GENEReviews

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Cerebral Cavernous Malformation, Familial

[*Familial Cavernous Hemangioma, Familial Cerebral Cavernous Angioma, Familial Cerebral Cavernous Malformation. Includes: CCM1, CCM2, CCM3, CCM4*]

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Summary

Disease characteristics. Cerebral cavernous malformations (CCMs) are vascular malformations consisting of closely clustered enlarged capillary channels (caverns) with a single layer of endothelium without normal intervening brain parenchyma or mature vessel wall elements. The diameters range from a few millimeters to several centimeters. The channels increase in size and number over time. CCMs have been reported in infants and children, but the majority of individuals present with symptoms between the second and fifth decades. Up to 25% of individuals with CCM remain symptom free throughout their lives. Approximately 50-75% of persons with CCM have symptoms, including seizures, focal neurologic deficits, nonspecific headaches, and cerebral hemorrhage. Familial cerebral cavernous malformation is defined as the occurrence of CCMs in at least two family members, and/or the presence of a disease-causing mutation in one of the genes associated with CCM and/or the presence of multiple CCMs.

Diagnosis/testing. CCM is diagnosed by histopathologic examination, cerebral angiography, or MRI. The three genes associated with familial CCM are *KRIT1*, *CCM2*, and *PDCD10*. A single mutation in the *KRIT1* gene (1363C>T) has been identified in about 70% of Hispanic families. Molecular genetic testing for all three genes is available on a clinical basis.

Genetic counseling. Familial CCM is inherited in an autosomal dominant manner. The occurrence of asymptomatic vascular lesions may prevent recognition of an autosomal dominant pattern of inheritance in a family. The proportion of cases caused by *de novo* gene mutations is unknown. Each child of an individual with CCM has a 50% chance of inheriting the mutation. Prenatal testing is available.

Diagnosis

Clinical Diagnosis

Cerebral cavernous malformation (CCM) is diagnosed by histopathologic examination, cerebral angiography, or MRI (Table 1).

Familial cerebral cavernous malformation is defined as the occurrence of CCMs in at least two family members [Verlaan, Davenport et al 2002] and/or the presence of a disease-causing mutation in one of the genes associated with CCM and/or the presence of multiple CCMs [Denier, Labauge et al 2004; Verlaan et al 2004].

Note: Individuals with a single CCM may have familial CCM; therefore, the presence of a single CCM in an individual with no family history of CCM does not exclude the diagnosis of familial CCM.

Histopathology. Cerebral cavernous malformations (CCMs) are vascular malformations consisting of closely clustered enlarged capillary channels (caverns) with a single layer of endothelium without normal intervening brain parenchyma or mature vessel wall elements. The diameters range from two to 55 millimeters (mean: 8 mm) [Rigamonti et al 1987, Zabramski et al 1994, Brunereau et al 2000].

Cerebral angiography. Cerebral angiography may reveal persistent opacification of irregular sinusoidal channels. However, cavernous malformations are rarely visualized on angiography because of the small size of the afferent vessels, the presence of thrombosis, and the relatively low flow in these lesions [Selman et al 2000].

MRI. The characteristic lesion of mixed signal intensity with a central reticulated core surrounded by a dark ring is presumed to be hemosiderin deposition from prior hemorrhage [Rigamonti et al 1987].

Table 1. Classification of CCM by MRI and Histopathology

	MR Signal	Histopathology	Clinical Correlation
Type 1	−SE T1: hyperintense core −SE T2: hyperintense core or hypointense core	Subacute hemorrhage	Acute hemorrhage; high frequency of bleeding relapse
Type 2	−SE T1: reticulated mixed signal core −SE T2: reticulated mixed signal core with surrounding hypointense rim	Lesions with hemorrhages and thromboses of varying ages	
Type 3	−SE T1: iso- or hypointensity −SE T2: hypointense lesion with hypointense rim magnifying the size of the lesion	Chronic hemorrhage with hemosiderin staining within and around the lesion	
Type 4	−SE T1: not seen −SE T2: not seen −GRE: punctate hypointense lesion	Tiny CCM or telangiectasia	Possibly represent true new lesions

Zabramski et al 1994
SE = spin echo
GRE = gradient echo

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. Familial cerebral cavernous malformation is associated with the following three genes:

- ***KRIT1***(aliases include *CCM1* and *CAM*)
- ***CCM2***(aliases include *MGC4607*, *C7orf22*) [Liquori et al 2003; Denier, Goutagny et al 2004; Verlaan et al 2004]
- ***PDCD10***(aliases include *CCM3*, *TFAR15*)

Other loci. In 20-40% of individuals with familial CCM, mutations are not detected in the known CCM genes. Evidence exists for additional CCM loci [Bergametti et al 2005, Guclu et al 2005, Verlaan et al 2005, Liquori et al 2006].

