Cerebral Cavernous Malformations, 3 Genes

Indications for Ordering

- Confirm diagnosis in an individual with cerebral cavernous malformations (CCM)
- Identify causative gene mutation(s) for familial CCM

Test Description

- Next generation sequencing
  - Targeted capture of all coding exons and intron/exon junctions followed by massively parallel sequencing
  - Sequence variants reported are confirmed by Sanger sequencing
- Deletion/duplication analysis
  - Custom-designed comparative genomic hybridization array

Tests to Consider

Primary test

Cerebral Cavernous Malformation (CCM) Panel, Sequencing and Deletion/Duplication, 3 Genes 2009326

- Preferred test to confirm a clinical diagnosis of and determine an etiology for CCM

Related tests

Cerebral Cavernous Malformation (CCM) Sequencing, 3 Genes 2009331

- Use to confirm a clinical diagnosis of and determine an etiology for CCM

Cerebral Cavernous Malformation (*CCM1*, *CCM2* and *CCM3*) Deletion/Duplication 2003172

- Useful if no mutations have been found using sequencing

Vascular Malformations Panel, Sequencing and Deletion/Duplication, 14 Genes 2007384

- Preferred test to confirm clinical diagnosis of a blood vessel disorder

Vascular Malformations Sequencing, 14 Genes 2007390

- Acceptable test to confirm clinical diagnosis of a blood vessel disorder

Familial Mutation, Targeted Sequencing 2001961

- Useful when a familial mutation identifiable by sequencing is known

Disease Overview

Blood vessel disorder characterized by cavernous malformations in the brain

- Malformations in familial form can increase in number and size over time
- Hyperkeratotic cutaneous capillary-venous malformations (HCCVMs) occur in a small percentage

Symptoms

- Headaches, seizures, and neurological deficits secondary to intracranial bleed
- ~25% of individuals with CCM remain asymptomatic

Incidence

- ~1/200 for all CCM
- Familial CCM – 1/2,000-10,000 individuals

Genetics

Genes – see table

Mutations – CCM can be sporadic or familial

Test Interpretation

Clinical sensitivity – ~80% for three genes combined

Results

- Positive – one copy of a pathogenic mutation in the *CCM1/KRIT1*, *CCM2,* or *CCM3*/*PDCD10* gene detected
  - Predictive of familial CCM
- Negative – no pathogenic mutation detected in the *CCM1*, *CCM2,* or *CCM3* gene in an individual clinically affected with CCM
  - Diagnosis of familial CCM is unlikely but not excluded
- Inconclusive – variants of unknown clinical significance may be identified in any of the 3 genes tested

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not determined or evaluated:
  - Deep intronic mutations
  - Regulatory region mutations
  - Breakpoints of large deletions/duplications
  - Mutations in genes not listed
- Small deletions or insertions may not be detected by massively parallel sequencing

Reference

Morrison L, Akers A. Cerebral Cavernous Malformation, Familial. 2003 Feb 24 [Updated 2011 May 31]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015 (www.ncbi.nlm.nih.gov/books/NBK1293/)

Gene Symbol	Gene Description	NM#	OMIM#	Condition	Inheritance	Familial CCM Attributable to Gene
CCM1/KRIT1	Ankyrin repeat containing	194456	604214	CCM1	AD	~55%
CCM2	Cerebral cavernous malformation 2	031443	607929	CCM2	AD	~ 5%
CCM3/PDCD10	Programmed cell death 10	007217	609118	CCM3	AD	~10%
AD = autosomal dominant						