CCM3 Mutations Are Associated with Early-Onset Cerebral Hemorrhage and Multiple Meningiomas

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Key Words

Cavernous angioma · CCM · CCM1 · CCM2 · KRIT1 · Meningioma · PDCD10

Abstract

Mutations of *CCM3/PDCD10* cause 10–15% of hereditary cerebral cavernous malformations. The phenotypic characterization of *CCM3*-mutated patients has been hampered by the limited number of patients harboring a mutation in this gene. This is the first report on molecular and clinical features of a large cohort of *CCM3* patients. Molecular screening for point mutations and deletions was used to identify 54 *CCM3*-mutated index patients. Age at referral and clinical on-

set, type of inaugural events and presence of extra-axial lesions were investigated in these 54 index patients and 22 of their mutated relatives. Mean age at clinical onset was 23.0 ± 16 years. Clinical onset occurred before 10 years in 26% of the patients, and cerebral hemorrhage was the initial presentation in 72% of these patients. Multiple extra-axial, dural-based lesions were detected in 7 unrelated patients. These lesions proved to be meningiomas in 3 patients who underwent neurosurgery and pathological examination. This 'multiple meningiomas' phenotype is not associated with a specific *CCM3* mutation. Hence, *CCM3* mutations are associated with a high risk of early-onset cerebral hemorrhage and with the presence of multiple meningiomas.

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Cavernous angiomas, also known as cerebral cavernous malformations (CCM; OMIM 116860), affect roughly 0.5% of the population and are characterized by abnormal enlarged capillary cavities without intervening brain parenchyma [Russell and Rubinstein, 1989]. CCM lesions are mostly parenchymal lesions affecting the brain and to a lesser extent the spinal cord. In the brain, CCM lesions are usually found in the subcortical white matter. However, CCM may arise in some patients from the dura mater. These dural-based lesions are mostly unique and most often located in the middle cranial fossa, but they may more rarely be encountered outside the middle cranial fossa, as in the convexity [Biondi et al., 2002].

Clinical CCM symptoms include recurrent headaches, focal neurological deficits, hemorrhagic stroke, and seizures [Zabramski et al., 1994; Zabramski et al., 1999; Labauge et al., 2007], but CCM can also be asymptomatic. CCM are sporadic or familial, and over 90% of the patients have a mutation in one of the 3 known genes *CCM1/KRIT1* (OMIM 604214) [Laberge-le Couteulx et al., 1999; Sahoo et al., 1999], *CCM2/MGC4607* (OMIM 607929) [Liquori et al., 2003; Denier et al., 2004] or *CCM3/PDCD10* (OMIM 609118) [Bergametti et al., 2005]. Linkage data on 20 large North American families suggested that 40% of the CCM families were linked to *CCM3* loci, but after identification of the gene, the proportion of *CCM3*-mutated families appeared to be much lower.

Less than 40 *CCM3* families have been reported so far [Guclu et al., 2005; Verlaan et al., 2005; Denier et al., 2006; Gault et al., 2006; Liquori et al., 2006, 2008; Lee et al., 2008; Choe et al., 2010]. This limited number of *CCM3*-mutated patients hampered the analysis of genotype-phenotype correlations. In a previous study on 333 CCM mutation carriers including 28 *CCM3* patients belonging to 17 families, we suggested that the proportion of *CCM3* patients with a childhood onset was higher compared to *CCM1* and *CCM2* patients [Denier et al., 2006]. We also showed in 4 unrelated *CCM3* patients the occurrence of multiple dural-based lesions; however, the pathological nature of these lesions was unknown since none of these patients had undergone neurosurgery [Labauge et al., 2009].

Herein, we conducted a molecular and clinical study on a larger *CCM3* patient cohort, focusing on the age at clinical onset, the type of inaugural event and the association with extra-axial dural-based lesions.

