

Familial Hemiplegic Migraine and Autosomal Dominant Arteriopathy with Leukoencephalopathy (CADASIL)

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a recently described familial cerebrovascular disorder shown to map to chromosome 19q12. Familial hemiplegic migraine has also been shown in some families to map close to the CADASIL locus. The fully developed CADASIL phenotype consists of recurrent strokes developing in the fourth decade, progressing to a pseudobulbar palsy, spastic quadriplegia, and subcortical dementia. In an Irish family 15 members were fully investigated by magnetic resonance scanning; 10 had typical magnetic resonance features of CADASIL. Five members of this family had familial hemiplegic migraine and 4 of these had magnetic resonance evidence of CADASIL. Two other members had migraine with and without aura as a presenting clinical symptom of CADASIL. This disorder has been shown by linkage analysis to map to the CADASIL locus at chromosome 19. The phenotype at presentation of CADASIL in this family was variable and age related and included familial hemiplegic migraine, migraine with and without aura, transient ischemic attacks, strokes, and spinal cord infarction. This family study increases our understanding of the spectrum of clinical manifestations of this underrecognized familial cerebrovascular disorder.

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In the last 20 years a number of families have been described with an autosomal dominant disorder characterized by recurrent strokes and stepwise progression of neurological deficits leading to a multiinfarct dementia and severe disability [1-8]. The onset has usually been in the fourth decade, with death in the seventh. The most recent studies described the magnetic resonance imaging (MRI) and pathological features and the inelegant but accurate name "cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy" (CADASIL) has been proposed [5, 9].

One of the more remarkable features of the phenotype, described initially in a French family, is that the disorder may be evident on MRIs of at-risk individuals before clinical symptoms or signs have developed [5]. In those asymptomatic family members, T2-weighted MRI showed extensive areas of increased signal in the white matter. Most recently, Tournier-Lasserre and

her colleagues [10] assigned the disease locus in two unrelated CADASIL French families to chromosome 19q12.

In three of the reported families [1-8] it was noted that some family members had suffered from migraine prior to the onset of the stroke syndrome (migraine with aura in 4 [3, 5, 6] and without aura in 1 [5]). In some families migraine was noted to be the most frequently encountered symptom [11, 12]. In the course of this investigation of an Irish family with CADASIL, it was noted that 4 family members who developed CADASIL had a history and preceding diagnosis of familial hemiplegic migraine (FHM). It has been reported that a gene for FHM maps to chromosome 19, close to or coincident with the gene locus proposed for CADASIL [13]. FHM may be distinguished from CADASIL by earlier onset, benign prognosis, and normal MRI findings. Although FHM and CADASIL are clearly distinct phenotypes, it is possible that both dis-

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orders may share a common genetic locus; thus, this clinical, radiological, and molecular genetic investigation was undertaken.

Materials and Methods

Family Pedigree

This family originating from County Longford in the midlands of Ireland is composed of two branches. Founders (I2 and I3) of these two branches had the same family name, lived in the same parish in the 1850s, and were probably siblings, although this has not been established by a genealogical research. Branch A includes 12 members who had clinical, biochemical, neuroimaging, and molecular genetic studies performed after giving their informed consent. Branch B includes 4 members examined so far; 3 have had MRI and molecular genetic studies. This study was sanctioned by the ethics committee of St. Vincent's Hospital, Dublin. Patients under the age of 20 were not examined.

Definitions

The phenotype of CADASIL was defined by, as a minimum requirement, the presence of characteristic abnormalities on MRI in a genetically at-risk family member with a pattern of autosomal dominant inheritance. The fully developed clinical syndrome consisted of recurrent episodes of focal brain deficits starting in midadult life leading often to residual motor disability with a pseudobulbar palsy and dementia. The characteristic MRI abnormality consisted of a leukoencephalopathy of varying severity on T2-weighted images and of multiple deep white matter infarcts seen on both T1- and T2-weighted images.

FHM was defined using the criteria of the International Headache Society as migraine with aura presenting with some degree of hemiparesis, which may be prolonged, and with at least one first-degree relative with identical attacks [14].

