Supplemental Tables

Supplemental Table 1. Characteristics of all enrolled Probands (n=51)

Characteristics		Sporadic CCM probands (n=8)	FCCM probands (n=33)	CCM probands unidentified the CCM type (n=10)	All multiple CCM probands (n=51)	*P-value**
Age at enrollment, y		44.63 ± 14.08	38.97 ± 17.79	44.8 ± 11.24	41.00 ± 16.15	0.409
Age at diagnosis of probands, y		42.85 ± 15.23	34.68 ± 17.87	39.42 ± 14.16	36.89 ± 16.82	0.241
Body mass index, kg/m^2		27.42 ± 3.16	23.16 ± 3.86	22.26 ± 3.57	23.65 ± 4.01	**0.006**
Sex, No. (%)	Male	5 (62.5)	23 (69.7)	5 (50.0)	33 (64.7)	>0.999
	Female	3 (37.5)	10 (30.3)	5 (50.0)	18 (35.3)	
Adult, No. (%)	No	0	7 (21.2)	0	7 (13.7)	0.310
	Yes	8 (100.0)	26 (78.8)	10 (100.0)	44 (86.3)	
ICH, No. (%)	No	2 (25.0)	21 (63.6)	3 (30.0)	26 (51)	0.109
	Yes	6 (75.0)	12 (36.4)	7 (70.0)	25 (49)	
Epilepsy, No. (%)	No	7 (87.5)	26 (78.8)	6 (60.0)	39 (76.5)	>0.999
	Yes	1 (12.5)	7 (21.2)	4 (40.0)	12 (23.5)	
FND without ICH, No. (%)	No	8 (100.0)	31 (93.9)	10 (100.0)	49 (96.1)	>0.999
	Yes	0	2 (6.1)	0	2 (3.9)	
NSWI, No. (%)	No	5 (62.5)	25 (75.8)	9 (90.0)	39 (76.5)	0.658
	Yes	3 (37.5)	8 (24.2)	1 (10.0)	12 (23.5)	
Number of lesions on the SWI sequence, No. (%)	≤5	7 (87.5)	2 (6.9)	4 (40.0)	13 (27.7)	**<0.001**
	6~25	1 (12.5)	8 (27.6)	3 (30.0)	12 (25.5)	
	>25	0	19 (65.5)	3 (30.0)	22 (46.8)	
Number of lesions larger than 4mm on the T2 sequence,	<10	8 (100.0)	17 (54.8)	9 (90.0)	34 (69.4)	**0.034**
	⩾10	0	14 (45.2)	1 (10.0)	15 (30.6)	

No. (%)

*P-values obtained by statistical tests in sporadic CCM patients and familial CCM patients. CCM, Cerebral cavernous vascular malformation. ICH, intracranial hemorrhage. FND, focal neurological deficits. NSWI, Non-specific symptoms without ICH.

Supplemental Table 2. Final diagnosis in patients with suspected CCM (n=15)

ID	Number of lesions observed on the SWI sequence	Genetic variation	Genetic variation of proband	The final diagnosis of CCM
1	≤5	*CCM2*	*CCM2*	Yes
2	6~25	*CCM2*	*CCM2*	Yes
3	≤5	No mutation	*CCM1*	No
4	≤5	*CCM2*	*CCM2*	Yes
5	≤5	*CCM1*	*CCM1*	Yes
6	≤5	No mutation	*CCM1*	No
7	≤5	*CCM1*	*CCM1*	Yes
8	≤5	*CCM1*	*CCM1*	Yes
9	≤5	No mutation	*CCM1*	No
10	≤5	No mutation	*CCM1*	No
11	≤5	No mutation	No mutation	Suspected
12	≤5	No mutation	CCM1	No
13	6~25	No mutation	No mutation	Suspected
14	1	No mutation	No mutation	Suspected
15	6~25	No mutation	No mutation	Suspected

CCM, Cerebral cavernous vascular malformation.