Patients and Methods

Genomic DNA sequencing and quantitative multiplex PCR of short fragments of the 3 known CCM genes allowed us to identify a consecutive series of 300 unrelated CCM probands harboring a loss of function mutation in 1 of the 3 CCM genes. Among these patients who were either enrolled in research programs or referred for molecular diagnosis, 189 were mutated in *CCM1*, 57 in *CCM2* and 54 in *CCM3*. Our study group was composed of these 54 probands and 22 of their mutated relatives. Partial information on some of these patients have been previously reported [Denier et al., 2006; Ahdab et al., 2008; Labauge et al., 2009; Choe et al., 2010].

CCM diagnosis was established on the basis of cerebral MRI and pathological data. Clinical information was collected through direct interview and reviewing of the medical and MRI charts. Clinical assessment included information on age at referral, age at clinical onset and characteristics of inaugural manifestations. MRI investigations were used to search for extra-axial lesions. Pathological data from the 3 patients who underwent surgery for extra-axial lesions were reviewed by experienced neuropathologists (F.C., S.M.-P., C.B.).

Results

CCM3 Mutations

A *CCM3* mutation was identified in 54 probands (table 1). Thirteen had a deletion encompassing one or several coding exons, including 8 whole gene deletions. Forty-one probands had a point mutation leading to a premature stop codon (table 1). Thirty-one different point mutations were identified including 6 recurrent ones (3 found twice, 2 found 3 times, and 1 found 4 times). Point mutations leading to an abnormal splicing accounted for 42% (13/31); nonsense mutation and small insertions or deletions leading to a frameshift and premature stop codon accounted each for 29% (9/31). Two deletions involved only noncoding exons. One was a deletion of exons 1–3 that happened de novo in a 5-year-old boy (C270) with typical multiple cerebral cavernomas (fig. 1). The second one was a deletion of exons 1 and 2 that cosegregated with the affected phenotype within family C085. They were both considered as probably deleterious. The de novo appearance of mutations was established in 4 probands (C052, C146, C107, and C270) and was deduced from familial haplotype analysis for the father of proband C044.

CCM3 Mutations Are Associated with Early-Onset Cerebral Hemorrhage

Thirty of the 54 probands were of the female sex (55.5%), and 24 were of the male sex (44.5%). Among the 54 probands, 5 were asymptomatic and were referred af-

Table 1. CCM3 mutations

Exons	Mutation (NM_007217)	Effect on splicing (cDNA analysis)	Theoretic effect on the protein	Family number	Reported in other families
01–02	deletion of exons 1–2		absence of protein synthesis	C085	
01–03	deletion of exons 1–3		absence of protein synthesis	C270	
01–10	whole gene deletion		absence of protein synthesis	C024 C045 ^a C052 ^a C146 ^a C224 C399 ^c C474 C556	Liquori et al. [2008]
03–04	deletion of exons 3–4		absence of protein synthesis	C518	
04	c.81delT		p.P28LfsX6	C436	
05	c.97-2A>G	exon 5 deletion	p.L33_K50del	C601	Lee et al. [2008]
05	c.103C>T		p.R35X	C055 ^a C377 C446	
05	c.113_114delGT		p.S39CfsX13	C211 ^a	
05	c.129_138 del		p.R45SfsX17	C560	
05	deletion of exon 5		p.L33_K50del	C043 ^a	
06	c.151-1G>C	exon 6 deletion	p.A51SfsX3	C523	Guclu et al. [2005]
06	c.175dupA		p.T59NfsX17	C594	
06	c.196delA				
06	c.212insA	several transcripts	p.K71Xfs	C304	Guclu et al. [2005]
06	c.223delA				
06	c.268+1dupG			C474	
07	c.269-1G>A	exon 7 deletion	p.E90GfsX3	C493	Guclu et al. [2005]; Verlaan et al. [2005]
07	c.275delT		p.M92Xfs	C418	
07	c.283C>T		p.R95X	C254 ^a C589	
07	c.322C>T		p.R108X	C571 C467 C313	
07	c.372_73delAG		p.R124Xfs	C357	
07	c.385C>T		p.Q129X	C031 ^a	
07	c.394_395delinsGATT	exon 7 deletion	p.E90GfsX3	C615	
08–10	deletion of exons 8–10			C433	
08	c.396-31_396-13delinsA	exon 8 deletion	p.D133HfsX10	C596	Verlaan et al. [2005]
08	c.396-3C>G	exon 8 deletion	p.D133HfsX10	C238 ^a	
08	c.396-2A>G				
08	c.401_402dupTA		p.A135X	C070 ^a	
08	c.418G>T		p.D133HfsX10	C502	
08	c.456T>G		p.Y152X	C128 ^a	Liquori et al. [2006]
08	c.474+1G>A				
08	c.474+1G>C		?	C327	
08	c.474+2T>C	exon 8 deletion	p.D133HfsX10	C223 ^a	Liquori et al. [2006]
08	c.474+5G>A	exon 8 deletion	p.D133HfsX10	C158 ^b C189	
09	c.475-1G>A	exon 9 deletion	p.A159GfsX42	C107 ^{a, b}	Guclu et al. [2005]
09	c.496G>T		p.E166X	C319 C572	
09	c.514A>T		p.K172X	C122	
09	c.534delA				
09	c.538delA		p.T180fs188X	C161 ^{b, d}	
09	c.557+1G>C		?	C141 ^a	
09	c.557+3_557+6del	exon 9 deletion		C044 ^a	
10	c.586C>T		p.R196X	C030 ^{a, b} C077 ^a C346 C520	Gault et al. [2006]; Liquori et al. [2006]
10	c.608T>G		p.L203X		