Neuroimaging

MRI examinations of the brain were performed using either a 0.5-T MR MAX General Electric scanner (12 family members) in Dublin or a Siemens 1.5-T machine at the National Hospital, Queen Square, London (3 members) (courtesy of Dr David Miller). Sagittal T1-weighted images (TR 440/TE 14/2 excitations), axial T2-weighted (2500–2900/100/1–2), and proton density (2500–2900/20–40/1–2) sections were used. Slice thickness was 5 mm and a 256 × 256 (sagittal) or 160 × 256 (axial) matrix was employed. Intravenous contrast material was not used. The neuroradiologist was blinded to the genetic information when he evaluated the MRIs.

Linkage Analysis

All potentially informative individuals who gave their informed consent had blood drawn. DNA was extracted from peripheral blood leukocytes. Six chromosome 19 markers spanning the interval containing the CADASIL gene (D19S413, DS19221, D19S226, D19S199, D19S244, D19S215) were selected for their informativity [15, 16]. Genetic linkage analysis was conducted as described previously [10]. The status for linkage analysis was based on MRI data.

All clinically affected individuals having an abnormal-appearing MRI were considered as affected, as were asymptomatic individuals born from an affected parent and having an abnormal-appearing MRI. Asymptomatic individuals with a normal MRI were considered as having an unknown status when they were younger than 35 and considered as healthy when older than 35. Linkage analysis was conducted using the allele frequencies observed for the selected markers in the CEPH families as previously described [10].

Results

Family Pedigree

Branch A (Fig 1) has been most thoroughly investigated; Branch B was discovered by serendipity (an abnormal computed tomography [CT] brain scan on a hospital employee presenting with common migraine) and only 4 members have been examined. Although both branches of the family now live in Dublin, they both originate from rural County Longford, Ireland. Genealogical research by one of us (E.Q.) led to linkage of the families in Generation II; however, in this sibship their death certificates (from the 1890s) indicated that they had died in their eighth and ninth decade from disorders unlikely to be associated with CADASIL. In the preceding generation, Subjects I2 and I3 had the same family name and lived in the same parish; they were probably siblings. Genetic analysis indicated that Branch A and B members belonged to the same family.

Summary of Clinical Features

Fifteen members of the family were fully assessed clinically and by MRI. By the imaging definition of the phenotype, 10 family members had CADASIL (see Fig 1). The ages at onset of clinical symptoms of CADASIL could be defined with accuracy in 6; the range was 20 to 35 years and the median age at onset was 28 years. If one accepts that the father (III12) of IV8, IV9, and IV11 had CADASIL, then the age of presentation may extend to 71 years. The diagnosis of possible CADASIL in the preceding generations (I to III) was based on history obtained from relatives and from death certificates that indicated a history of premature strokes. Some family members, notably III3 to III7, emigrated to the United States and contact was lost.

The modes of presentation of the 10 patients with CADASIL and the father (III12) of 3 affected members were as follows:

- A. Asymptomatic, diagnosed during family study (V1).
- B. Minimal transient focal neurological symptoms lasting minutes (V8 and IV11) or recurrent hemisensory and hemiparetic symptoms lasting from hours to days with complete remission (V6 and IV9).

