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Clinical and genetic analysis of a large Dutch family with autosomal dominant vascular retinopathy, migraine and Raynaud's phenomenon

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Summary

We describe an extended Dutch family with a new hereditary disorder: autosomal dominant vascular retinopathy, migraine and Raynaud's phenomenon. Information was obtained on 289 family members (151 males, 138 females), of whom 198 were personally interviewed. Retinopathy was found in 20 (6.9%) of the family members, migraine in 65 (22.5%) and Raynaud's phenomenon in 50 (17.3%). A combination of all three symptoms was found in 11 subjects. In a genetic linkage analysis we firstly excluded several candidate loci. Subsequently, 75% of the autosomal genome was excluded in a genome-wide search. The following conclusions were drawn. First, genetic factors are involved in Raynaud's phenomenon. Secondly, the genetic linkage of migraine with vascular retinopathy and Raynaud's phenomenon supports a vascular aetiology of this disorder. Finding the gene for this family may help to elucidate the genetic background of migraine and of vascular disorders in general.

Keywords: vascular retinopathy; Raynaud's phenomenon; migraine; hereditary; autosomal dominant

Abbreviations: CADASIL = cerebral autosomal dominant arteriopathy with stroke-like episodes and leukoencephalopathy; HVR = hereditary vascular retinopathy; MQ = memory quotient; WMS = Wechsler Memory Scale

Introduction

It has now been generally accepted that genetic factors play an important role in migraine (Russell and Olesen, 1995; Haan *et al*., 1997). The study of migraine genetics is difficult because migraine is a common, complex, probably multifactorial, and polygenetic disease (Russell and Olesen, 1995; Haan *et al*., 1997). Several methods are at present being used to investigate genetic factors in migraine. These include large population-based studies as well as the study of well-defined families with migraine or rare hereditary migraine variants such as familial hemiplegic migraine, a rare autosomal dominant form of migraine with aura (Whitty, 1986; Haan *et al*., 1994).

Prompted by the high frequency of (non-hemiplegic) migraine in families with hereditary multi-infarct dementia, also called cerebral autosomal dominant arteriopathy with stroke-like episodes and leukoencephalopathy (CADASIL) (Tournier-Lasserve *et al*., 1991; Chabriat *et al*., 1995; Wielaard *et al*., 1995), familial hemiplegic migraine could be assigned to chromosome 19p in 50% of the families investigated (Joutel *et al*., 1993, 1994; Ophoff *et al*., 1994). Further studies showed that familial hemiplegic migraine and CADASIL were not allelic (Dichgans *et al*., 1996), and recently genes for CADASIL (Joutel *et al*., 1996) and familial hemiplegic migraine (Ophoff *et al*., 1996) were found. The familial hemiplegic migraine locus on chromosome 19 appears to be involved in 'normal' migraine with and without

aura (May *et al*., 1995; Terwindt *et al*., 1997). The example of CADASIL-familial hemiplegic migraine-'normal' migraine shows that comorbidity of migraine with hereditary disorders can be of importance in elucidating the genetic background of migraine. Migraine is associated with several other hereditary disorders, resulting in a large number of candidate regions for linkage studies (Haan *et al*., 1997). Here we present the clinical and genetic data of a large Dutch pedigree characterized by hereditary vascular retinopathy (HVR), Raynaud's phenomenon and migraine. The results may be relevant to the elucidation of the genetics of both migraine and vascular disorders in general.

Method

Subjects

Between 1985 and 1988 five members of a pedigree independently sought medical attention in three separate eye departments (Storimans *et al*., 1991). They were found to suffer from an unknown retinal vaso-occlusive disorder. After recognition of the hereditary nature of this disease, a rapidly increasing number of family members was contacted and investigated prospectively. First, attention was given mainly to ophthalmological signs and symptoms, but in recent years almost all patients were revisited and re-examined because it had become clear that a large proportion of family members also suffered from migraine and Raynaud's phenomenon. Patients without eye disease and spouses were included in this investigation. All subjects investigated in this prospective study were 18 years or older, because until now no patient had shown signs or symptoms of retinopathy before that age. All family members and spouses gave their informed consent. Information was obtained on 289 family members (151 males, 138 females) of all generations. 198 subjects of generations II, III and IV were interviewed personally, whereas information on the remaining 91 was obtained through their relatives. Information on 101 spouses (51 males, 50 females), used as the control group, was obtained by direct interview (48 spouses) or through relatives (53).