Supplementary Table 3. Genetic mutations in 3 classical CCM gene

Single nucleotide variants									
Gene	Rs number	Variant Conseq	Nucleotide alteration	Amino acid change	chromosomal location (GRch37)	Phenotype	Clinvar	Number of family	Novel
CCM1	rs2131525596	deletion	c.1141del	Asp381Ilefs*4	chr7: 91855843-91855846	CCM	Pathogenic	1	N
CCM1	rs1563267100	Insertion and Deletion	c.1255-1_1256del	--	chr7:91852291-91852293	CCM	Pathogenic	1	N
CCM1	rs1563267100	splice Region	c.1255-1G>T	--	chr7:91852293	CCM	Pathogenic	1	N
CCM1		duplication	c.1507dup	Thr503Arg fs*17	chr7:91851271		Not Reported	1	Y
CCM1	rs2131435199	nonsense	c.1561C>T	Gln521*	chr7:91851218	CCM	Pathogenic	1	N
CCM1		deletion	c.1654del	Ile552*	chr7:91844001	--	Not Reported	1	Y
CCM1	rs1490051866	duplication	c.1933_1936dup	Thr646Ilefs*10	chr7:91842597-91842598	--	Not Reported	1	Y
CCM1		duplication	c.255dupT	Ile86Tyrfs*35	chr7:91870313	--	Not Reported	1	Y
CCM1	rs137853139	missense	c.410A>G	Asp137Gly	chr7:91865802	CCM	Pathogenic	1	N
CCM1	rs1563305064	splice Region	c.729+1G>C	--	chr7:91864716	CCM	Pathogenic	1	N
CCM1	rs886039659	nonsense	c.802C>T	Gln268*	chr7:91864165	--	Pathogenic	1	N
CCM1	--	deletion	c.803del	Gln268Argfs*8	chr7:91864164	--	Not Reported	1	Y
CCM1	--	nonsense	c.981T>G	Tyr327*	chr7:91863771	--	Not Reported	1	Y
CCM2	--	nonsense	c.475C>T	Gln159*	chr7:45108044	--	Not Reported	1	N
CCM2	--	deletion	c.502_503del	Leu169Valfs*66	chr7:45108069-45108070	--	Not Reported	1	N
CCM2	rs755800734	nonsense	c.55C>T	Arg19*	chr7:45077876	CCM	Pathogenic	4	N
CCM2	--	deletion	ex.2del	--	chr7: 45067212-45078045	--	Not Reported	1	Y
CCM3	--	deletion	c.558_567del	Lys186fs	chr3:167402168	--	Not Reported	1	Y
CCM3	--	deletion	c.373del	Val125*	chr3:167413406	--	Not Reported	1	Y

CCM3	--	delines	c.491_493delinsGG	Lys164Argfs*5	chr3:167405086-167405088	--	Not Reported	1	Y
Copy number variations									
Gene	Description	Variant Conseq	Performance	Copy number loss region	chromosomal location (GRch37)	Phenotype	Clinvar	Number of family	Novel
CCM1	A deletion of 7.96Mb (copy number =1)	Copy number loss	contains 77 genes, 48 of which encode proteins	7q21.11q21.3	chr7:g.86273209-94232784del	CCM	Pathogenic	1	N
CCM1	Heterozygous deletion of the whole gene	Copy number loss	exons 1-4 are not encoded	7q21.2	chr7:91875220-91875414 chr7:91874741-91874909 chr7:91874216-91874485 chr7:91873316-91873463	CCM	Pathogenic	1	N

