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SHORT REPORT

Genetic heterogeneity and absence of founder effect in a series of 36 French cerebral cavernous angiomas families

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Cerebral cavernous angiomas malformations (CCM) can be inherited as an autosomal dominant condition. *CCM1*, a yet unidentified gene mapping on 7q21–q22, was shown to be involved in all CCM Hispano-American families, with a strong founder effect. Genetic heterogeneity in non Hispano-American families was established in two families.

We conducted a genetic linkage analysis on 36 French CCM families using eight microsatellite markers mapping within the *CCM1* interval. Admixture analysis showed that 65% of these families were linked to the *CCM1* locus. Haplotypes analysis of *CCM1*-linked families did not show any evidence for a strong founder effect.

Keywords: cavernous angiomas; chromosome 7; founder effect; genetic heterogeneity

Introduction

Cavernomas are abnormally enlarged capillary cavities without intervening brain parenchyma. Main clinical symptoms include seizures, cerebral haemorrhage, headache and focal neurological deficits. They may occur with an autosomal dominant pattern of inheritance.[1] In 1995, in a large Hispano-American family, Dubovsky *et al*[2] mapped a gene, *CCM1*, to chromosome 7q, within a 33 cM interval. This genetic mapping was further confirmed in a large number of Hispano-American families and a strong founder effect was observed in that ethnic group.[3–7] The size of the genetic interval likely to contain *CCM1* was reduced to 4 cM, between markers D7S2410 and D7S689.[5] Only eight non Hispano-American families have been analysed so far.[4,5,8–10] Two of them were not linked to *CCM1*, establishing the genetic heterogeneity of this condition.[9]

We report linkage data on 36 French Caucasian CCM families using a panel of eight polymorphic microsatellite markers mapping within the D7S2410–D7S689 interval.

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Material and methods

We selected 36 French families for genotyping (Figure 1). Clinical, neuroimaging features and status criterias were detailed elsewhere.[10,11] All families were Caucasian and originated from France. A total of 220 potentially informative meioses, including 157 affected individuals, were analysed.

Seven polymorphic microsatellites spanning the *CCM1* interval (D7S2410, D7S2409, D7S646, D7S689, D7S1813, D7S1789, D7S558) were chosen from the Généthon linkage map[12] and from the Cooperative Human Linkage Center. M65B was identified by SL, based on sequencing data of a

