequencing with Reflex to (CCM3) Sequencing**

For specific collection, transport, and testing information, refer to the ARUP website at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).