Based on exclusion of the *PDCD10* gene in a large family that shows linkage to CCM3 but not to CCM1 or CCM2, Liquori et al (2006) propose a putative CCM4 locus at 3q26.3-q27.2.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Predictive testing
- Prognostication
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- ***KRIT1* targeted mutation analysis.** A single mutation in the *KRIT1* gene (1363C>T), referred to as the "common Hispanic mutation," was identified in about 70% of affected families of Hispanic heritage (8/12 individuals) [Johnson et al 1995, Gunel et al 1996, Sahoo et al 1999]. Laurans et al (2003) identified this mutation in 72% (31/43) of individuals of Mexican heritage; this included 18/21 (86%) with a positive family history of CCM and 13/22 (59%) with no family history of CCM. No other common mutation has been detected in families of other ethnic derivation.
- **Sequence analysis: *KRIT1***
  - **Non-Mexican individuals with a positive family history and/or multiple CCMs.** Cave-Riant et al (2002) identified a *KRIT1* mutation in 43% (52/121) of probands with at least one affected relative and/or multiple CCMs on cranial MRI. Verlaan et al (2004) identified *KRIT1* mutations in approximately 30% of individuals with multiple CCMs who had no family history of CCMs.
  - **Non-Mexican simplex CCM.** The mutation detection rate in non-Hispanic individuals with no family history of CCM (i.e., simplex cases) ranges from none in 103 for whom a positive family history was rigorously excluded [Laurans et al 2003], none in 72 with or without multiple CCMs [Reich et al 2003], and none in 21 with a single lesion and no family history of CCM [Verlaan et al 2004] to one in 12 (8%) [Davenport et al 2001].
- **Sequence analysis: *CCM2***
  - **Familial CCM.** Between 13% [Verlaan et al 2004] and 20% [Craig et al 1998; Verlaan, Davenport et al 2002] of individuals with familial CCM have mutations in the *CCM2* gene [Liquori et al 2003; Denier, Goutagny et al 2004].
  - **Simplex CCM.** No *CCM2* mutations were seen in 31 individuals with no family history of CCM [Verlaan et al 2004].
- **Sequence analysis: *PDCD10***
  - **Familial CCM.** Although initial estimates suggested that 40% of individuals with familial CCM may be linked to *PDCD10* (the CCM3 locus) [Craig et al 1998; Verlaan, Davenport et al 2002], recent data indicate that this number is too high. In studies of families with CCM who had no evidence of a mutation in *KRIT1* or *CCM2* by sequence analysis, a *PDCD10* sequence alteration was found in 40% (8/20) [Bergametti et al 2005], 13% (2/15) [Verlaan et al 2005], 7% (4/61) [Guclu et al 2005], and 10% (3/29) [Liquori et al 2006].

Molecular genetic testing: Research. Mutations in the three known CCM genes are not identified in 20-40% of individuals from families with CCM. If no mutation is detected in the *KRIT1*, *CCM2*, or *PDCD10* genes, research testing may be performed to identify families that demonstrate linkage to the CCM4 locus.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in Cerebral Cavernous Malformation

Test Methods	Mutations Detected	Mutation Detection Rate	Test Availability
Targeted mutation analysis	*KRIT1* "common Hispanic mutation" (1363C>T)	Hispanic heritage: 70% [1]	Clinical Testing
Sequence analysis	*KRIT1* sequence alterations	~30-40%	
	CCM2 sequence alterations	~20%	Clinical Testing
	PDCD10 sequence alterations	~10-20%	Clinical Testing
Direct DNA [2]	CCM4 locus	Unknown	Research only

1. Probands with at least one affected relative and/or multiple CCMs [Cave-Riant et al 2002, Verlaan et al 2004]
2. Direct DNA methods may include mutation analysis, mutation scanning, sequence analysis, or other means of molecular genetic testing to detect a genetic alteration associated with CCM4.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in *KRIT1,CCM2,* or *PDCD10*.