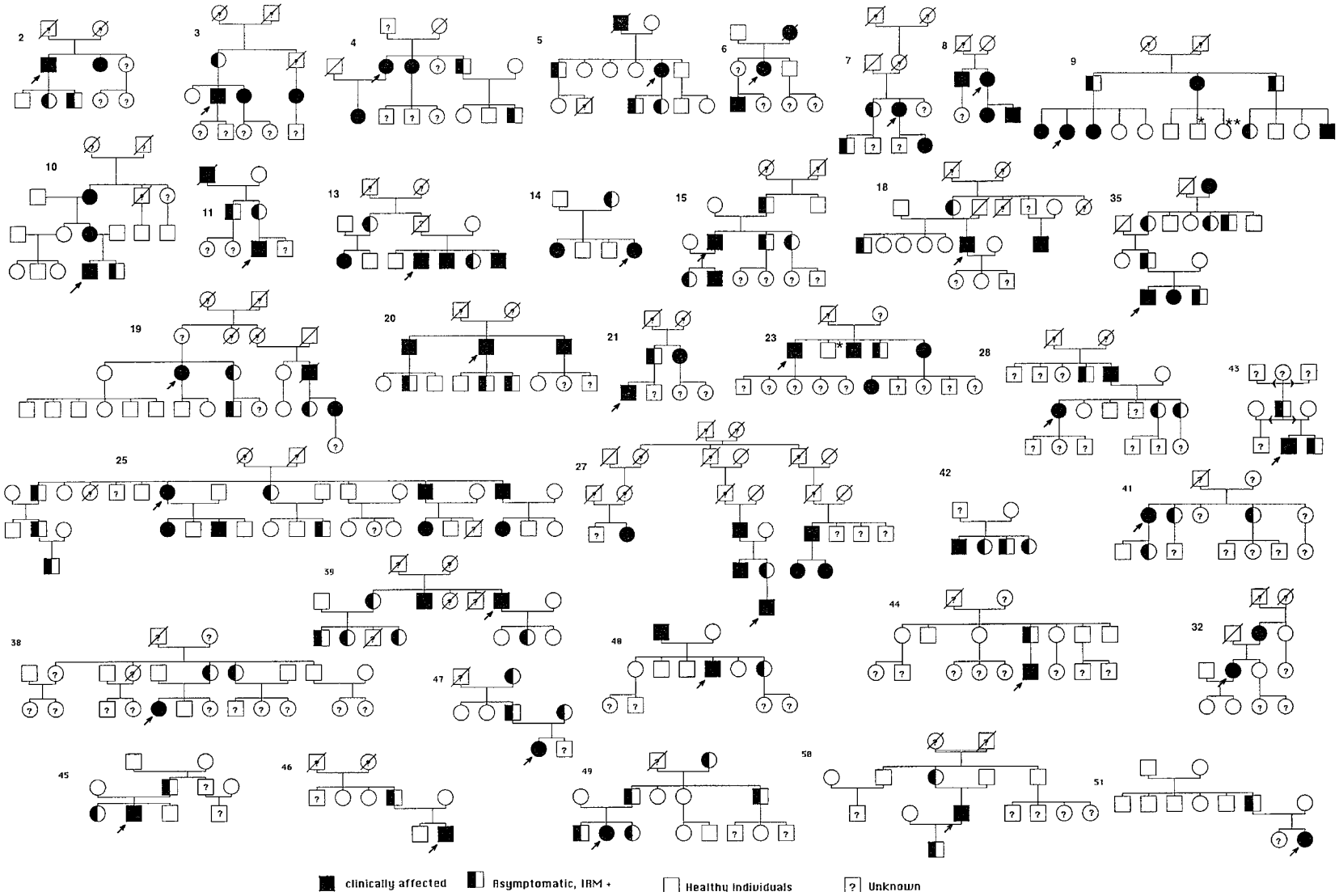

Figure 1 *Pedigrees of the 36 CCM families. Solid symbols: symptomatic CCM patients having cavernous angiomas on cerebral MRI; half filled symbols: asymptomatic individuals having cavernomas on MRI; open symbols: asymptomatic individuals having a normal MRI; ?:members of unknown status. * = recombinant individual in families F9, F23. An additional recombinant event occurred in F27 (see text)*

Table 1 Pairwise linkage data (1)