Ophthalmological examination

In 147 of the family members extensive ophthalmological examination was performed, with a determination of best corrected visual acuity and refraction, motility of the eyes, slitlamp examination of the anterior segment, lens and vitreous body, ophthalmoscopy, and fundus photography. Fluorescein angiography was performed in 86 of the patients. Details of the methods of the ophthalmological investigation have been published elsewhere (Storimans *et al*., 1991). The vascular retinopathy was divided into four stages, as follows. Stage I: retinopathy limited to capillaries; microaneurysms and telangiectatic dilatations of capillaries in and around the macula may be present; the foveal avascular zone may be enlarged because of occlusion of capillaries in the arcade; occlusion may also be located in capillaries outside the foveal area; cotton-wool spots may show on ophthalmoscopy. Stage II: occlusion of small arterioles and venules, causing areas of non-perfusion larger than one-quarter of the optic disc surface, preferentially located at the posterior pole; intraretinal haemorrhages may occur. Stage III: occlusion of branches of large retinal arteries; the retinal periphery may also show avascular areas. Stage IV: proliferative retinopathy with extensive avascular areas, even up to the optic disc; newly formed vessels and vitreous haemorrhages may occur.

Migraine classification, Raynaud's phenomenon classification, neuropsychological examination, and neuroimaging

Patients and family members (n = 198) and their spouses (n = 48) were visited at home to be interviewed. The diagnosis of migraine was based on a standard questionnaire using the criteria of the International Headache Society (Headache Classification Committee of the International Headache Society, 1988). The diagnosis of Raynaud's phenomenon was likewise made according to standardized criteria (Miller *et al*., 1981).

A global measure of memory (memory quotient, MQ) was obtained in 173 family members aged 16 years or older by means of Wechsler's Memory Scale Form I (WMS) (Wechsler, 1945). The premorbid MQ was estimated by inquiring into education and profession. Results were categorized as 'significant', 'possible' and 'no decline'. As a control group 46 spouses were chosen. Twelve patients with retinopathy (II-13, III-14, III-15, III-17, III-41, III-42, III-44, III-73, III-76, III-77, III-84, and IV-32) and one family member without retinopathy (III-30) underwent an extensive neuropsychological examination. This examination included assessment of the following. (i) Intelligence: the Dutch version of the Wechsler Adult Intelligence Scale (WAIS) (Stinissen *et al*., 1970) or the translated Wechsler Adult Intelligence Scale, Revised (WAIS-R) (Wechsler, 1981). (ii) Mnestic functions: the WMS, digit span, Knox Cube Imitation Test for Visual Memory (Knox, 1914), two 10-word learning lists with auditory and visual presentation respectively (Jennekens-Schinkel *et al*., 1985). (iii) Calculation: calculations presented orally and in writing. Language: comprehension, word-finding, naming [31 pictures of the Object Naming Test (Oldfield and Wingfield, 1965)], word fluency, reading and writing. (iv) Graphic constructional abilities: copying of geometric and perspective figures and drawings. (v) Gnosis and praxis: according to the schedule in Strub and Black (1985). Reaction times: according to the Vienna Reaction Unit (Dr G. Schufried, A2340 Mödling, Austria). (vi) Manual dexterity: according to Schufried Motorische Leistungsbatterie (Dr G. Schufried, A2340 Mödling, Austria).

The grade of cognitive impairment was determined as the discrepancy between the estimated premorbid IQ [based on

education, profession and intact abilities (Haan *et al*., 1989)] and the current IQ and MQ. Impairment was categorized as 'none' (discrepancy less than 10 points), 'mild' (11–15 points), 'moderate' (16–25 points) and 'severe' (more than 25 points). In addition, two independent observers made a qualitative judgment concerning impairment with respect to specific disorders in the areas of calculation, language, constructional abilities, gnosis and praxis, which was done on the basis of the scores achieved or performance levels in the tests (Haan *et al*., 1990*b*).

In seven patients with vascular retinopathy (III-14, III-15, III-17, III-41, III-42, III-76 and III-77) cerebral MRI was performed on a 1.5 Tesla Philips Gyroscan (T1, repetition time 600 ms, echo time 30 ms; T2, repetition time 300 ms, echo time 60 ms). In one patient (III-44) angiography of carotid and intracranial arteries was performed.

Laboratory testing

Extensive laboratory investigation was performed in some of the patients with vascular retinopathy, with or without migraine or Raynaud's phenomenon. This included routine chemical and haematological investigation, determination of antiphospholipid antibodies (antinuclear factor), anti-cardiolipin antibodies (IgG/IgM), antibodies to extractable nuclear antigens, lupus anticoagulant, rheumatoid factors, protein spectrum, protein C, protein S, plasma cholesterol and high-density lipoprotein cholesterol, triglycerides, amino acids, essential fatty acids, lactate, complement components, cryoglobulins, cold-agglutination, HLA-B27, copro-porphyrin, uroporphyrin, α-D-galactosidase, vitamins, and thyroid function. Extensive coagulation studies (activated partial thromboplastin time, prothrombin time, fibrinogen, anti-thrombin III) and rheological testing (viscosity and fragility of red blood cells) were also done. Muscle and skin biopsies were performed in one patient with severe vascular retinopathy (II-11).

