

A FOUNDER MUTATION AS A CAUSE OF CEREBRAL CAVERNOUS MALFORMATION IN HISPANIC AMERICANS

MURAT GÜNEL, M.D., ISSAM A. AWAD, M.D., KARIN FINBERG, B.S., JOHN A. ANSON, M.D., GARY K. STEINBERG, M.D., PH.D., H. HUNT BATJER, M.D., THOMAS A. KOPITNIK, M.D., LESLIE MORRISON, M.D., STEVEN L. GIANNOTTA, M.D., CAROL NELSON-WILLIAMS, B.S., AND RICHARD P. LIFTON, M.D., PH.D.

Abstract Background. Cerebral cavernous malformation is a vascular disease of the brain causing headaches, seizures, and cerebral hemorrhage. Familial and sporadic cases are recognized, and a gene causing familial disease has been mapped to chromosome 7. Hispanic Americans have a higher prevalence of cavernous malformation than do other ethnic groups, raising the possibility that affected persons in this population have inherited the same mutation from a common ancestor.

Methods. We compared the segregation of genetic markers and clinical cases of cavernous malformation in Hispanic-American kindreds with familial disease; we also compared the alleles for markers linked to cavernous malformation in patients with familial and sporadic cases.

Results. All kindreds with familial disease showed linkage of cavernous malformation to a short segment of

chromosome 7 (odds supporting linkage, $4 \times 10^{10}:1$). Forty-seven affected members of 14 kindreds shared identical alleles for up to 15 markers linked to the cavernous-malformation gene, demonstrating that they had inherited the same mutation from a common ancestor. Ten patients with sporadic cases also shared these same alleles, indicating that they too had inherited the same mutation. Thirty-three asymptomatic carriers of the disease gene were identified, demonstrating the variability and age dependence of the development of symptoms and explaining the appearance of apparently sporadic cases.

Conclusions. Virtually all cases of familial and sporadic cavernous malformation among Hispanic Americans of Mexican descent are due to the inheritance of the same mutation from a common ancestor. (N Engl J Med 1996;334:946-51.)

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CEREBRAL cavernous malformation is a vascular disorder of the brain characterized by abnormal vascular spaces lined by a single layer of endothelium without intervening neural parenchyma or identifiable mature vessel-wall elements.^{1,2} There is almost always evidence of prior hemorrhage, characterized by the accumulation of hemosiderin. This disease was recognized as a common clinical entity after the advent of magnetic resonance imaging (MRI), which demonstrates a characteristic lesion of variable signal intensity surrounded by a dark ring attributable to hemosiderin (Fig. 1).^{3,4} Before the introduction of MRI, patients with cavernous malformation were typically classified as having an idiopathic seizure disorder or an angiographically occult vascular malformation. Both MRI and autopsy studies suggest a prevalence of cavernous malformation of 0.5 percent, although the prevalence of symptomatic disease is much lower.^{5,6}

Symptomatic disease typically begins in the third through fifth decades of life.^{5,7-9} Treatment ranges from therapy with antiepileptic drugs in patients with seizures to surgical excision of accessible lesions in patients with recurrent hemorrhage or intractable seizures.¹⁰⁻¹³

Although the pathogenesis of cavernous malformation is unknown, a familial predisposition has been rec-

ognized, with up to 55 percent of patients having an affected relative.¹⁴⁻²³ Genetic linkage studies have recently mapped a gene causing cavernous malformation to a segment of the long arm of chromosome 7 (7q).^{24,25}

Familial and sporadic cases are particularly evident among Hispanic Americans of Mexican descent.^{14,15,21-23} The disproportionate number of cases in this population raises the possibility that a common mutation inherited from a shared ancestor (a founder mutation) may be responsible for the disease. If identified, such a founder mutation would permit both the development of a highly specific genetic test for the disease and an assessment of whether apparently sporadic cases in this group are in fact genetic and due to the same mutation.