No of individuals sampled				*D7S2410* *Z at θ =*				*M65B* *Z at θ =*				*D7S646* *Z at θ =*				*D7S689* *Z at θ =*			
Fam.	*A*[a]	*H*[a]	*U*[a]	*0.00*	*0.01*	*0.05*	*0.10*	*0.00*	*0.01*	*0.05*	*0.10*	*0.00*	*0.01*	*0.05*	*0.10*	*0.00*	*0.01*	*0.05*	*0.10*
3	4	1	0	1.04	1.01	0.92	0.79	1.05	1.03	0.93	0.81	0.27	0.26	0.22	0.17	0.23	0.22	0.19	0.15
9	8	7	1	1.10	1.10	1.08	1.00	1.62	1.64	1.67	1.61	1.68	1.67	1.61	1.48	0.32	0.31	0.28	0.23
10	4	6	0	1.01	0.99	0.90	0.79	0.00	0.00	0.00	0.00	1.12	1.09	0.99	0.87	0.82	0.80	0.74	0.65
13	6	2	0	0.66	0.66	0.67	0.64	1.69	1.66	1.52	1.35	–	–	–	–	0.25	0.24	0.21	0.18
19	5	10	0	0.18	0.16	0.09	0.03	1.10	1.07	0.97	0.83	1.73	1.69	1.52	1.30	–0.06	–0.06	–0.05	–0.05
23	4	1	1	0.16	0.18	0.22	0.24	1.15	1.13	1.04	0.93	1.46	1.44	1.33	1.20	0.19	0.19	0.17	0.14
25	12	12	1	5.90	5.80	5.41	4.89	3.38	3.33	3.12	2.83	4.85	4.80	4.54	4.17	4.77	4.70	4.37	3.94
27	8	1	0	–1.20	–0.32	0.21	0.34	2.23	2.17	1.94	1.64	2.55	2.49	2.26	1.96	2.02	1.98	1.80	1.56
40	3	4	0	1.36	1.33	1.23	1.10	–0.02	–0.02	–0.02	–0.02	–0.02	–0.02	–0.02	–0.02	1.36	1.33	1.23	1.10
4	5	1	0	0.50	0.49	0.44	0.38	–0.23	–0.17	–0.02	0.07	–1.81	–0.90	–0.32	–0.12	0.76	0.74	0.66	0.56
5	4	7	0	0.43	0.44	0.47	0.47	0.69	0.70	0.71	0.68	–0.13	–0.08	0.05	0.13	–0.13	–0.13	–0.12	–0.11
6	1	2	2	0.09	0.09	0.07	0.05	–0.47	–0.43	–0.33	–0.24	–0.46	–0.43	–0.33	–0.24	0.11	0.10	0.09	0.07
7	4	0	1	0.23	0.22	0.18	0.13	0.57	0.55	0.49	0.40	0.55	0.54	0.47	0.39	0.57	0.55	0.48	0.40
8	4	0	0	0.23	0.22	0.18	0.13	0.57	0.55	0.49	0.40	–0.03	–0.03	–0.03	–0.02	0.27	0.25	0.21	0.15
11	3	0	0	0.27	0.26	0.23	0.19	0.27	0.26	0.23	0.19	0.27	0.26	0.23	0.19	0.27	0.26	0.23	0.19
14	3	2	0	0.32	–0.32	–0.29	0.24	0.02	0.02	0.02	0.02	–0.16	–0.14	–0.07	–0.01	–0.16	–0.14	–0.06	–0.01
15	5	1	0	0.52	0.53	0.53	0.52	0.37	0.39	0.45	0.46	–0.51	–0.48	–0.36	–0.25	–0.51	–0.48	–0.36	–0.25
18	3	4	3	0.60	0.61	0.64	0.62	0.30	0.31	0.34	0.33	0.26	0.26	0.24	0.22	0.34	0.36	0.40	0.40
21	3	0	0	0.27	0.25	0.21	0.15	0.24	0.23	0.19	0.14	0.27	0.25	0.21	0.15	0.27	0.26	0.23	0.19
28	5	5	0	0.64	0.65	0.66	0.63	–0.48	–0.45	–0.36	–0.28	0.27	0.26	0.23	0.19	0.27	0.26	0.23	0.19
32	2	2	0	0.23	0.22	0.18	0.14	0.26	0.25	0.20	0.15	0.23	0.20	0.18	0.14	–0.51	—0.48	–0.36	–0.25
35	8	4	0	0.34	0.36	0.40	0.19	0.00	0.00	0.00	0.00	–0.44	–0.41	–0.30	–0.21	0.10	0.10	0.16	0.19
38	3	0	2	0.24	0.23	0.20	0.16	0.22	0.21	0.17	0.12	0.21	0.20	0.16	0.01	0.24	0.23	0.20	0.17
41	4	1	1	0.74	0.72	0.64	0.53	0.75	0.73	0.65	0.55	0.50	0.49	0.44	0.38	0.70	0.68	0.61	0.50
42	4	0	0	0.00	0.00	0.00	0.00	0.67	0.66	0.59	0.51	0.66	0.64	0.58	0.50	0.66	0.64	0.58	0.50
43	3	1	0	0.41	0.40	0.36	0.31	0.41	0.40	0.36	0.31	0.41	0.40	0.36	0.31	–0.10	–0.10	–0.08	–0.06
44	2	6	0	–1.70	–1.53	–1.07	–0.72	–1.44	–1.31	–0.92	–0.60	–0.37	–0.34	–0.25	–0.18	–0.48	–0.45	–0.34	–0.24
45	3	2	0	–0.44	–0.41	–0.32	–0.23	–0.44	–0.41	–0.32	–0.23	–0.44	–0.41	–0.32	–0.23	–0.44	–0.41	–0.32	–0.23
46	2	3	0	–0.54	–0.50	–0.37	–0.26	–1.22	–1.12	–0.83	–0.56	–1.03	–0.96	–0.72	–0.52	–0.51	–0.47	0.36	–0.25
47	4	2	0	–0.18	–0.17	–0.16	–0.14	–1.35	–1.02	–0.55	–0.32	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	3	2	0	–0.22	–0.19	–0.08	0.00	–0.53	–0.49	–0.37	–0.26	–0.25	–0.21	–0.10	–0.01	–0.52	–0.51	–0.38	–0.27
51	2	5	0	–0.70	–0.63	–0.46	–0.30	–0.70	–0.64	–0.46	–0.30	–0.22	–0.21	–0.17	–0.13	0.00	0.00	0.00	0.00
2	4	1	0	–3.07	–1.14	–0.50	–0.26	–3.07	–1.14	–0.50	–0.25	–2.94	–1.14	–0.50	–0.26	–2.94	–1.14	–0.50	–0.26
20	6	4	0	–2.80	–1.80	–1.05	–0.68	0.27	0.29	0.32	0.32	–2.89	–1.60	–0.85	–0.51	–2.80	–1.80	–1.05	–0.68
39	7	2	0	–4.64	–1.89	–0.69	–0.23	–2.05	–0.11	0.45	0.57	–2.10	–1.33	–0.71	–0.44	–2.06	–0.13	0.43	0.56
49	6	5	0	–2.71	–1.80	–1.07	–0.72	–3.09	–0.37	0.23	0.41	–4.88	–0.98	–0.26	0.03	0.00	0.00	0.00	0.00
Summary lod scores				–2.39	5.24	9.22	10.2	2.75	9.9	12.4	12.6	–3.79	6.65	10.2	10.8	4.1	8.8	10.3	10.1
H2[†]				Z_{max}=5.2 α=0.73 θ=0.05				Z_{max}=6.3 α=0.88 θ=0.05				Z_{max}=5.7 α=0.49 θ=0.00				Z_{max}=5.2 α=0.73 θ=0.05			
H1[†]				Z_{max}=5.1 α=1.00 θ=0.05				Z_{max}=6.3 α=1.00 θ=0.10				Z_{max}=5.4 α=1.00 θ=0.10				Z_{max}=5.1 α=1.00 θ=0.05			