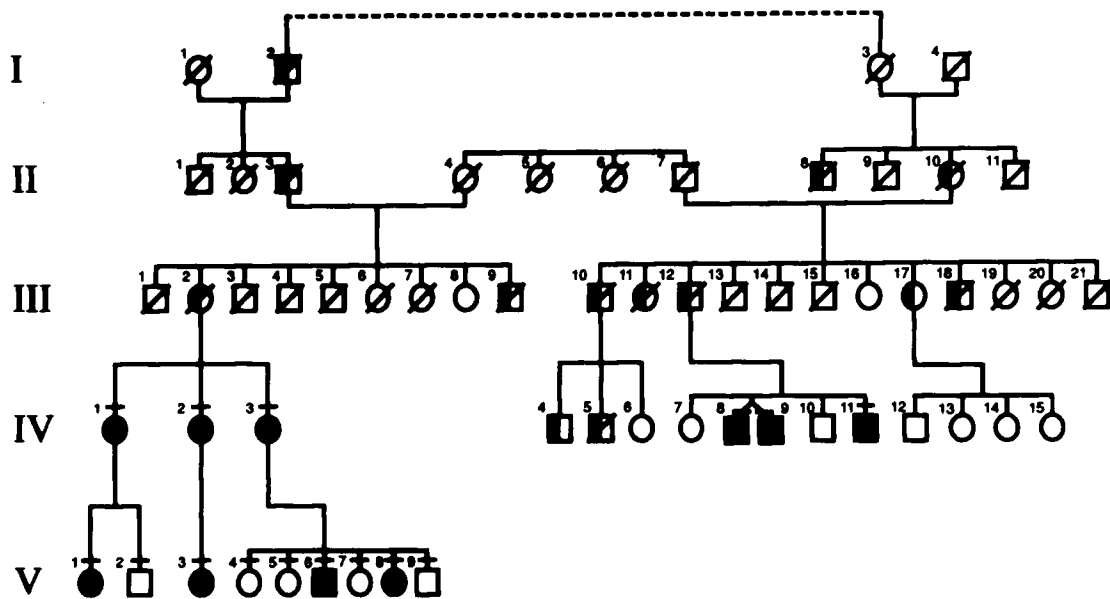


Fig 1. Family tree of an Irish family with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Branch A in text refers to the descendants of III2 and Branch B in text refers to the descendants of III12. Subjects who were fully examined clinically and by magnetic resonance imaging (MRI) are indicated by horizontal bars. Subjects with CADASIL are indicated by filled figures, probable CADASIL subjects are indicated by half-filled figures, and diagonal bars indicate dead family members. Squares represent men; circles, women.

- C. Recurrent focal neurological deficits with residual and cumulative disability (IV1, IV2, and IV3).
- D. Migraine with aura (V6) and without aura (IV8).
- E. FHM (V3), which also preceded the presenting symptom in IV1, IV2, and IV3.
- F. Spinal cord infarction (no MRI; presumed CADASIL, III12).

The progression of CADASIL in the fifth and sixth decades is illustrated by 3 siblings (IV1–IV3). Two of these women developed a progressive stepwise deterioration in neurological and functional status associated with multiple strokelike episodes and a severe dependent state. One sibling (IV1), despite a severe initial deficit at the age of 28 and recurrent episodes of hemiplegic migraine, remained well with minimal functional disturbance.

Migraine and Familial Hemiplegic Migraine

Four subjects with CADASIL had a history of FHM dating back to childhood (IV1–3 and V3), 1 patient with CADASIL had migraine with aura (V6), in 1 patient migraine without aura was the only presenting symptom (IV8), and 1 patient had FHM without MRI evidence of CADASIL (V5).

Illustrative Case Histories

BRANCH A: INDEX PATIENT (IV3). Sixty years old at the time of writing, this woman presented at the age of 37 with episodes since childhood of transient hemiparesis associated with severe headache; a diagnosis of hemiplegic migraine was made. She first attended St. Vincent's Hospital in 1975 with weakness in the right side of the face and the right arm and a right extensor plantar response; these symptoms cleared in 2 days. She continued to attend intermittently as an outpatient and from 1985 had many admissions because of episodes of hemiparesis that did not completely resolve. CT showed multiple widespread hypodensities in the cerebral white matter. Stepwise deterioration continued and she became completely dependent and chair bound with severe dysarthria, echolalia, verbal perseveration, disorientation in time and place, spastic quadriplegia, pseudobulbar palsy, left-limb parietal signs, and urinary incontinence. At the time of writing, she still had "small attacks" with headache and increased confusion lasting a few hours. Extensive investigations for recurrent and familial stroke disorders including mitochondrial disease and hypercoagulable states were negative. Since 1980 she was taking a variety of medications without response, including the usual prophylactic antimigraine drugs, calcium channel blockers, anticonvulsants, and anticoagulants. MRI in 1993 showed cerebral atrophy, severe leukoencephalopathy, and multiple subcortical infarcts. Diagnosis: FHM and CADASIL.

