

### **Cerebral Cavernous Malformation 3 (CCM3) PDCD10 Mutation Detection by Sequencing**

Cerebral cavernous malformations (CCM) are congenital vascular anomalies of the brain that can cause significant neurological disabilities, including intractable seizures and hemorrhagic stroke. Three loci for autosomal dominant CCM (*CCM1*, *CCM2* and *CCM3*) map to chromosome region 7q21-q22, to 7p15-p13 and to 3q25.2-27 respectively. Using a genomic sequence-based positional cloning strategy, *KRIT1*, encoding a protein that interacts with the Krev-1/rap1a tumor suppressor, has been identified as the *CCM1* gene (Nat Genet. 23:189-193, 1999; Hum Mol Genet. 8:2325-2333, 1999). The second gene detected that can cause CCMs was identified as *MGC4607* (Am J Hum Genet.73:1459-1464, 2003). *MGC4607*, similar to the *KRIT1* binding partner ICAP1 $\alpha$ , encodes a protein with a PTB (phospho-tyrosine binding) domain. This protein may be part of the complex pathway of integrin signaling, that when perturbed, causes abnormal vascular morphogenesis in the brain leading to CCM formation. Most recently mutations within the programmed cell death 10 (*PDCD10*) gene was shown to cause cerebral cavernous malformations in some families. (Am J Hum Genet. 76:42-51., 2005). *PDCD10* is highly conserved in both vertebrates and invertebrates. Its role in CCM vascular morphogenesis is yet to be defined.

Mutations in the *CCM1* gene, *KRIT1* may account for up to 40% of familial CCM cases. Other CCM kindreds harbor other mutations in other CCM associated genes with mutations in the *CCM2* gene accounting for perhaps an additional 20% of familial cases and mutations in the recently identified *CCM3* gene and perhaps other still unidentified genes accounting for the remaining 40% of cases. Identification of these other mutations has potential clinical significance for presymptomatic diagnosis of CCM in this population and their families. The identification of a *CCM3* associated mutation entails extraction of genomic DNA from blood, PCR amplification of 7 separate exons (4-10) of the *PDCD10* gene, sequencing and electrophoretic separation of product, and comparison of this patient specific sequence with "typical" sequence. The sequence of exons 1, 2 and 3 of the *CCM3* gene are not determined since the start codon is in exon 4.

#### **Specimen Requirements**

- Collect 2-5 ml of whole blood in EDTA (purple top tube) or ACD (yellow top tube). 5 ml is the preferred volume.
- Only one blood tube is required for multiple tests.
- Ship whole blood specimens at room temperature.
- Do not freeze blood.
- During hot weather, include a frozen ice pack in the shipping container. Do not allow the ice pack to come in direct contact with the specimen tube.
- In cold weather, include an unfrozen ice pack to help moderate extremes in temperature. The DNA in whole blood is stable for at least 48 hours at 21°C, 5-7 days at 4°C.

#### **CPT Codes and Cost**

<i>CCM3</i> Mutation Test DNA Seq		<b>\$725.00</b>
Molec Diag, Ascertainment	83890	
Molec Diag, Isolation	83891	
Molecular Diag, Amplif x7	83898	
Mutat Id By Seq, Single Seg x7	83904	
Molecular Diag, Separation	83894	
Interpretation And Report	83912	

**Accreditation Info. CLIA ID #: 52D1027685** (expires 1/18/07) (CAP#: 7185561, AU ID: 1407125 expires 12/20/06)

#### ***Ship to:***

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