[a]Number of individuals sampled: A=Affected, H=Healthy and U=Unknown status.
[†]HOMOG data obtained under the hypotheses of Heterogeneity (H2) and Homogeneity (H1).

Table 1 Pairwise linkage data (2)

No of individuals sampled				*D7S2409* Z at θ =				*D7S1813* Z at θ =				*D7S1789* Z at θ =				*D7S558* Z at θ =			
Fam.	*A*[a]	*H*[a]	*U*[a]	*0.00*	*0.01*	*0.05*	*0.10*	*0.00*	*0.01*	*0.05*	*0.10*	*0.00*	*0.01*	*0.05*	*0.10*	*0.00*	*0.01*	*0.05*	*0.10*
3	4	1	0	0.21	0.20	0.17	0.13	0.23	0.22	0.19	0.08	0.22	0.21	0.18	0.14	1.04	1.01	0.92	0.79
9	8	7	1	1.62	1.64	1.67	1.61	2.49	2.47	2.36	2.17	2.62	2.60	2.49	2.29	0.32	0.31	0.28	0.23
10	4	6	0	0.25	0.25	0.24	0.21	0.78	0.77	0.72	0.65	1.12	1.09	0.99	0.87	–0.31	–0.28	–0.20	–0.13
13	6	2	0	1.63	1.60	1.46	1.29	1.35	1.32	1.20	1.05	1.12	1.10	0.99	0.87	0.79	0.77	0.69	0.59
19	5	10	0	1.32	1.29	1.16	0.99	2.41	2.36	2.18	1.94	0.11	0.11	0.10	0.10	0.35	0.34	0.32	0.29
23	4	1	1	–0.28	–0.29	–0.30	–0.28	1.46	1.44	1.33	1.19	0.30	0.30	0.28	0.26	1.16	1.14	1.03	0.90
25	12	12	1	1.70	1.70	1.65	1.55	2.83	2.78	2.57	2.30	1.50	1.47	1.34	1.17	0.52	0.51	0.47	0.41
27	8	1	0	2.31	2.25	2.03	1.75	0.23	0.22	0.17	0.13	2.67	2.61	2.38	2.08	1.40	1.34	1.13	0.89
35	8	4	0	1.54	1.54	1.51	1.43	1.54	1.54	1.51	1.43	–0.44	–0.41	–0.30	–0.21	0.94	0.95	0.95	0.92
40	3	4	0	1.36	1.33	1.23	1.10	1.36	1.33	1.23	1.10	1.36	1.33	1.23	1.10	1.36	1.33	1.23	1.10
4	5	1	0	–2.93	–1.02	–0.40	–0.19	–2.11	–1.11	–0.50	–0.25	0.19	0.18	0.16	0.13	0.50	0.49	0.44	0.38
5	4	7	0	0.13	0.14	0.19	0.21	0.36	0.35	0.33	0.30	0.17	0.16	0.12	0.08	–0.23	–0.23	–0.22	–0.19
6	1	2	2	0.12	0.12	0.11	0.09	0.30	0.30	0.26	0.21	0.26	0.25	0.22	0.18	–0.01	0.00	0.00	0.01
7	4	0	1	0.55	0.54	0.47	0.39	0.26	0.26	0.23	0.19	0.56	0.54	0.48	0.40	–2.39	–1.28	–0.63	–0.37
8	4	0	0	–0.05	–0.05	–0.04	–0.03	0.26	0.25	0.22	0.18	–0.04	–0.04	–0.03	–0.03	0.27	0.26	0.23	0.19
11	3	0	0	0.21	0.20	0.18	0.14	0.56	0.55	0.50	0.44	0.26	0.25	0.22	0.18	–2.59	–1.38	–0.72	–0.44
14	3	2	0	0.00	0.00	0.00	0.00	–0.16	–0.14	0.06	0.01	0.02	0.02	0.02	0.02	0.00	0.00	0.00	0.00
15	5	1	0	–0.15	–0.12	–0.04	–0.03	0.42	0.43	0.47	0.48	–0.18	–0.15	–0.06	0.01	0.03	0.03	0.02	0.02