^a Patients reported in Denier et al. [2006]. ^b Patients reported in Labauge et al. [2009]. ^c Patient reported in Choe et al. [2010]. ^d Patient reported in Ahdab et al. [2008].

Fig. 1. Cerebral MRI of proband C270. Multiple CCM lesions in a 5-year-old boy harboring a de novo mutation removing *CCM3* exons 1–3.

Fig. 2. Proportion of patients with an inaugural cerebral hemorrhage depending on age at clinical onset.

Table 2. Age at onset and inaugural manifestation

Age at onset years	Probands	Inaugural manifestation		
		cerebral hemorrhage	epilepsy	other
0–10	11	8	3	0
11–20	9	5	2	2
21–30	10	5	4	1
31–40	10	3	3	4
41–50	1	0	0	1
>51	2	0	2	0

ter the fortuitous discovery of CCM on an MRI performed for another reason. Twenty-five probands had at least one symptomatic relative (familial cases), and 27 probands reported having no symptomatic relative (isolated cases). Information was not available for 2 probands. Analysis of both parents of 6 clinically sporadic cases was performed and showed that the mutation appeared de novo for 4 patients and was inherited from an asymptomatic parent for the other 2. Forty-eight probands had multiple lesions on MRI, and 3 had a single lesion. Two of them were aged 1.2 and 13 years at onset respectively; the third proband was a 10-year-old boy for whom cavernoma was discovered in a context of developmental delay and known multiple cavernoma in an aunt.

Age at referral ranged between 1.2 and 71.8 years (mean age at referral: 28.9 ± 16.8 years). Age at clinical onset was available for 43 probands. Mean age at clinical onset was 23.0 ± 16.0 years. The first manifestation was a cerebral hemorrhage for 21 patients (49%), but the nature of the first clinical manifestation was different depending on the age at clinical onset (table 2, fig. 2). Cerebral hemorrhage was the main inaugural manifestation in patients under 20 years of age, and it was the first event in 72% of the children younger than 10. The proportion of patients whose first clinical manifestation was a cerebral hemorrhage decreased with age. Among the 13 patients with a clinical onset later than 30 years, only 3 patients started their clinical manifestations with a cerebral hemorrhage.

A *CCM3* mutation was detected in 22 relatives. Mean age at referral was 34.8 ± 19.3 years. Ten of them were symptomatic for cavernomas, 11 were asymptomatic, and the clinical status was unknown for the last one. Sixteen had multiple cavernomas, and one had a single cavernoma lesion and MRI. Data were not available for 4 patients.