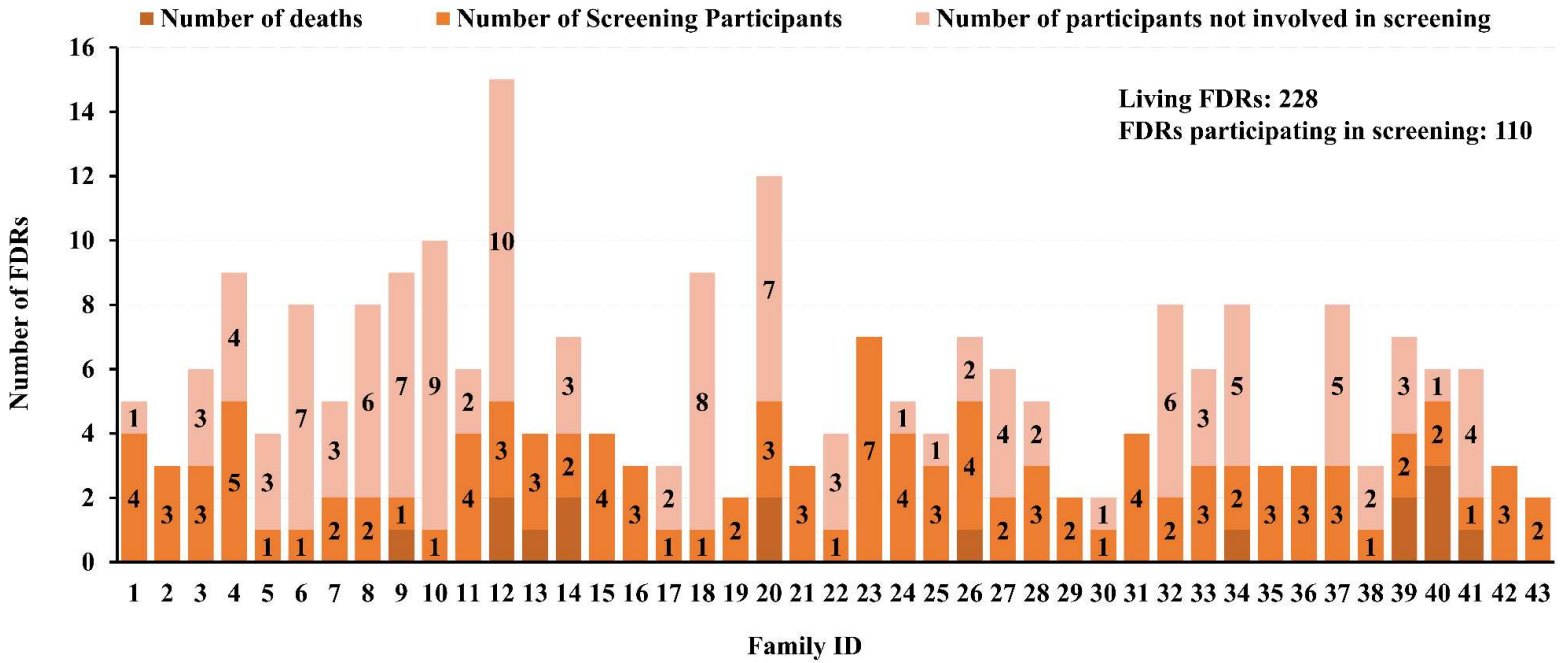
Novel, novel mutation. Y, yes. N, no. CCM, Cerebral cavernous malformation.

Supplementary Table 4. Comparison of characteristics, symptoms and number of lesions in FCCM patients with different genotypes (n=64)