18	3	4	3	1.08	1.06	0.98	0.87	0.16	0.17	0.18	0.16	0.26	0.26	0.24	0.22	0.00	0.00	0.00	0.00
21	3	0	0	0.25	0.24	0.21	0.18	–0.04	–0.04	–0.03	–0.02	0.22	0.21	0.17	0.12	0.23	0.22	0.18	0.13
28	5	5	0	0.62	0.63	0.64	0.61	0.64	0.65	0.66	0.62	0.63	0.64	0.65	0.62	–0.23	–0.17	–0.04	0.04
32	2	2	0	0.23	0.22	0.18	0.13	0.26	0.25	0.20	0.16	–0.44	–0.41	–0.30	–0.21	0.03	0.03	0.02	0.02
38	3	0	2	0.18	0.17	0.13	0.09	0.20	0.19	0.15	0.11	0.20	0.19	0.15	0.10	0.24	0.23	0.20	0.16
41	4	1	1	–0.30	–0.28	–0.19	–0.12	0.17	0.16	0.14	0.11	0.49	0.48	0.43	0.37	0.50	0.49	0.44	0.38
42	4	0	0	0.59	0.58	0.52	0.45	0.66	0.64	0.58	0.50	0.61	0.59	0.54	0.46	0.60	0.59	0.52	0.45
43	3	1	0	0.41	0.40	0.36	0.32	0.41	0.40	0.36	0.31	–0.09	–0.09	–0.07	–0.06	–0.10	–0.10	–0.08	–0.06
44	2	6	0	–0.19	–0.19	–0.21	–0.20	–1.44	–1.31	–0.92	–0.60	–0.70	–0.64	–0.46	–0.30	–0.27	–0.24	–0.14	–0.07
45	3	2	0	–0.44	–0.41	–0.32	–0.23	–0.44	–0.41	–0.32	–0.23	–0.44	–0.41	–0.32	–0.23	–0.44	–0.41	–0.32	–0.23
46	2	3	0	–0.45	–0.42	–0.32	–0.23	–1.22	–1.13	–0.82	–0.57	–1.22	–1.12	–0.81	–0.57	–1.22	–1.12	–0.82	–0.57
47	4	2	0	–0.17	–0.16	–0.12	–0.08	–0.48	–0.45	–0.34	–0.24	–0.36	–0.33	–0.23	0.00	–0.61	–0.56	–0.41	–0.29
50	3	2	0	0.55	0.54	0.49	0.43	0.58	0.57	0.52	0.45	–0.25	–0.21	–0.10	–0.14	–0.19	–0.16	–0.07	–0.01
51	2	5	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	–0.22	–0.21	–0.17	–0.13	–0.48	–0.45	–0.34	–0.24
2	4	1	0	–2.95	–1.16	–0.51	–0.27	–3.07	–1.15	–0.50	–0.26	–3.07	–1.15	–0.50	–0.26	–2.94	–1.14	–0.50	–0.26
20	6	4	0	–1.80	–0.85	–0.26	–0.05	–1.87	–0.85	–0.25	–0.04	–1.87	–0.85	–0.25	–0.04	–2.32	–1.36	–0.71	–0.44
39	7	2	0	0.17	0.16	0.14	0.11	–2.11	–1.72	–0.68	–0.23	–2.08	–1.70	–0.68	–0.23	–4.90	–2.15	–0.96	–0.48
49	6	5	0	0.15	0.18	0.25	0.30	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.90	0.89	0.84	0.77
Summary lod scores				7.47	12.0	13.3	12.7	6.98	11.3	14	13.8	3.49	6.87	9.1	9.36	–8.05	–0.1	3.75	4.89
H2[†]				Z_{max}=6.6 α=1.00 θ=0.05				Z_{max}=7.6 α=0.92 θ=0.05				Z_{max}=4.7 α=1.00 θ=0.10				Z_{max}=2.5 α=0.53 θ=0.00			
H1[†]				Z_{max}=6.6 α=1.00 θ=0.05				Z_{max}=7.5 α=1.00 θ=0.10				Z_{max}=4.7 α=1.00 θ=0.10				Z_{max}=2.4 α=1.00 θ=0.10			