METHODS

Patients

The study protocol was approved by the Human Investigation Committee at Yale University School of Medicine. Informed consent was obtained from the study participants. Twenty-two patients with cavernous malformation, who described themselves as Hispanic Americans, were identified from neurosurgical records at the University of New Mexico and Stanford University; two Hispanic-American kindreds affected by familial cavernous malformation were identified by the University of Texas Southwestern Medical School and the University of Southern California. Eleven of the index patients had surgically documented cavernous malformation, and 13 had diagnostic findings on MRI.

Detailed family trees were assembled, and family medical histories were obtained. The ancestors of 22 patients were from Mexico, and the origin of 2 families was uncertain. None of these families were known to be related to one another; tracing family trees to at least the great-grandparents of each index patient identified no ancestors shared by two or more kindreds.

Control Subjects

For the estimation of the allele frequencies, 16 Hispanic spouses of the index patients and 33 unrelated, healthy Hispanic volunteers recruited by the University of New Mexico ($n = 19$) and Stanford University ($n = 14$) served as controls. In addition, 62 independent chro-

From the Howard Hughes Medical Institute (M.G., K.F., C.N.-W., R.P.L.), the Section of Neurosurgery (M.G., I.A.A.), and the Departments of Cell Biology (M.G.) and Medicine and Genetics (C.N.-W., R.P.L.), Yale University, New Haven, Conn.; the Departments of Neurosurgery (J.A.A.) and Neurology (L.M.), University of New Mexico, Albuquerque; the Department of Neurosurgery, Stanford University, Palo Alto, Calif. (G.K.S.); the Department of Neurosurgery, Northwestern University, Chicago (H.H.B.); the Department of Neurosurgery, University of Texas Southwestern Medical Center, Dallas (T.A.K.); and the Department of Neurosurgery, University of Southern California, Los Angeles (S.L.G.). Address reprint requests to Dr. Lifton at Yale University School of Medicine, Howard Hughes Medical Institute, Boyer Center for Molecular Medicine, 295 Congress Ave., New Haven, CT 06510.

Dr. Günel is the recipient of a scholarship from the American College of Surgeons. Dr. Lifton is an investigator of the Howard Hughes Medical Institute.

mosomes not linked to cavernous malformation in the study kindreds were used as controls. There were no significant differences in allele frequencies among these groups for any of the markers studied.

Genotyping and Analysis of Linkage and Linkage Disequilibrium

Genomic DNA was prepared from venous blood.²⁶ Highly informative genetic markers on chromosome 7q were genotyped by the polymerase chain reaction.²⁵ The genotypes were assessed independently by two investigators who were unaware of the subjects' status.

For the analysis of linkage, subjects with diagnostic findings on surgery or MRI were classified as affected. Asymptomatic subjects over the age of 20 with no history of seizures, headaches, or cerebral hemorrhage were classified as unaffected, whereas asymptomatic subjects 20 years of age or younger were classified as having an unknown phenotype. All phenotypes were assigned prospectively.

Linkage analysis²⁷ was performed, with cavernous malformation specified as an autosomal dominant trait with a gene frequency of 0.001, penetrance of 80 percent, and prevalence of sporadic cases of 0.001.²⁵ Changing the estimates of penetrance or the prevalence of sporadic cases had small effects on the lod score and did not affect the location of the mutant gene.

Haplotypes (the string of particular alleles for different markers present on individual chromosomes) were constructed on the basis of linkage within families. The likelihood of finding specific haplotypes by chance was calculated as the product of the allele frequencies on control chromosomes. The allele frequencies in the patients and controls and disease penetrances in different age groups were compared by the chi-square test.²⁸ The ages of symptomatic and asymptomatic gene carriers were compared by a two-tailed t-test.²⁸

We calculated P_{excess} , an indicator of the degree of departure of marker-allele frequencies in patients from those found in controls, with the following equation:

$$P_{\text{excess}} = (P_{\text{patients}} - P_{\text{controls}}) / (1 - P_{\text{controls}}),$$