BRANCH A: PATIENT V5. At the age of 32 this woman had an episode of severe headache with confusion and was admitted to a county hospital for 4 weeks; she did not remember 2 weeks of this period. Subsequently she had four episodes of severe hemicranial headache during which she had heaviness and weakness in an arm opposite the side of the headache. On one occasion she had dysphasia 1 hour after onset of the headache. Normally she would go to sleep at the onset of the headache and her symptoms would have cleared on

wakening. MRI in 1994 was normal. Diagnosis: FHM only, not CADASIL.

BRANCH B: INDEX PATIENT (IV8). This 36-year-old man, a hospital employee, presented to his neurologist with a history of two severe migraine headaches on alternate sides of his head. These headaches were not associated with an aura or any other focal neurological symptoms. Neurological examination revealed normal findings; a CT scan showed three white matter hypointensities consistent with infarction. Results of a full investigation for cerebrovascular disease were normal; an MRI showed features consistent with a leukoencephalopathy. Diagnosis: CADASIL and common migraine.

BRANCH B: PATIENT III12. The father of IV8, IV9, and IV11 died in 1988 at the age of 77, six years after the onset of a spastic paraplegia. In April 1982 he was admitted to the neurology ward as an emergency (under the care of M. H.), having suddenly developed a weakness of both legs and retention of urine. He had a history of severe migraine attacks all his life. Examination showed a moderate weakness of both legs and a sensory level to pinprick to T-10 without sacral sparing but with preservation of posterior column sensation. The weakness progressed over the day to a marked paraparesis (grade 2 MRC in leg flexors). Radiographs of the spine, cerebrospinal fluid analysis, myelography (repeated once),

and brain CT were normal; a diagnosis of spinal cord infarction in the anterior spinal artery territory was made. Over the next 18 months he improved to walking a few steps with bilateral support and was able to self-transfer. He died at home 6 years later. Diagnosis: probable CADASIL.

MRI Findings

Ten family members had MRI abnormalities and were thus defined as having the CADASIL phenotype; 5 had normal-appearing MRIs (Table). There was no evidence of cerebellar atrophy on any scan. The most severely affected on clinical examination was the index patient in Branch A (IV3); she had also the most marked MRI findings. The MRI demonstrated symmetrical confluent high-signal areas on proton density and T2-weighted images throughout the deep white matter of both cerebral hemispheres, with symmetrical involvement of both temporal lobes. Multiple focal low-signal areas on T1-weighted images indicated cystic or necrotic lesions within the diffuse white matter abnormalities (Fig 2). In addition, separate discrete punctate lesions up to 2 cm were seen throughout the brainstem, thalami, basal ganglia, cerebral peduncles, and pons. There were also changes of ventricular dilatation and of atrophy of the corpus callosum.

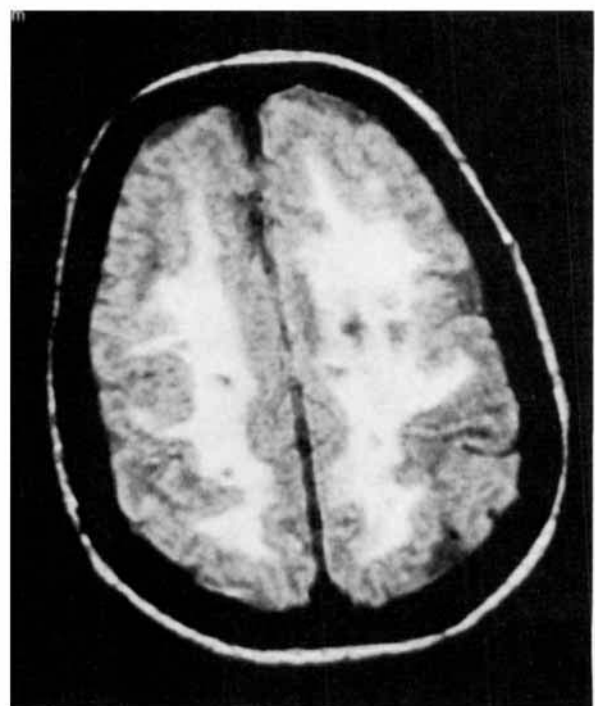
Summary of Features of Fully Investigated Family Members with Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) and Familial Hemiplegic Migraine (FHM) or Migraine