[a]Number of individuals sampled: A=Affected, H=Healthy and U=Unknown status.
[†]HOMOG data obtained under the hypotheses of Heterogeneity (H2) and Homogeneity (H1).

bacterial artificial chromosome (RG085C05) mapped within the D7S2410–D7S689 interval.

Linkage analysis was performed as previously described.[10] Parameters for linkage analysis were based on a combination of epidemiological[13] and clinical/Magnetic Resonnance Imaging (MRI) data from the French CCM families.[11] Briefly, large autopsies and MRI series estimated the prevalence of cavernous angiomas in the general population to be close to 0.5–1%.[13] In the French population, 10–20% of these cavernous angiomas are hereditary (ETL, unpublished results). The penetrance was estimated to be close to 90% when MRI was used to establish the status.[11] Therefore linkage parameters were established as follows: phenocopy prevalence of 0.01, gene frequency of 0.001 and 90% penetrance.

Multilocus analysis of the four most informative markers (D7S2410, M65B, D7S646 and D7S689) was computed after recoding each marker to a three alleles system which did not change significantly the results of the two-point analysis for any of the latter markers. Genetic linkage analysis of a subset of CEPH families and of our families, as well as physical mapping data,[12] (SL, unpublished results) strongly suggest that the most likely order of markers used for multipoint linkage analysis is D7S2410–(*0.03*)–M65B–(*0.005*)–D7S646–(*0.005*)–D7S689. Homogeneity was assessed using the admixture test implemented in the HOMOG program package.

Results

Significant lod scores were obtained for family 25 with several markers (Table 1). Lod scores higher than 1 were obtained in eight additional families (families 3,9,10,13,23,27,35,40) with at least two markers. Negative lod scores values <-2 were obtained for four families (families 2, 20, 39, 49).

HOMOG admixture analyses of multipoint data are shown in Table 2. The percentage of families linked to *CCM1* was estimated to be close to 65%. Nine families displayed a conditional probability *PP* to be linked to the *CCM1* locus above 0.95 and four families had a $PP < 0.1\%$.

Analysis of the *CCM1* haplotypes of the nine families having a conditional probability to be linked $>95\%$ showed that none of these families shared the Hispano-American haplotype (Figure 2). Some alleles such as *M65B*-133bp were frequent but there was no significant difference of frequency when compared with our control population (spouses and unlinked haplotypes) using the *p-excess* methodology.[6] Comparative analysis of the nine linked haplotypes (Figure 2) did not show evidence for a founder effect.