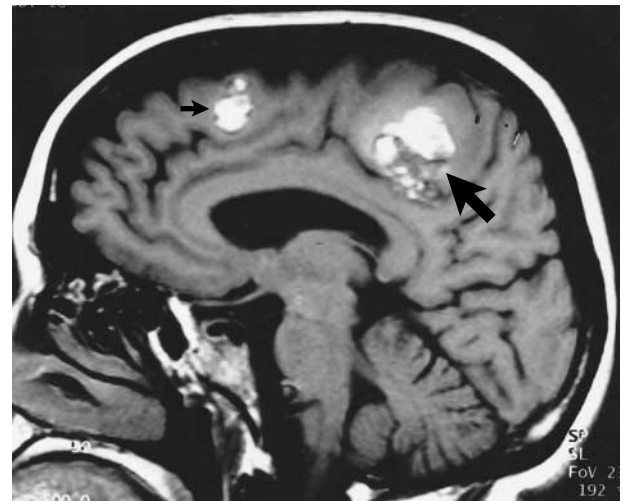
where P_{patients} and P_{controls} denote the frequency of a particular allele on cavernous-malformation and control chromosomes, respectively.^{29,30}

RESULTS

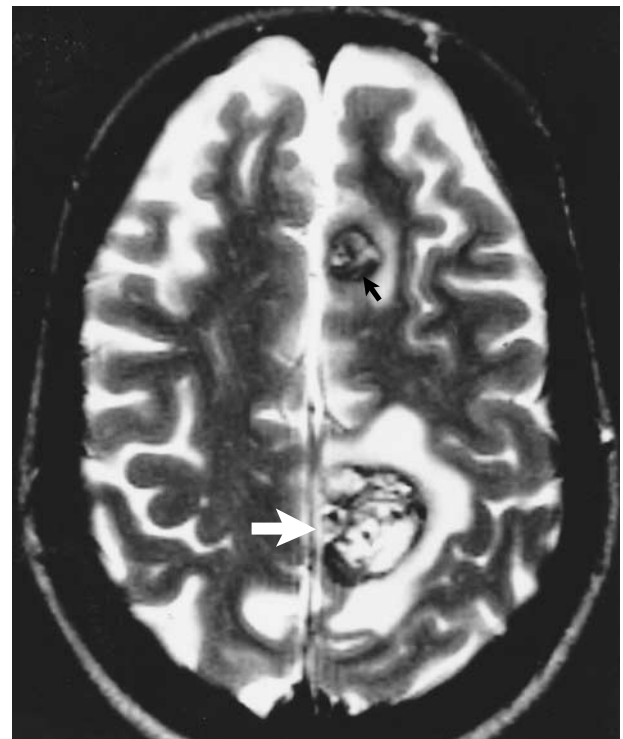
One or more additional cases of cavernous malformation were identified among the relatives of 14 of the 24 index patients (58 percent) — a figure consistent with prior estimates for the familial form of the disease in Hispanic Americans.¹⁵ Thus, a total of 57 patients (31 female and 26 male) with a diagnosis of cavernous malformation were studied: 47 members of 14 kindreds with familial cavernous malformation and 10 patients with sporadic cases. The patients ranged in age from 2 to 69 years. Four symptomatic patients were given a diagnosis before the age of 10, 34 were given a diagnosis between the ages of 10 and 40, and initial symptoms developed in 9 patients after the age of 40. Ten patients were asymptomatic. Signs and symptoms included headache in 28 patients, seizure disorder in 22, and cerebral hemorrhage in 24.

Analysis of Linkage

Since prior studies have supported linkage of cavernous malformation to a large segment of 7q,^{24,25} we compared the segregation of genetic markers on 7q to the segregation of cavernous malformation in the 10 families with 2 or more living affected members. Analysis showed strong evidence favoring linkage of cavernous malformation to a segment of 7q in all families. For example, every affected member of Family 1 inherited allele 6 of locus D7S657, whereas none of the unaffected family members inherited this allele (Fig. 2A). Similar