CCM3 Mutations Are Associated with Extra-Axial Lesions and Multiple Meningiomas

Multiple intracranial, dural-based lesions were detected in 7 unrelated patients from families C30, C107, C158, C161, C346, C399, and C615 (fig. 3a, b). Three of these patients (from families C346, C399 and C616) underwent

Fig. 3. Families with multiple dural-based lesions. **a** Pedigrees of the 7 families with multiple dural-based lesions. Squares and circles indicate males and females, respectively. The probands are indicated by arrows. **b** Cerebral MRI and pathological data of 2 patients with pathologically proven meningiomas. **A–D** Mother of proband C399. Axial T2-weighted gradient-echo sequences (**A**) show multiple parenchymal cavernous angiomas. Sagittal (**B**) and axial (**C**) gadolinium-enhanced dural lesions on T1-weighted images. **D** Paraffin sections colored with hematein eosin. Meningo-

thelial meningioma with typical whorl formations (arrowheads). **Inset** A high-power magnification showing central clearing of nuclei (arrow). Scale bar = 100 μ m. **E–H** Father of proband C615. Axial T2-weighted gradient-echo sequences (**E**) show multiple parenchymal cavernous angiomas. Axial (**F**) and coronal (**G**) gadolinium-enhanced T1-weighted sequences (**E**) show left frontal and sphenoidal dural lesions. **H** Typical pattern of a transitional meningioma: prominent whorls and several psammoma bodies (hematoxylin-eosin-saffron staining, magnification: $\times 100$).

neurosurgery. Pathological analysis of the lesions identified in all 3 patients typical grade I transitional meningiomas (fig. 3b).

Within family C346, the mother of the proband, born in 1950, had multiple parenchymal CCM lesions but was asymptomatic with regard to her CCM lesions. However, she underwent surgery for a supra-sellar meningioma at age 43. Pathological analysis showed a typical grade I transitional meningioma. Her daughter, born in 1974, had a peripheral facial palsy leading to the identification of an extra-axial cavernous angioma of the internal auditory canal and multiple parenchymal cerebral CCM lesions.

Within family C399, the mother of the proband, born in 1953, presented in 2007 a loss of vision of her right eye and a right trochlear nerve palsy. Cerebral MRI showed multiple parenchymal CCM lesions, multiple dural-based lesions seen as hypointense lesions on gadolinium-enhanced T1 sequences with a dural tail sign and a meningioma of the right optical canal nerve that was surgically removed (fig. 3b, A–C). Pathological analysis showed a typical meningothelial meningioma (fig. 3b, C). Her daughter, born in 1970, was symptomatic and her MRI showed a spinal and multiple parenchymal CCM lesions. No extra-axial dural-based lesion was detected.

Within family C615, the father of the proband, born in 1953, underwent neurosurgery for parenchymal CCM in 1992 and 2001 (fig. 3b, E–G). In 1993, a meningioma of the right larger sphenoidal wing was detected which was operated upon. In 2005, 3 novel meningiomas (left frontal, left small sphenoidal wing and left pterional bone) were surgically removed. Pathological analysis of all 4 lesions showed grade I transitional meningiomas (fig. 3b, H). His daughter, born in 1988, developed paresthesias of the right leg, arm and trunk, and was diagnosed as having multiple cerebral parenchymal CCM lesions in 2010. Her MRI does not show extra-axial lesions.

The 4 remaining patients were the probands of families C30, C107, C158, and C161 (3 women and 1 man; mean age: 48 years, range: 42–64 years). MRI of these patients were highly stereotyped and showed: (1) multiple parenchymal cavernous angiomas, and (2) multiple dural-based lesions with similar MR patterns, i.e. hypointense on T1 and hyperintense on T2 sequences, markedly enhanced by gadolinium injection, and with a diffuse dural enhancement. The number of dural lesions increased with age in 3 of them (C30, C161 and C158). Since none of these 4 patients underwent surgery, it was therefore not possible to establish the pathological nature of these lesions which may either be extra-axial, dural-based cav-

ernous angiomas mimicking meningiomas or true meningiomas.

The association of multiple extra-dural lesions and multiple meningiomas was not detected so far in any of the probands mutated in *CCM1* (189 patients) or *CCM2* (57 patients).

