

Cerebral Cavernous Malformations via *KRIT1/CCM1* Exon 10 “Common Hispanic” Mutation Detection (Test #125)

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 α , 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; Liquori et al. Am J Hum Genet 80:69-75, 2007). Hispanic patients often carry the identical *CCM1/KRIT1* Exon 10 nonsense mutation (1363 C>T).

Description of This Particular Test: The identification of the familial Hispanic *KRIT1/CCM1* mutation entails bidirectional DNA sequencing of the full coding region of *KRIT1* exon 10. This test should be ordered first if the patient has Hispanic ancestry. PreventionGenetics also offers sequencing tests for the full *CCM1*, 2, and 3 genes and a test for the most common *CCM2* gene deletion.

Indications for Test: Patients who have American Southwest Hispanic heritage **and** multiple CCMs or a single CCM and family history are candidates for this test. Genetic testing of presymptomatic family members can identify patients who may benefit from more intensive clinical monitoring.

Sensitivity:

Test	Mutations Detected	Mutation Detection Rate
<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, Other <i>CCM2</i> deletions	~15% (~30% in <i>CCM1/2/3</i> mutation negative patients) ~10% (No clinical testing currently available)
<i>CCM3/PDCD10</i> Sequencing	nonsense, splice, small indel Currently undetectable	~7% ~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: *CCM1* “common Hispanic” Mutation Test by Sequencing \$190

CPT Codes:

Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification X1	83898	\$ 20	Mutation Ident by Sequencing X1	83904	\$ 30
Separation	83894	\$ 20	Interpretation and Report	83912	\$ 50

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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