

## Cerebral Cavernous Malformations via *KRIT1/CCM1* Gene Sequencing (Test #120)

**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, *CCM2* 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).

**Description of This Particular Test:** This test involves bidirectional DNA sequencing of the coding regions of all 16 coding exons of the *KRIT1* gene plus about 50 bp of flanking non-coding DNA on either side. We also perform sequencing of any single exon in this gene for family members of patients with known mutations and to confirm research results.

**Indications for Test:** Suspected *familial* cerebral cavernous malformations and/or *multiple* CCMs in a person without a known family history. Genetic testing of presymptomatic family members can identify candidates for more intensive clinical monitoring. Testing is not recommended for patients with no family history and only a *single* sporadic lesion.

### 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:** *KRIT1* Gene Sequencing **\$840**

### CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x16	83898	\$ 260	Sequencing x16	83904	\$ 380
Separation	83894	\$ 50	Interpretation/Report	83912	\$ 80

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

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