Discussion

We report herein the largest series of *CCM3*-mutated patients. The analysis of this consecutive series of 54 probands and their relatives allowed us (1) to confirm the association of *CCM3* mutations with early-onset cerebral hemorrhage, (2) to show for the first time that these mutations may be associated in some patients with the development of multiple meningiomas, and (3) to show that this association is specifically encountered in *CCM3*-mutated patients and not detected in *CCM1* or *CCM2* mutants.

We present 7 patients with both parenchymal CCM lesions and multiple dural-based lesions, and we show that this very unusual phenotype is strongly associated with mutations in *CCM3*. These lesions, multiple in all cases except one (mother of proband C346), have the typical MRI features of meningiomas. They are isointense on T1, slightly hyperintense on T2 sequences, and strongly and homogeneously enhanced by gadolinium injection with a dural tail sign in most of them. However, these features have been previously reported in patients showing extra-axial histologically proven cavernous angiomas [Perry et al., 1993; Kanaan et al., 2001; Biondi et al., 2002; Guermazi et al., 2005]. In most cases, these patients were preoperatively considered as having a meningioma. These previously reported patients had only one single dural-based lesion and no parenchymal CCM lesion except one patient showing both multiple parenchymal CCM and dural-based histopathologically proven cavernous angiomas [Lewis et al., 1994]. Herein, we have been able to show for the first time that in some patients, these dural-based lesions are typical meningiomas and not extra-axial cavernous angiomas. In one of our patients (father of proband C615), 4 distinct meningiomas were surgically removed. In 2 other patients, surgery of one of their multiple lesions was performed, and pathological analysis disclosed a typical meningioma. Altogether, these data strongly suggest that *CCM3* mutations are associated with both multiple meningiomas and multiple extra-axial cavernous angiomas. The penetrance of this ‘meningioma’ phenotype is incomplete.

It is also of note that the mutations observed in patients with multiple meningiomas do not differ from those observed in patients showing solely parenchymal cerebral cavernous angiomas. Indeed, the same mutation, R196X, was identified in one family with multiple meningiomas (C346), but also in families C077 and C520 in which no dural-based lesion was detected. The complete *CCM3* deletion is associated with multiple meningiomas in family C399, whereas in 7 other families, showing a complete deletion of *CCM3*, no dural-based lesion was detected in any affected member. The absence of dural-based lesions in patients carrying similar mutations suggests that these mutations have either an incomplete penetrance or, most likely, involve modifying genes.

Meningiomas are the most frequent primary central nervous system tumors in adult patients, and numerous studies have been conducted to identify the genes and mechanisms involved in their genesis and progression [Mawrin and Perry, 2010]. Loss of function mutations in the *NF2* gene have been involved in the majority of these tumors. A variety of additional cytogenetic anomalies, mutations of several other tumor suppressor genes and genes involved in the Wnt signaling pathway have been involved in both *NF2*-mutated and *NF2*-nonmutated meningiomas [Mawrin and Perry, 2010; Clark et al., 2013]. However, to our knowledge, neither the *CCM3* locus nor the *CCM3* gene have previously been involved in sporadic or familial meningioma. *CCM3* encodes an adaptor

protein which is part of the cytosolic CCM complex, but *CCM3* is also part of several multiprotein complexes including serine/threonine kinases STK24, STK35 and MST4, and the STRIPAK complex [Ma et al., 2007; Voss et al., 2007; Goudreaux et al., 2009; Faurobert and Albiges-Rizo, 2010]. Many components of this complex are involved in cell cycle regulation and apoptosis with *CCM3* having a proapoptotic role in vitro [Chen et al., 2009; Fidalgo et al., 2010]. In addition, *Ccm3* ablation in the mouse has recently been shown to be responsible for increased cell proliferation and cell survival/resistance to apoptosis through an activation of the Akt signalling pathway [Louvi et al., 2011]. At present, the mechanisms leading from *CCM3* mutations to meningioma are unknown. Future work including genomic analysis of the meningioma lesions of our patients should help to decipher the mechanisms and signaling pathways which may be involved. It may also help to unravel specific functions of *CCM3* since neither *CCM1* nor *CCM2* mutations lead to this phenotype.

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