Family Member	Age (yr) at Onset (O) and Examination (E)	FHM/Migraine?	Clinical Evidence of CADASIL?	Magnetic Resonance Imaging Finding
IV1	O: 28 E: 63	FHM	Yes	Abn
IV2	O: 47? E: 61	FHM	Yes	Abn
IV3	O: 47? E: 60	FHM	Yes	Abn
V1	Asymptomatic E: 35	No	No	Abn
V2	E: 33	No	No	Nm
V3	Asymptomatic E: 39	FHM	No	Abn
V4	E: 37	No	No	Nm
V5	E: 36	FHM	No	Nm
V6	O: 27 E: 34	Migraine	Yes	Abn
V7	E: 29	No	No	Nm
V8	O: 24 E: 27	No	Yes?	Abn
V9	E: 24	No	No	Nm
IV8	O: 35 E: 36	Migraine	No	Abn
IV9	O: 33 E: 35	No	Yes	Abn
IV11	O: 20? E: 30	No	Yes?	Abn

Nm = normal; Abn = abnormal.



A



B

Fig 2. Brain MRI of the index patient (IV3). Axial proton density sections at the level of the bodies of the lateral ventricles (A) and centrum semiovale (B) show confluent, severe, high-signal leukoencephalopathy, with discrete punctate low-signal lesions indicating cystic or necrotic lesions.

By comparison, MRI of Patient V3, who presented with only FHM, demonstrated confluent symmetrical high-signal areas on T2-weighted and proton density images in the anterior temporal lobes and the occipital lobes (Fig 3). This subject also had punctate lesions up to 1 cm in diameter in the cerebral hemispheres, thalami, and basal ganglia. Linear areas of high signal intensity were seen throughout both external capsules.

In the index patient of Branch B who presented with only migraine without aura (IV8), the MRI demonstrated areas of high-signal intensity on proton density and T2-weighted images in the deep white matter bilaterally. This patient also had punctate lesions up to 1 cm in diameter in the pons, basal ganglia, and thalami (Fig 4).

Linkage Analysis

Significant lod scores were obtained with markers D19S226 (maximum lod score: 3.91 at $\Theta = 0$) and D19S244 (maximum lod score: 3.18 at $\Theta = 0$). Linkage analysis with additional closely linked markers showed positive lod scores. These data strongly establish linkage of the disorder present in this family with the CADASIL locus, which was demonstrated previously to be bracketed by D19S216 and D19S215. Haplotype

analysis (Fig 5) showed recombination events in 3 affected individuals. One was observed in 1 individual (V8) with D19S413. The 2 others with D19S215 were Patients V1 and V3. D19S413 and D19S215 bracket a 20-cM interval encompassing the 14-cM interval DS19221 to D19S215 containing the gene responsible for CADASIL.

Discussion

Clinical Aspects of CADASIL

Of the 12 members of Branch A descended from III2, 7 were found to be affected by CADASIL. The clinical course followed a similar pattern, with some interindividual difference in severity. The age of onset of symptoms of CADASIL in this family seems remarkably consistent. It is clear, however, on the basis of MRI studies, that this disorder is established and clearly definable in susceptible subjects before it becomes symptomatic; in Patients V1 (asymptomatic) and V3 (preceding FHM only) MRI showed considerable leukoencephalopathy. In addition in 2 individuals with a single transient symptom (V8 and IV11) the MRI was again quite abnormal.

In Branch B the siblings of Generation IV presented in a typical manner; however, their father had a more unusual neurological disorder, which does not appear to have been described in other families with CADASIL. At the age of 71 he developed an acute spastic paraparesis that was considered to be a spinal cord infarct; it is unlikely that the signs were due to cerebral



Fig 3. Brain MRI of Patient V3 who presented with only a history of familial hemiplegic migraine. This axial proton density scan shows marked confluent symmetrical high signals in the anterior temporal and occipital lobes.