Genetic analysis

Genomic DNA was isolated from freshly collected blood as previously described (Miller *et al*., 1988). Analysis was carried out by performing multiplex polymerase chain reactions on all individual samples (Weber and May, 1989). The polymerase chain reaction was performed in a 15 μl reaction volume, using 30 ng of each oligonucleotide, 1×Supertaq buffer (HT Biotechnology), 200 μM dTTP, dGTP and dATP, 2 μM dCTP, and 0.7 μCi [α-^{32}P]dCTP (3000 Ci/mmol; Amersham) and 0.06 U SuperTaq (HT Biotechnology); 50 ng genomic DNA was subjected to 30 cycles of amplification (30 s at 94°C, 2 min at 55°C and 1 min at 72°C). The polymerase chain reaction products were separated through 6% polyacrylamide gels containing 7 M urea (Severn Biotech, Worcestershire, UK). After electrophoresis the gels were dried and exposed overnight to X-ray film (Kodak X-AR). Marker genotypes were subsequently determined for each individual. The autosomal genome was screened for linkage with microsatellite markers from the Dutch Microsatellite Marker Collection, which contains more than 300 highly polymorphic markers. The markers are uniformly distributed over the human genome based on mapping data from the Genome Data Bank and the Cooperative Human Linkage Centre.

Linkage analysis was conducted with the highest odds for being a gene carrier for the most distinct phenotype, the retinopathy. Genetic linkage analysis was performed in a selection of 60 family members, including all patients with retinopathy, and some first-degree family members of these patients for allele reconstruction (Fig. 1). The vascular retinopathy was regarded as an autosomal dominant disorder with a penetrance of 0.90 and a gene frequency of 0.0001. Because of the poorly understood genetics of this syndrome, the phenotypes were categorized using different liability classes (Table 1). Family members with retinopathy have a liability of being a gene carrier of 9000 : 1. Healthy spouses have a much better chance than healthy family members of not being a gene carrier. Family members with Raynaud's phenomenon or migraine or both are considered to have an even chance of being a gene carrier. Two-point lod scores were calculated using the MLINK and LINKMAP programs of the LINKAGE package, version 5.1 (Lathrop *et al*., 1984). According to the conventional criterion, a lod score smaller than –2 was accepted as evidence for exclusion of linkage between the tested marker and the vascular retinopathy. Markers giving a lod score higher than 3 were considered as linked with retinopathy. With the simulation program XLINK a mean lod score of 4.19 (0.89–6.25) at $\theta = 0.000$ was calculated for the model of this family. The exclusion maps constructed were based on two-point lod scores for each marker. In this study the total autosomal genome length was taken to be 3699 cM (Dib *et al*., 1996). Genetic testing was first aimed at candidate loci (Table 2). After exclusion of these loci the genetic analysis continued as a genome-wide search.

Results

Ophthalmological investigation

Twenty patients suffered from HVR. A detailed illustration of abnormalities can be found elsewhere (Storimans *et al*., 1991); Fig. 2 gives an example. Fluorescein angiography of the retina was normal in 68 and abnormal in 18 (seven males, 10 females) of the 86 investigated family members. Two patients (I-1 and II-5) could not be investigated, but were reportedly blind when they died. Age at onset of the HVR ranged from 26 to 62 years, but was difficult to establish because most patients consulted their ophthalmologist only when the retinopathy was rather advanced, while in the later years of the study several young asymptomatic patients were identified with abnormalities on fluorescein angiography. There was a characteristic pattern of microangiopathy of the