Clinical Description

Natural History

CCM has been reported in infants and children, but the majority of individuals present with symptoms between the second and fifth decades. In one study, 9% of individuals were symptomatic before age ten years, 62-72% between ten and 40 years, and 19% after age 40 years [Gunel et al 1996]. Brunereau et al (2000) and Labauge et al (2001) determined that new lesions appear at a rate of between 0.2 lesions and 0.4 lesions per patient-year. They and others [Zabramski et al 1999] emphasized the dynamic nature of CCM. Other evidence of change observed on MRI over time includes appearance of acute, often asymptomatic, hemorrhages (0.7%/lesions/year) that increase in size and change in signal intensity over time [Labauge et al 2001].

It had been assumed that individuals with familial CCM generally have multiple lesions while individuals who represent simplex cases (i.e., a single occurrence in a family) have a single lesion; however, in a study of 138 individuals (62 symptomatic and 76 asymptomatic) with a *KRIT1* mutation, Denier, Labauge et al (2004) found that 26 individuals (20%) appeared to have only one lesion when evaluated with T2-weighted MRI. Further examination with gradient-echo sequence MRI of 12 of these apparently symptom-free individuals revealed multiple lesions in eight (66%) and only one detectable lesion in four (33%). Additionally, eight of the symptom-free individuals showed no lesion at all. Thus, approximately 13% of individuals with a *KRIT1* mutation had only one lesion detected when examined with T2-weighted MRI and about 2% had only one lesion detected when examined with gradient-echo sequence MRI.

Others have identified an increasing number of lesions in families by generation: 5-12 lesions in children and adolescents; 20 lesions in parents; and more than 100 lesions in grandparents [Horowitz & Kondziolka 1995, Siegel et al 1998].

Brunereau et al (2000) and Labauge et al (2001) determined that 76-86% of lesions were supratentorial and 16-24% infratentorial. Of the infratentorial lesions, almost half occurred in the brainstem. Brainstem lesions are frequently associated with symptoms [Fritschi et al 1994]. Lesions occasionally occur in the spinal cord.

Up to 25% of individuals with CCM remain symptom free throughout their lives [Siegel 1998]. This percentage may be an underestimate because many asymptomatic persons go unrecognized. Otten et al (1989) reported an absence of symptoms in 90% of individuals with CCMs ascertained in autopsy.

Approximately 50-75% of persons with CCM become symptomatic. Affected individuals most often present with seizures (40-70%), focal neurologic deficits (35-50%), nonspecific headaches (10-30%), and cerebral hemorrhage. In the most recent study, Denier, Labauge et al (2004) found seizures in 55%, focal neurological deficits in 9%, nonspecific headaches in 4%, and cerebral hemorrhage in 32%.

Individuals may experience a number of serious neurologic problems resulting from intracranial hemorrhage and mass effects, including focal and generalized epileptic seizures, progressive neurologic deficit, headaches, muscle weakness, paralysis, loss of sensation, and hearing or vision deficiencies. Cavernous malformation can lead to death from cerebrovascular accident. Of note, severe hemorrage from CCM is less common than hemorrage from arteriovenous malformations (AVM) [Selman et al 2000].

Retinal, skin, and liver lesions have occasionally been reported [Dobyns et al 1987, Labauge et al 1999, Eerola et al 2000, Chen et al 2002].

Genotype-Phenotype Correlations

The lack of reported individuals homozygous for *KRIT1* mutation suggests the possibility of homozygote lethality.

A few mutations have been associated with vascular skin lesions: 699ΔG [Eerola et al 2000], Q698X [Chen et al 2002].

Penetrance

The discovery of the genetic causes for CCM permits correlation of the presence of a mutation with clinical presentation. Denier, Labauge et al (2004) found that: 1) 62% of individuals with a mutation in *KRIT1* were symptomatic; 2) 58% of those with a mutation who were at least 50 years old had symptoms related to CCM; 3) 45 of 53 symptom-free individuals with *KRIT1* mutations had lesions on MRI, three had indications of a type IV lesion and five had no clinical or MRI findings of CCM. The fact that the penetrance of CCM is incomplete based on clinical symptoms and neuroimaging studies indicates that the familial nature of CCM may be overlooked in some individuals [Denier, Labauge et al 2004].

