

Cerebral Cavernous Malformations via *PDCD10/CCM3* Gene Sequencing (Test #123)

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).

Description of This Particular Test: This test involves bidirectional DNA sequencing of the coding regions of all 7 coding exons (exons 4-10) of the *PDCD10/CCM3* 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 patients who may benefit from more intensive clinical monitoring.

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, 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: *PDCD10/CCM3* Gene Sequencing **\$540**

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x7	83898	\$ 140	Sequencing x7	83904	\$ 210
Separation	83894	\$ 40	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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