Fig 4. Brain MRI of Patient IV8 who presented with migraine without aura. This T2-weighted axial scan shows scattered linear and punctate high-signal abnormalities in the white matter, caudate nuclei, and thalami.

infarction because of the sensory level, the prominent bladder symptoms, and the normal CT scan. Given the fact that his wife remains well, it must be considered that spinal cord infarction may be a presenting feature of CADASIL. This family illustrates the multiple clinical presentations of CADASIL, which also in part appear to be age related: FHM presenting in the first decade, migraine in the 20s to 30s, transient ischemic attacks in the 30s, a progressive multiinfarct dementia in the 40s to 60s, and spinal cord infarction in the eighth decade. Despite treatment with a variety of vasodilators, antimigraine drugs, anticonvulsants, and anticoagulants, this disorder progressed in Patients IV2 and IV3.

This disorder follows a pattern characteristic of many autosomal dominant disorders: late onset and variable severity of the phenotype. The clinical features in this family are broadly similar to those reported in varying degrees of detail [1–8]. In particular, the spectrum of symptoms, age at onset, age of maximum disability, and death, and MRI findings closely resemble those in the French families [4–6]. The most unusual feature of this family is the association with FHM, which is discussed below. As well as the CADASIL families reported [1–8], there have been scattered case reports in the American and Japanese literature which may be examples of this disorder [17–19].

The differential diagnosis of an autosomal dominant stroke syndrome is large and includes coagulopathies, cardiac disorders, Fabry's disease, angiopathies, MELAS syndrome, and dyslipoproteinemias [20]. Most of these disorders may be excluded by investigation; cerebral amyloid angiopathy is most unlikely in our patients in the absence of cerebral hemorrhage [21].

Clinical Features of Familial Hemiplegic Migraine

Five members of Branch A, and one child of Patient V3 not fully investigated, have or had a disorder consistent with FHM, 1 member (V6) presented with classic migraine, and 1 subject in Branch B (IV8) had common migraine. The association of FHM and CADASIL is of interest in view of linkage analysis studies suggesting that the loci for both disorders reside within an interval of about 30 cM on chromosome 19 [13]. All families with clinical evidence of CADASIL tested to date have shown conclusive linkage to chromosome 19 (E. Tournier-Lasserre, unpublished observations, 1995). In this family strong evidence of linkage to the CADASIL locus on chromosome 19 has been established. Although the association of migraine and CADASIL has been described [11, 12], this family is the first in which both FHM and migraine with and without aura have been described as a clinical presentation of CADASIL. Only 1 member of the present family had FHM without CADASIL (V5). In this person migraine