A

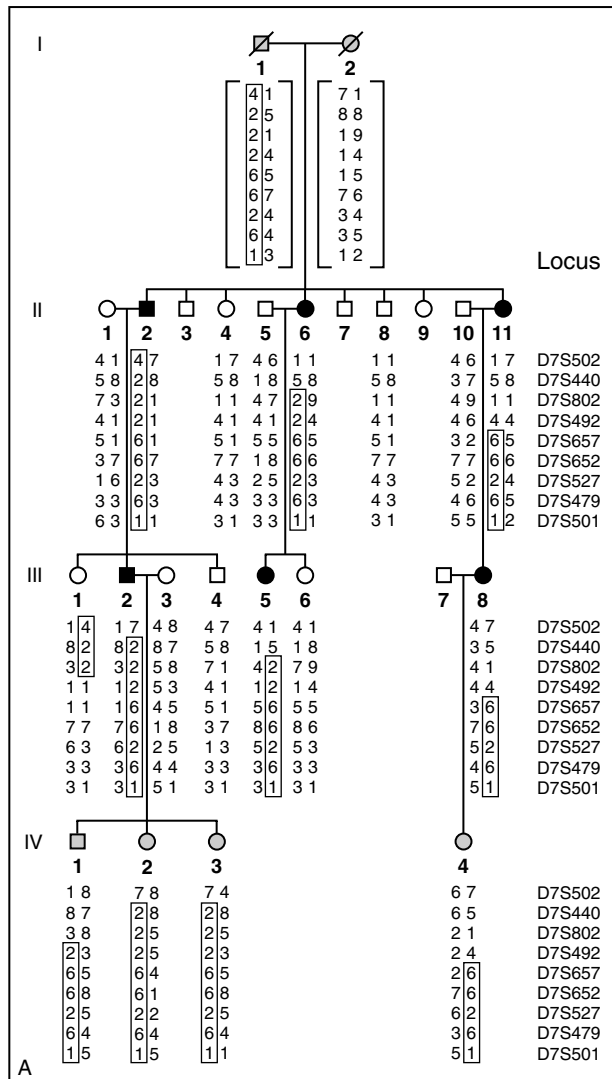


B

Figure 1. Sagittal T₁-Weighted (Panel A) and Axial T₂-Weighted (Panel B) Magnetic Resonance Images Demonstrating the Typical Appearance of Cavernous Malformation.

The small and large arrows indicate lesions within the frontal lobe and the Rolandic area, respectively. In both images there are areas of heterogeneous signal intensity surrounded by black rings indicative of hemosiderin deposition from previous microhemorrhages (more readily seen in Panel B). The high-intensity signal (white) is due to recent hemorrhage within the lesion.

analyses can be performed in all families with this and additional markers. The odds of the observed linkage results' occurring by chance were calculated and compared with the likelihood of observing these results under the specified model of linkage (Fig. 2B). In all 10 families combined, the odds favoring linkage to D7S657 with no recombination were $4 \times 10^{10}:1$ (lod score, 10.6).



Nearby markers, D7S492 and D7S479, did not completely cosegregate with the disease, which indicates that the disease gene was located in a 7-cM segment between D7S492 and D7S479. These findings are consistent with the hypothesis that all cases of cavernous malformation in these kindreds are due to a mutation in the same gene, but they provide no indication of whether the same or independent mutations cause the disease in different kindreds.

Evidence That All Familial Cases Are Due to the Same Mutant Chromosome

To assess the possibility that different kindreds with familial cavernous malformation inherited the same mutation from a common ancestor, we compared the alleles for markers closely linked to the cavernous-malformation gene in affected members of different kindreds (Fig. 3). If all these families had independent mutations in the same gene, these mutations would have occurred on unrelated chromosomes; consequently, alleles of genetic markers linked to the disease gene would show no greater similarity to one another in different kindreds than expected by chance, and marker alleles and cavernous-malformation mutations would be said to be in linkage equilibrium. Alternatively, if different families had all inherited the identical mutation from a common ancestor, the alleles of markers closely linked to the disease gene would be identical to one another, since they would all have descended from the same ancestral chromosome. In this case, knowledge that a chromosome carries a mutation at the cavernous-malformation locus would be predictive of the genotype at a flanking locus, and these alleles would be said to be in linkage disequilibrium.

