

## Cerebral Cavernous Malformations via *CCM2* Exon 2-10 Deletion Testing (Test #124)

**Brief Clinical Description:** Cerebral cavernous malformations (CCMs) are congenital vascular anomalies of the brain that can cause significant neurological disabilities, including intractable seizures and hemorrhagic stroke. CCMs represent 5-15% of all cerebral vascular malformations and occur in ~0.5 percent of the general population. CCMs have been reported in infants and children, but the majority of patients present with symptoms between the second and fifth decades. CCMs occur in a sporadic form in which patients usually present with one or two lesions and no family history, and a familial form characterized by multiple lesions, and usually a strong family history. Perhaps 50% of “sporadic” cases with multiple lesions may in fact be members of an undiagnosed affected family. Not all patients with CCMs are clinically symptomatic. For additional information, see Zabramski et al. *J Neurosurg* 80: 422-432, 1994, Johnson 2006 GeneReviews (<http://www.geneclinics.org/>), and Angioma Alliance (<http://www.angiomaalliance.org/>).

**Genetics:** Familial CCMs show autosomal dominant inheritance. Three causative genes for CCMs have been identified: *KRIT1* (or *CCM1*) encoding a protein that interacts with the Krev-1/rap1a tumor suppressor, *MGC4607* (or *CCM2*) similar to the *KRIT1* binding partner ICAP1 $\alpha$ , and *PDCD10* (or *CCM3*) the programmed cell death 10 gene. Almost all causative mutations (in all three genes) are either nonsense, frameshift, splicing or deletion; missense mutations are rare. (Denier et al. *Ann Neurol* 60:550-556, 2006; Plummer et al. *Curr Neurol Neurosci Rep* 5:391-396, 2005). Recently, Liquori et al. (*Am J Hum Genet* 80:69-75, 2007) reported that deletions in *CCM2*, especially a 78 kb deletion of exons 2-10, were a frequent cause of CCMs.

**Description of This Particular Test:** This test involves amplification of patient DNA with a specific pair of PCR primers that flank the common *CCM2* exon 2-10 deletion. From chromosomes carrying the deletion, an 839 bp PCR product is produced. In normal chromosomes, the PCR primers are ~78 kb apart, and no PCR product is generated. PreventionGenetics also offers sequencing tests for the full *CCM1*, 2, and 3 genes.

**Indications for Test:** Suspected familial cerebral cavernous malformations and/or multiple CCMs in a person without a known family history. Of the patients previously shown to be free of mutations that are detectable by sequencing the three CCM genes, about 30% have been reported carry the *CCM2* exon 2-10 deletion.

**Sensitivity:**

| <u>Test</u>                         | <u>Mutations Detected</u>                                 | <u>Mutation Detection Rate</u>  |
|-------------------------------------|---|---|
| <i>CCM1/KRIT1</i> “Common Hispanic” | <i>KRIT1</i> exon 10 (1363C>T)                            | ~70% (with American Southwest Hispanic heritage)  |
| <i>CCM1/KRIT1</i> Sequencing        | nonsense, splice, small indel                             | ~40%  |
| <i>CCM2/MGC4607</i> Sequencing      | nonsense, splice, small indel                             | ~15%  |
| <i>CCM2</i> deletion testing        | <i>CCM2</i> del exon 2-10,<br>Other <i>CCM2</i> deletions | ~15% (~30% in <i>CCM1/2/3</i> mutation negative patients)<br>~10% (No clinical testing currently available) |
| <i>CCM3/PDCD10</i> Sequencing       | nonsense, splice, small indel<br>Currently undetectable   | ~7%<br>~15%   |

**Turn Around Time:** Maximum of 40 days, although many tests are completed in 2-3 weeks.

**Specimen Requirements:** See page 4 of the Requisition Form.

**Price:** *CCM2/MGC4607* Exon 2-10 deletion testing **\$190**

**CPT Codes:**

|                                  |              |              |                      |              |              |
|----------------------------------|--------------|--------------|----------------------|--------------|--------------|
| <b>Ascertainment</b>             | <b>83890</b> | <b>\$ 30</b> | <b>DNA Isolation</b> | <b>83891</b> | <b>\$ 40</b> |
| <b>Amplification X1</b>          | <b>83898</b> | <b>\$ 20</b> | <b>Separation</b>    | <b>83894</b> | <b>\$ 50</b> |
| <b>Interpretation and Report</b> | <b>83912</b> | <b>\$ 50</b> |                      |              |              |

**Accreditation Info.** CLIA ID #: 52D1027685 (expires 1/18/113) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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