Genetics of cerebral cavernous malformations (CCM)

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Cerebral cavernous malformations (CCM) are vascular lesions that have a prevalence of 1:225 among the general population. Data from large genetic databases suggest that up to 7% of all cases are hereditary.

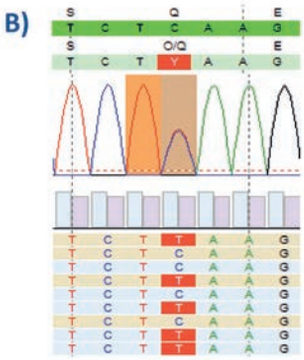
The main characteristics of familial CCM are a positive family history and / or the occurrence of multiple cavernomas in an affected individual. Familial / hereditary CCM is caused by mutations in one of three genes: *CCM1*, *CCM2* and *CCM3*. 60-63% of patients with hereditary cavernomas carry disease-causing variants in *CCM1*, another 18-19% in *CCM2* and 18-22% in *CCM3* (Fig. 1A).
Familial CCMs are inherited in an autosomal dominant manner which means that 1st degree relatives (parents, siblings, children) are at a risk of 50% to be a carrier of the familial variant. Almost all known disease-causing variants lead to a premature stop codon, i.e. protein synthesis is prematurely discontinued (Fig. 1B). Alternatively, one of the two gene copies of *CCM1*, *CCM2* or *CCM3* may also be deleted completely or in part.

Diagnostic genetic testing always starts with a blood sample from an affected individual to search for a mutation in *CCM1*, *CCM2* or *CCM3*. If the inclusion criteria for a molecular genetic analysis are strictly followed, the probability of finding a mutation in familial CCM is very high. Disease-causing variants are found in 87% to 98% of all cases with a positive family history and in about 60% of patients with multiple cavernomas and a negative family history. For the latter, somatic mutations might be a reason for the reduced mutation detection rate. Such variants may only be present in vascular cells and escape standard DNA diagnostics from white blood cells. The severity of CCM can vary widely. Unfortunately, the type of mutation does not allow for a prediction of the individual clinical outcome.
On the one hand, mutation carriers without any symptoms during their lifetime have been observed (= incomplete penetrance). On the other hand, infancy onset of headaches, seizures or even transient stroke-like symptoms (e.g. dizziness, vision changes, weakness of one side of the body) have occasionally been reported in the relevant literature.

If a disease-causing variant is identified in an affected person, predictive genetic testing is an option for at-risk family members (Fig. 1C). However, this may only be initiated after genetic counselling. Exclusion of the familial mutation reduces the disease risk to the level of the general population and makes special clinical and MRI check-ups unnecessary. One asymptomatic parent of CCM patients may be a carrier of a familial variant and may have small or clinically inconspicuous CCMs. In rare cases, CCM mutation carriers without family history may have a new (= de novo) germline mutation that can be passed on to offspring in the same way as inherited ones. Nowadays, the three CCM genes are analysed simultaneously in a single sequencing run using modern techniques. For patients with less well-defined vascular malformations, other disease genes can also be screened in parallel using a next generation sequencing (NGS) panel analysis.

A)

gene	mutation frequency	mean age at genetic testing	penetrance	symptoms
CCM1	60-63 %	30.5 years	63 %	• epileptic seizures • neurologic deficits • hemorrhagic stroke • headaches
CCM2	18-19 %	40 years	55 %	
CCM3	18-22 %	18 years	68 %	



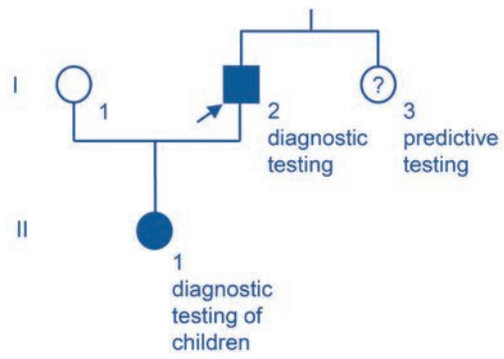


Figure 1:
A) Summary of mutation frequency, penetrance and symptoms of familial CCM caused by mutations in *CCM1*, *CCM2* or *CCM3*.

B) Most *CCM* mutations lead to a premature stop codon. An example of such a heterozygous *CCM1* mutation (= one of the two alleles has changed) is shown here. The codon CAA, which codes for the amino acid glutamine, has changed to a TAA stop / termination codon.

C) Pedigree of a family with CCM. Several cavernomas have been identified for the father (I:2, blue arrow) and his minor daughter (II:1). Squares = males, circles = females, blue-filled symbols = clinically and/or neuroradiologically affected; ? = at-risk family member.

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