Anticipation

Anticipation has not been observed.

Prevalence

A particularly high incidence in individuals of Mexican descent has been noted. Linkage studies revealed that both familial and nonfamilial cases in this population could be attributed to inheritance of the same mutation from a common ancestor [Johnson et al 1995, Gunel et al 1996]. The fairly common occurrence of asymptomatic vascular lesions in individuals with this disorder suggests that the population incidence of familial CCM has been routinely underestimated [Verlaan, Davenport et al 2002; Johnson et al 2004].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

CCMs occur in 0.4-0.5% of the general population and represent 5-15% of all cerebral vascular malformations [Rigamonti et al 1988]. Cavernous malformations occur in two forms: a "sporadic" form, in which individuals usually present with one or two lesions and no family history of neurologic disease, and the familial form, characterized by multiple lesions and a strong family history of related neurologic deficits. Multiple lesions are thought to be more common in the familial form of CCM.

Five percent of individuals with intractable temporal lobe epilepsy have CCM [Spencer et al 1984].

Differential diagnosis includes Von Hippel-Lindau disease, hereditary hemorrhagic telangiectasia, and blue rubber bleb nevus syndrome [Chen et al 2002].

Management

Treatment of Manifestations

- Surgical removal of lesions associated with intractable seizures or focal deficits from recurrent hemorrhage or mass effect [Heros & Heros 2000, Selman et al 2000, Folkersma & Mooij 2001]. Microsurgical techniques rely upon intra-operative ultrasound examination for precise localization. Thirteen individuals, seven with epileptic seizures and six with progressive focal neurologic deficits, improved postoperatively; none required re-operation [Folkersma & Mooij 2001].
- If a large number of lesions are present a surgical approach is not justified. Very large single lesions can be difficult to ablate.
- Treatment of seizures

Surveillance

MRI is indicated in individuals experiencing new neurologic symptoms.

Testing of Relatives at Risk

Surveillance of asymptomatic adults and children known to have the disease-causing mutation identified in an affected family member or at risk for CCM based on family history with MRI examination at four or five year intervals has been recommended by some clinicians; however, asymptomatic lesions are rarely treated. Therefore, the clinical utility of such routine screening is yet to be determined.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Familial cerebral cavernous malformation is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Many individuals diagnosed with familial CCM have a symptomatic parent. However, the fairly common occurrence of asymptomatic vascular lesions may prevent recognition of an autosomal dominant pattern of inheritance in a family [Denier, Labauge et al 2004].
- A proband with CCM may also have the disorder as the result of a *de novo* gene mutation; however, the proportion of cases caused by *de novo* gene mutations is unknown as the frequency of subtle signs of the disorder in parents has not been thoroughly evaluated and molecular genetic testing data are insufficient. One individual with a *de novo* germline mutation has been reported [Lucas et al 2001].
- Parents of a proband can be screened by brain MRI.

Note: Although many individuals diagnosed with CCM have a symptomatic parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or reduced penetrance in the parent with the disease-causing mutation.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to sibs of inheriting the mutation is 50%.
- If the disease-causing mutation cannot be detected in the DNA of the either parent, the risk to sibs is low but greater than that of the general population because the possibility of germline mosaicism exists. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with CCM has a 50% chance of inheriting the mutation.

Other family members. The risk to other family members depends upon the genetic status of the proband's parents. If a parent is found to be affected or to have a disease-causing mutation, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible nonmedical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk, genetic counseling, and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100% or molecular genetic testing is available on a research basis only. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation(s) has/have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Cerebral Cavernous Malformation, Familial

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
CCM1	*KRIT1*	7q11.2-q21	Krev interaction trapped 1
CCM2	*CCM2*	7p13	CCM2 protein
CCM3	*PDCD10*	3q26.1	Programmed cell death 10
CCM4	Unknown	3q26.3-27.2	Unknown

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Cerebral Cavernous Malformation, Familial

116860	CEREBRAL CAVERNOUS MALFORMATIONS; CCM
603284	CEREBRAL CAVERNOUS MALFORMATIONS 2; CCM2
603285	CEREBRAL CAVERNOUS MALFORMATIONS 3; CCM3
604214	KREV INTERACTION TRAPPED 1; KRIT1
607929	CCM2 GENE; CCM2
609118	PROGRAMMED CELL DEATH 10; PDCD10

Table C. Genomic Databases for Cerebral Cavernous Malformation, Familial

Gene Symbol	Entrez Gene	HGMD
KRIT1	889 (MIM No. 604214)	KRIT1
CCM2	83605 (MIM No. 603284)	CCM2
PDCD10	11235 (MIM No. 609118)	PDCD10

For a description of the genomic databases listed, click here.