Analysis of marker D7S689, which showed no recombination with cavernous malformation in these families, revealed that 47 of 47 disease chromosomes from

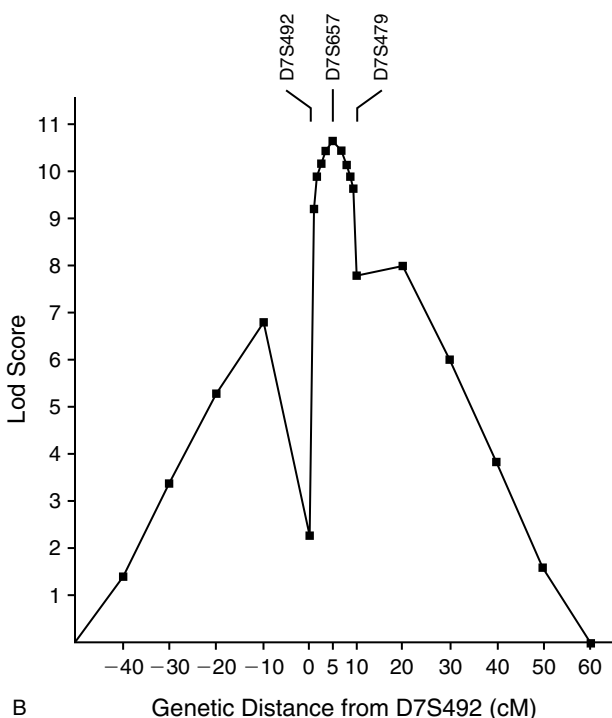


Figure 2. Linkage of Cavernous Malformation to Chromosome 7q. Panel A shows the pedigree of four generations of Family 1. Squares denote male family members, circles female family members, symbols with a slash deceased members, solid symbols affected members, open symbols unaffected members, and gray symbols members with unknown disease status (these family members either were asymptomatic subjects under the age of 20 or had died). Below each symbol, the genotypes of marker loci on chromosome 7q are shown in their map order, with the locus nearest the centromere at the top (D7S502). Marker alleles that are identical on chromosomes containing the cavernous-malformation mutation in different kindreds are enclosed by a box. The most likely ancestral haplotypes in generation I were inferred and are shown in brackets (the distinction between maternal and paternal haplotypes is arbitrary). Asymptomatic subjects IV-1, IV-2, IV-3, and IV-4 have all inherited the segment of chromosome 7q containing the cavernous-malformation locus. All four are less than 20 years old, a fact that reflects the age-dependent nature of the development of symptoms.

Panel B shows the results of linkage analysis of cavernous malformation and markers D7S492, D7S657, and D7S479. The genetic distance of each marker from D7S492 is indicated.³¹ The lod scores for the linkage of cavernous malformation to each position on the map are shown. The maximal lod score was 10.6 with no recombination with D7S657, suggesting that the disease locus lies between D7S492 and D7S479. The lod - 1 support interval (approximating the 95 percent confidence interval) for the location of the cavernous-malformation locus spans a 7-cM segment of chromosome 7q.