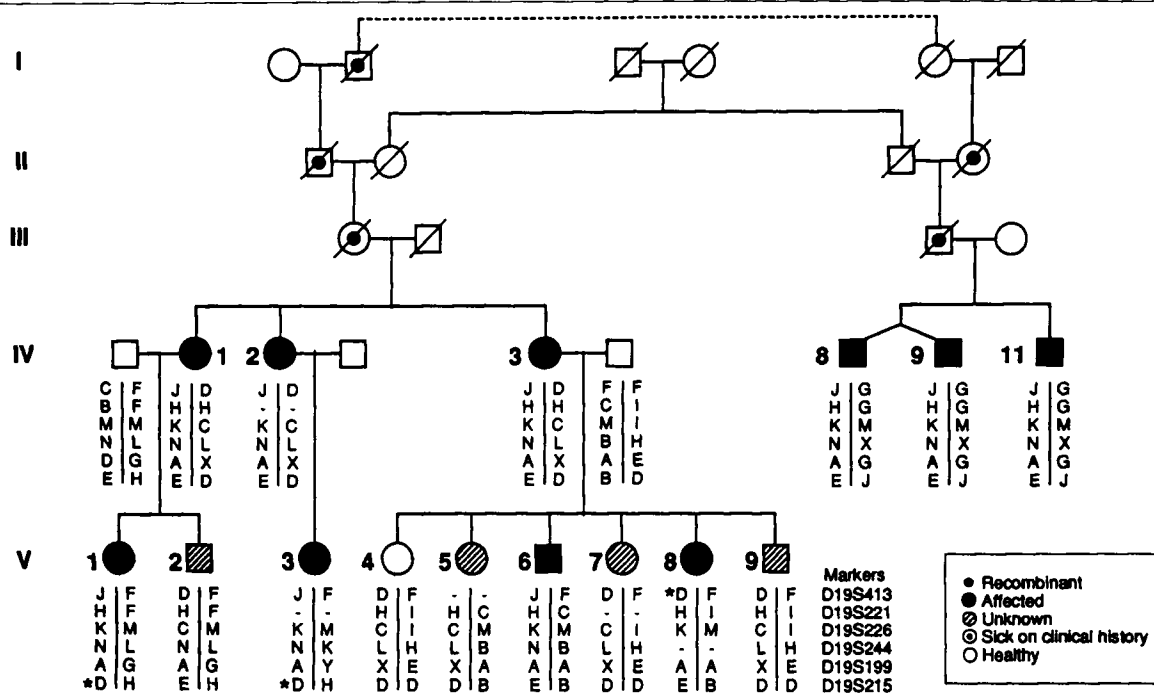


Fig 5. Simplified family tree with genotypes using six chromosome 19 markers for linkage analysis. The "affected" haplotype is JHKNAE. Three recombinants are noted by asterisks. The numerical identification of family members is the same as in Figure 1.

started at the age of 32 with prominent episodes of hemiparesis, hemianesthesia, dysphasia, and a severe confusional episode in association with migraine. This 36-year-old did not have CADASIL by MRI criteria and did not carry the CADASIL "affected" alleles with all analyzed markers on linkage analysis. Two possible explanations exist to explain this finding, including (a) all the patients with FHM including Patient V5 have a disorder due to an abnormality of the CADASIL gene but Patient V5 is a double recombinant; or (b) Patient V5 does not have an abnormal CADASIL gene, her MRI is normal, and the FHM is a phenocopy, that is, due to another mechanism. This question in relation to V5 and the question of the existence of an allelism of chromosome 19 FHM gene and the CADASIL gene will only be resolved when the gene for CADASIL is identified. Although linkage of FHM to chromosome 19 was first noted by Joutel and colleagues in two families [13] and confirmed in three families by Dutch authors [22], two FHM families in the latter study failed to demonstrate such linkage. If one accepts that FHM is part of the phenotype of CADASIL, then it is clear that the gene may be expressed before the age of 10 years. It is recognized that CADASIL may present as migraine either without (Patient IV8) or with aura (Patient V6) and in two families CADASIL subjects had migraine as a predominant presenting feature [11, 12].

Given that there is no diagnostic test for migraine, the diagnosis of FHM, using recognized criteria, depends on the clinical history with symptoms and signs of a hemiplegia and a positive family history [14]. There have been reports of associated neurological deficits in families with FHM including a progressive cerebellar disorder and essential tremor [23], but the association of CADASIL and FHM has not been described.

MRI and the Pathology of CADASIL

There is only one neuropathological study of a patient who died with CADASIL [8], a member of the family described previously [5]. The most striking change noted was a concentric thickening of the vessel wall of small arteries penetrating the white matter, associated with an extensive granular eosinophilic deposit in the media and a reduplication of the internal elastic lamella. There were multiple small deep infarcts and diffuse myelin loss. Stains for amyloid were negative and a mitochondrial disorder had been excluded by DNA, muscle histology, and biochemical studies. It is likely that the diffuse changes on proton density and T2-weighted images represent myelin loss. Within the high signal areas in the scan of 1 patient, low-signal foci on T1 energies consistent with necrosis were seen; it is probable that these foci represent lacunar or small cystic infarcts. The MRI appearance of CADASIL is not in itself diagnostic of the disorder and only becomes so in the context of an appropriate family history and when other causes of small-vessel disease have been discounted, as discussed above.

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