KRIT1

Normal allelic variants: *KRIT1* comprises 16 coding exons.

Pathologic allelic variants: About 74 mutations have been published to date [Verlaan, Davenport et al 2002, Cave-Riant et al 2002; Denier, Goutagny et al 2004]. Fifty percent are frameshifts, 24% are nonsense, 24% are changes in the invariant splice junctions, and one mutation was an 84-base pair deletion [Verlaan, Davenport et al 2002]. The mutations are evenly distributed from exon 9 to exon 18 [Verlaan, Davenport et al 2002; Verlaan, Siegel et al 2002].

Normal gene product: The Krit1 protein is 736 amino acids in length. It may have a tumor suppressor function. Guzeloglu-Kayisli et al (2004) demonstrated *KRIT1* expression in endothelial cells. They found that *KRIT1* is expressed during capillary-like tube formation in early angiogenesis and may play a key role in vessel formation, development, and/or maintenance. In a ccm1 murine knock out, Whitehead et al (2004) found ubiquitous expression in early embryogenesis and evidence for homozygous lethality. Their studies suggest that the *KRIT1* gene exerts its effect primarily in the vascular rather than in the supporting neuronal tissue.

Abnormal gene product: The approximately 74 mutations examined to date lead to alteration in gene product via the formation of a premature termination codon, supporting a loss-of-function mechanism [Verlaan, Davenport et al 2002].

CCM2

Normal allelic variants: *CCM2* has ten coding exons.

Pathologic allelic variants: Initially, Liquori et al (2003) found five frame shift mutations, one nonsense mutation, and two spicing mutations; all, if translated, result in a truncated protein. Subsequently, Denier, Goutagny et al (2004) showed ten additional mutations: two large deletions and eight point mutations. One mutation altered the initiation codon, two led to the deletion of exon 1, five led to premature stop codons, one led to the splicing of exon 3 without a frame shift, and one was a missense mutation.

Normal gene product: Malcavernin (MGC4607), a protein with a PTB (phospho-tyrosine binding) domain, is similar to the KRIT1 binding partner ICAP1. This protein may be part of the complex pathway of integrin signaling, which, when perturbed, causes abnormal vascular morphogenesis in the brain leading to CCM formation. Marchuk named this gene product for its role in CCM development.

Abnormal gene product: Little is known about MGC4607 function. Haploinsufficiency is a likely mode of action for at least some of these mutations.

PDCD10

Normal allelic variants: *PDCD10* has ten exons; the coding region starts with exon 4.

Pathologic allelic variants: Bergametti et al (2005) described seven distinct mutations in eight families: one deletion of the entire gene, one abnormal splicing of exon 5, three nonsense mutations, and two splice-site mutations.

Normal gene product: The gene encodes a 212 aa protein with no known domains. It is thought to be involved in apoptotic pathways.

Abnormal gene product: The nature of the mutations detected to date suggests a role for haploinsufficiency.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Angioma Alliance
107 Quaker Meeting House Road
Williamsburg VA 23188
Email: info@angiomaalliance.org
angiomaalliance.org

National Library of Medicine Genetics Home Reference
Cerebral cavernous malformation

American Epilepsy Society
342 North Main Street
West Hartford CT 06117-2507
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Email: info@aesnet.org
www.aesnet.org

Epilepsy Foundation of America
4351 Garden City Drive
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Phone: 800-EFA-1000 (800-332-1000); 301-459-3700
Fax: 301-577-4941

Email: webmaster@efa.org
www.efa.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

- 13 July 2006 (ej) Revision: additional information on CCM4; prenatal testing available for *KRIT1*, *CCM2*, and *PDCD10*
- 31 May 2005 (me) Comprehensive update posted to live Web site
- 1 September 2004 (ej) Revision: change in testing
- 18 March 2004 (ej) Revision: identification of *CCM2* gene
- 24 February 2003 (me) Review posted to live Web site
- 5 February 2002 (ej) Original submission