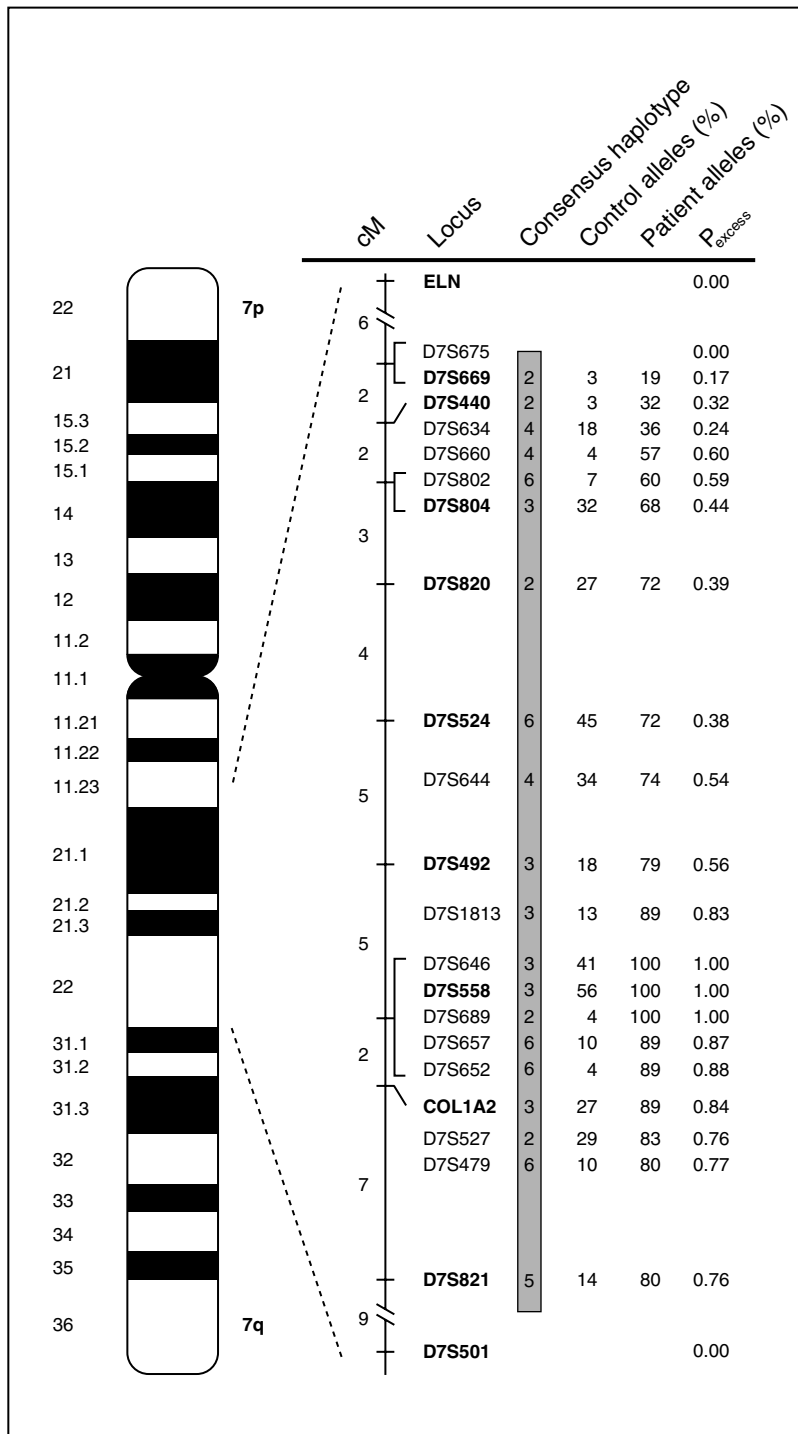


Figure 3. Identical 7q Haplotypes in Patients with Cavernous Malformation.

At the left, a diagram of chromosome 7 is shown. Adjacent to this, marker loci in the region 7q11.23–22 are shown in their map order.³¹ Markers recently used to construct an integrated genetic map are indicated in bold, and the distances in centimorgans (cM) between adjacent markers are shown to the left of the loci.³¹ Additional markers in each interval are also shown; loci that have not been separated by recombination are in brackets. The consensus haplotype for marker alleles found on disease chromosomes is shown. The frequency of each of these alleles on 98 chromosomes from Hispanic control subjects without cavernous malformation and on disease chromosomes from 47 members of 14 kindreds with familial disease is shown to the right of the consensus haplotype. The value for P_{excess} , an indicator of the strength of linkage disequilibrium of cavernous-malformation mutations and marker alleles, is shown for each locus (see the Methods section). Linkage disequilibrium is present over a long segment of chromosome 7, and P_{excess} reaches a maximum of 1.0 with loci D7S646, D7S558, and D7S689.

affected subjects of 14 kindreds with familial cavernous malformation carried allele 2 of this marker, as compared with only 4 of 98 chromosomes from Hispanic control subjects ($P < 0.001$) (Fig. 3). This finding provides strong evidence of linkage disequilibrium between cavernous malformation and this marker in these families and is corroborated by analysis of other markers tightly linked to the cavernous-malformation gene (Fig. 3). The degree of linkage disequilibrium is expressed as P_{excess} ; this value is zero if the allele frequencies in patients and controls are identical, and 1.0 if every disease allele carries the same allele of a polymorphic marker. In this analysis, P_{excess} was equal to or approximated 1.0 in the vicinity of D7S689 and diminished gradually toward zero in both directions from this location (Fig. 3). This peak location is within the interval containing the cavernous-malformation gene that was defined by linkage analysis within families.