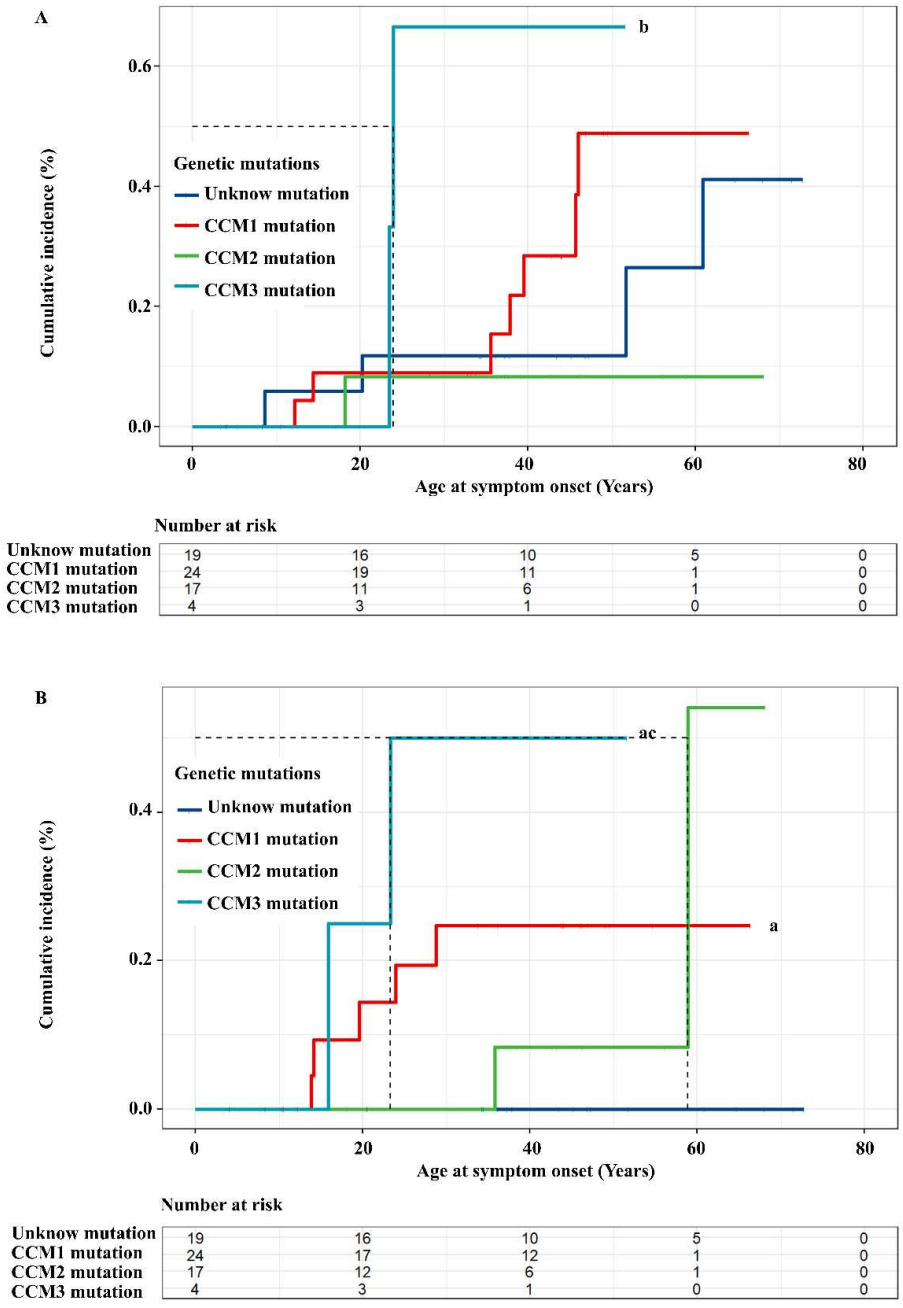
Characteristics		Unknow mutation (n=19)	*CCM1* (n=24)	*CCM2* (n=17)	*CCM3* (n=4)	*P value*
Age at enrollment, y		41.74 ± 20.87	37.42 ± 16.10	34.76 ± 18.94	32.75 ± 15.84	0.651
Age at diagnosis of probands, y		41.23 ± 21.15	33.18 ± 15.03	31.89 ± 19.44	28.56 ± 15.76	0.338
Body mass index, kg/m^2		24.26 ± 4.91	23.25 ± 3.14	22.81 ± 4.76	20.56 ± 4.90	0.424
Sex, No. (%)	Male	12 (63.2)	14 (58.3)	10 (58.8)	1 (25.0)	0.612
	Female	7 (36.8)	10 (41.7)	7 (41.2)	3 (75.0)	
Adult, No. (%)	No	3 (15.8)	6 (25.0)	4 (23.5)	1 (25.0)	0.909
	Yes	16 (84.2)	18 (75.0)	13 (76.5)	3 (75.0)	
Diagnosed by the appearance	No	14 (73.7)	9 (37.5)	10 (58.8)	1 (25.0)	0.063
of symptoms, No. (%)	Yes	5 (26.3)	15 (62.5)	7 (41.2)	3 (75.0)	
Number of lesions on the	≤5	4 (23.5)	4 (17.4)	4 (23.5)	0	0.525
SWI sequence, No. (%) [a]	6~25	5 (29.4)	6 (26.1)	3 (17.6)	0	
	>25	6 (35.3)	13 (56.5)	9 (52.9)	2 (66.7)	
	1	2 (11.8)	0	1 (5.9)	1 (33.3)	
Number of lesions larger than	<10	11 (73.3)	17 (70.8)	12 (75.0)	0	**0.041**
4mm on the T2 sequence [b]	≥10	4 (26.7)	7 (29.2)	4 (25.0)	4 (100.0)	

Note: a Four patients with FCCM did not receive SWI sequence examination due to their young age or metal stents, which were not suitable for enhanced MRI examination; b Five patients with FCCM did not receive T2WI sequence examination due to their young age or metal stents, which were not suitable for enhanced MRI examination. CCM, Cerebral cavernous malformation.

Supplementary Figures



Supplementary Figure 1. The number of members of each family and the number of members enrolled in the study. FDRs, First degree relatives.



Supplementary Figure 2. Cumulative incidence in FCCM patients with different genotypes. A. Cumulative intracranial hemorrhage in FCCM patients with different genotypes; B. Cumulative epilepsy in FCCM patients with different genotypes.