Four recombinant events were observed within the nine linked families. Three of them were observed in healthy individuals having a normal MRI and aged 35 and 33 years old (F9*, F9**) and 56 years old (F23*).

Table 2 HOMOG analysis of multipoint data

Families	*A*[a]	*H*[a]	*U*[a]	*Cond prob*	*lower limit*	*upper limit*
3	4	1	0	0.96	0.88	0.99
9	8	7	1	0.99	0.98	1.00
10	4	6	0	0.96	0.89	0.99
13	6	2	0	0.99	0.94	1.00
19	5	10	0	0.99	0.99	1.00
23	4	1	1	0.97	0.86	0.99
25	12	12	1	1.00	1.00	1.00
27	8	1	0	0.99	0.96	1.00
40	3	4	0	0.98	0.94	0.99
4	5	1	0	0.26	0.01	0.62
5	4	7	0	0.81	0.29	0.95
6	1	2	2	0.77	0.54	0.92
7	4	0	1	0.88	0.71	0.96
8	4	0	0	0.87	0.69	0.96
11	3	0	0	0.78	0.55	0.92
14	3	2	0	0.58	0.32	0.82
15	5	1	0	0.80	0.58	0.93
18	3	4	3	0.88	0.72	0.96
21	3	0	0	0.78	0.55	0.92
28	5	5	0	0.89	0.74	0.97
32	2	2	0	0.85	0.67	0.95
35	8	4	0	0.90	0.75	0.97
38	3	0	2	0.77	0.53	0.92
41	4	1	1	0.92	0.81	0.98
42	4	0	0	0.91	0.77	0.97
43	3	1	0	0.83	0.62	0.94
44	2	6	0	0.04	0.01	0.14
45	3	2	0	0.40	0.19	0.69
46	2	3	0	0.12	0.04	0.33
47	4	2	0	0.14	0.04	0.37
50	3	2	0	0.44	0.21	0.73
51	2	5	0	0.27	0.11	0.55
2	4	1	0	0.01	0.00	0.02
20	6	4	0	0.01	0.00	0.04
39	7	2	0	0.00	0.00	0.00
49	6	5	0	0.00	0.00	0.01
H2				Zmax=9.12	α=0.65	θ=0.017
H1				Zmax=3.93	α=1.00	θ=0.012

[a]Number of individuals sampled: A=Affected, H=Healthy and U=Unknown status.
*HOMOG data obtained under the hypotheses of Heterogeneity (H2) and Homogeneity (H1).

F* was recombinant at D7S2410 and carried the 'healthy' alleles for the other markers. F9** carried the whole affected haplotype due either to a double recombination event within the *CCM1* interval or to the incomplete penetrance of this condition. F23* was recombinant with D7S2410 and was no more recombinant with telomeric markers. In family F27, a recombination event also occurred with marker D7S2410 within an affected individual: affected individuals belonging to two of the three branches of this family did not share any allele for this marker. No other recombination event was detectable in this family.

	Hisp.-Am	F3	F9	F10	F13	F19	F23	F25	F27	F40
D7S2410	279	273	263	263	267	273	265	271	279	267
D7S2409	NC	219	223	223	221	221	223	223	223	219
D7S1813	137	127	135	133	131	125	131	127	131	123
D7S1789	137	133	129	131	129	133	129	133	129	139
MS65B	ND	133	135	133	139	133	133	133	131	133
D7S646	185	185	197	181	183	181	185	197	197	185
D7S558	107	107	103	103	103	115	111	103	107	107
D7S689	129	127	127	125	127	127	127	129	127	139

Figure 2 *Comparison of the Hispano-American CCM1 haplotype with the haplotypes observed in French chromosome 7 linked families. Polymorphic markers are shown on the left. Numbers indicate the sizes of the linked alleles. NC: not comparable since the primers used to amplify D7S2409 were different.*

Conclusion

Herein we confirmed the genetic heterogeneity of this condition and showed that *CCM1* is the main locus in the French population, the proportion of families linked to chromosome 7 being close to 65%. Haplotypes analysis within linked families did not support the existence of a strong founder effect.

Analysis of these families as well as of additional families with new microsatellite markers mapping within the *CCM1* interval is needed to refine this interval further. It will be a crucial step for the identification of the *CCM1* gene, since no strong candidate has yet been mapped within the interval.

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