Analyses of haplotypes allow one to determine how long a piece of the original founder chromosome, in this case chromosome 7, is conserved among different subjects. Affected patients from 10 kindreds had identical haplotypes (identical alleles for each different genetic marker) over an interval of at least 22 cM, since the alleles for all 15 markers from D7S820 to D7S821 were identical. In unrelated Hispanic subjects, this haplotype would be expected to be found by chance on 1 chromosome in 7.8×10^{12} . The finding of this same haplotype in members of 10 kindreds provides a strong indication that these shared segments were derived from a common ancestral chromosome.

Affected subjects from 4 other kindreds with familial cavernous malformation shared haplotypes with these 10 families over shorter segments, ranging from 16 to 1 cM. These shared haplotypes all included at least a portion of the interval containing the cavernous-malformation gene identified by linkage analysis. The likelihood of finding these haplotypes by chance ranges from 9.2×10^{-3} to 2.6×10^{-7} . These findings indicate that the patients in all the families inherited the same cav-

Table 1. Age Dependence of the Symptoms of Cavernous Malformation.

AGE (YR)	SYMPTOMATIC PATIENTS	ASYMPTOMATIC CARRIERS	TOTAL	PERCENT SYMPTOMATIC
1-10	3	12	15	20
11-20	3	4	7	43
21-30	10	3	13	77
31-50	15	8	23	65
≥51	8	6	14	57
Total	39	33	72	54

ernous-malformation mutation by descent from a common ancestor.

Penetrance of Symptomatic Disease

The identification of a conserved haplotype in kindreds with familial cavernous malformation provides an opportunity to determine the proportion of persons who have inherited the cavernous-malformation mutation who are clinically symptomatic (the penetrance of the trait). Sixty-eight members of families with two or more living affected members were screened for the conserved haplotype. Thirty-three asymptomatic subjects harboring the entire conserved haplotype spanning the interval from D7S492 to D7S479 were identified, including 10 subjects in whom the disease had been previously diagnosed by MRI. The mean (\pm SE) age of these subjects was significantly lower than that of symptomatic subjects (25 ± 3.5 vs. 37 ± 2.5 years, $P=0.004$), suggesting that the asymptomatic subjects are at risk for symptomatic disease in the future.

From these data, age-specific penetrances of symptomatic disease can be estimated (Table 1). The prevalence of symptomatic disease varied significantly with age, being low until the age of 20 (27 percent) and increasing to 66 percent after the age of 20 ($P=0.002$). The prevalence of symptomatic disease never increased above 76 percent in any decade, indicating that penetrance of the disease is age-dependent and less than 100 percent in all age groups.

Evidence That Sporadic Cases Are Also Genetic

The finding that all patients with familial disease had inherited the same mutation from a common ancestor, coupled with the knowledge that disease penetrance was incomplete, raised the question of whether Hispanic patients with apparently sporadic cases of cavernous malformation may have inherited the same mutation. To test this possibility, we determined the chromosome 7q genotypes and haplotypes of 10 patients with sporadic cavernous malformation. Eight of these patients had the same long haplotypes as patients with familial disease, which extended 12 to 30 cM and included identical alleles for 10 to 21 markers that span the location of the cavernous-malformation gene; the likelihoods of these haplotypes' occurring by chance range from 2×10^{-13} to 2.4×10^{-6} . The remaining two kindreds shared a portion of the conserved haplotype within the interval containing the cavernous-malformation gene, with likelihoods that these are chance findings of 2.4×10^{-3} and 0.14. These results indicate that

virtually all sporadic cases in this group were genetic and due to the inheritance of the same mutation as was inherited by patients with familial disease.

Refined Location of the Cavernous-Malformation Gene

Knowledge of a founder cavernous-malformation mutation in this population can be used to refine the location of the disease gene. The founder chromosome had one specific allele at each marker locus. The span of this ancestral haplotype has been reduced in subsequent generations by recombination, with ancestral alleles for markers more closely linked to the mutation being retained and more distant marker alleles being exchanged for alleles that are representative of the general population. Consequently, identification of the minimal set of marker alleles shared by all patients who inherited the founder mutation can be used to define the location of the disease gene; this approach, called disequilibrium mapping, takes advantage of many more meiotic events than can be observed in individual families. In patients with familial disease, all disease chromosomes had the same alleles for markers D7S646, D7S558, and D7S689. These findings strongly suggest that the cavernous-malformation gene lies very near these loci, refining the position of the mutant gene considerably from that obtained by meiotic mapping in individual kindreds.

DISCUSSION

Although cavernous malformation has been recognized as an autosomal dominant trait in some families, 50 percent of cases have been classified as sporadic.¹⁵⁻²² In the present study, virtually all cases in Hispanic Americans of Mexican descent, including apparently sporadic cases, could be attributed to inheritance of the same mutation from a common ancestor. The apparent paradox of sporadic cases' being due to the same mutation as familial cases can be explained by incomplete penetrance, with some carriers remaining asymptomatic. The only argument against this interpretation is the finding of one patient with a sporadic case who harbored only a small segment containing two marker alleles of the conserved haplotype in the linked interval. This patient could have either the same mutation or an independent mutation that occurred by chance on a chromosome with these alleles. This issue will be definitively resolved by the identification of the common cavernous-malformation mutation in Hispanic Americans.

Meiotic mapping within families localized the cavernous-malformation gene to a 7-cM interval in Hispanic Americans, and disequilibrium mapping refined the location of the gene within this interval to a much smaller segment near loci D7S646, D7S558, and D7S689, greatly aiding the search for the underlying mutant gene. This interval can be excluded as the position of the cavernous-malformation gene in several non-Hispanic kindreds²⁵ (and unpublished data), indicating that in at least some of these kindreds the disease is due to a mutation at other loci.

The long length of the conserved haplotype in many of the families studied suggests that in some cases the common ancestor with cavernous malformation may

have been in a relatively recent generation. This possibility seems surprising given that the families were from diverse geographic locations and that no blood relationships were found between different kindreds, but it may reflect the relatively recent migration of a founder from Mexico to the United States. If so, some patients with cavernous malformation who live in Mexico might prove to share very small segments of the ancestral haplotype, permitting very precise mapping of the cavernous-malformation gene, as has been accomplished for several other diseases with founder mutations.^{29,30}

The present findings have implications for the genetic diagnosis of cavernous malformation in Hispanic persons. To date, definitive diagnosis has relied on characteristic findings on MRI or surgery. Our demonstration that the disease is commonly due to the inheritance of a founder mutation in this ethnic group indicates that genetic testing can be used for the preclinical diagnosis of cavernous malformation. Moreover, once the disease-causing mutation in this population has been identified, a single direct test of high sensitivity and specificity will be available and applicable to this group. The advantages and drawbacks of such testing will have to be carefully considered in each case.

The ability to identify carriers of cavernous-malformation mutations also provides the potential to recognize affected subjects in other diagnostic groups. For example, 20 percent of patients with intractable temporal-lobe epilepsy harbor intracranial mass lesions; cavernous malformation accounts for one fourth of these lesions.³² If a simple genetic test becomes available, it may be used to identify patients with cavernous malformation among Hispanic Americans with intractable epilepsy.

Finally, these findings have implications for the pathogenesis of cavernous malformation in non-Hispanics, among whom familial and sporadic cases have been recognized.^{1,16-20} The finding that virtually all sporadic cases among Hispanic Americans are in fact genetic raises the possibility that many apparently sporadic cases in non-Hispanic patients will also prove to be genetic. The present findings provide the framework for a unified understanding of the pathogenesis of this disease.

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