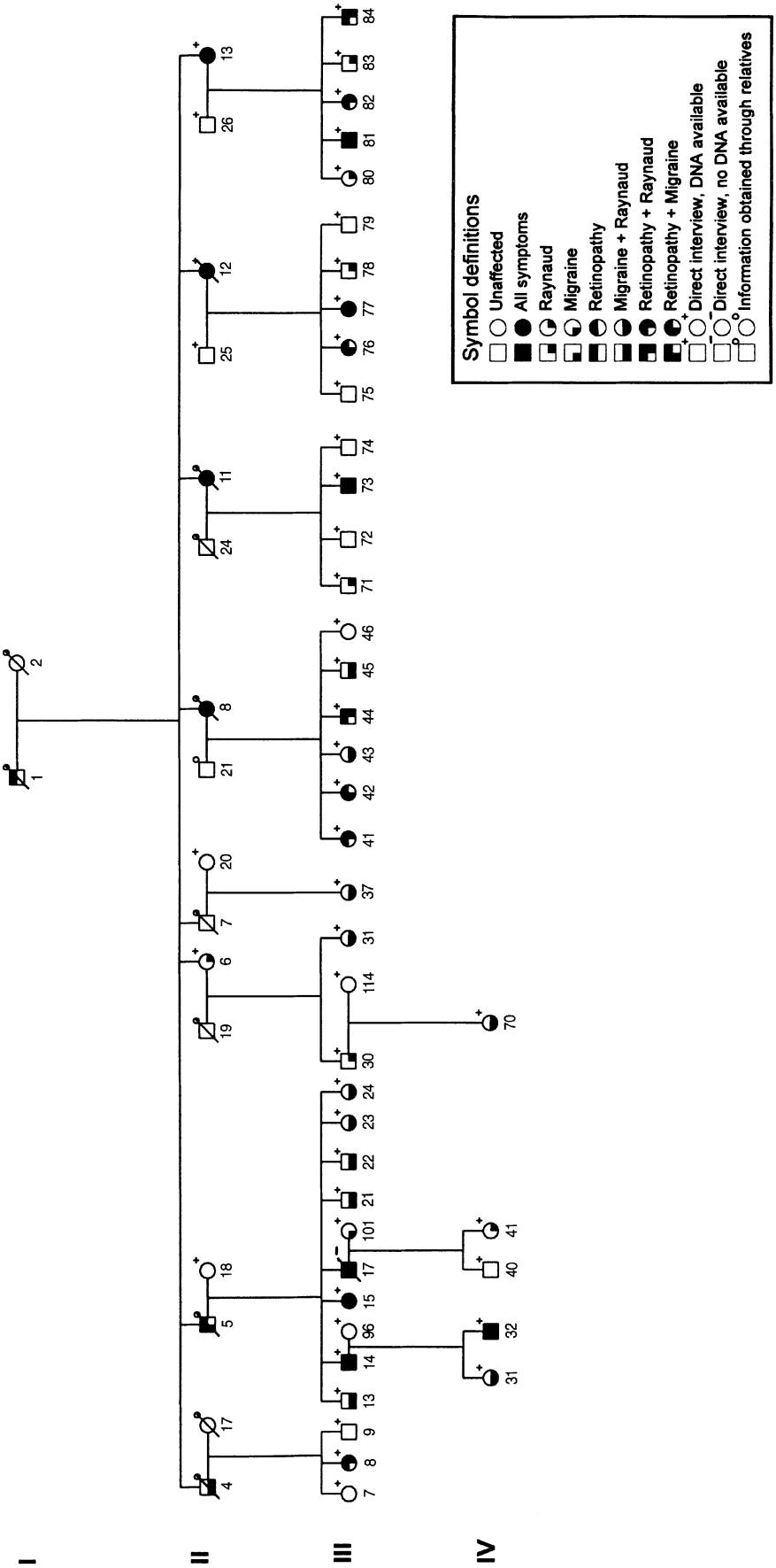

Fig. 1 Pedigree used in linkage analysis (complete pedigree is too large to be shown).

retina, usually starting in and around the posterior pole, and around the optic disc. Capillary occlusions were detectable with fluorescein angiography in patients from 25 to 30 years of age, larger vascular occlusions were found in patients around 40 years of age, and central and peripheral vascular occlusions resulting in large peripheral ischaemic areas extending almost to the optic disc occurred at later ages. All patients with signs of retinopathy showed microaneurysms and telangiectatic capillaries, preferentially in and around the macula. Capillary occlusion usually started in the perifoveal arcade, causing enlargement of the perifoveal avascular zone. Avascular areas showing as cotton-wool patches on ophthalmoscopy were located at the posterior pole, around the optic disc and in the midperiphery. Peripheral vascular occlusion resulted in ischaemic areas in the periphery, sometimes extending to the optic disc and macula. In advanced cases new vessel formation resulted in proliferative retinopathy, with vitreous haemorrhages and neovascular glaucoma. Arteriolar tortuosity was observed in some cases. In the most advanced cases larger retinal arteries were occluded and shunt vessels had developed. Retinal veins were involved in a small number of patients. Optic atrophy secondary to vascular abnormalities was observed in six patients. Visual acuity was remarkably spared, even in eyes with considerable ischaemia in and around the macula. Almost half of the patients had a visual acuity of >0.8, whereas only a minority of the patients had a severe visual handicap caused by recurrent vitreous haemorrhages, ischaemia of the foveal area or optic atrophy.

Table 1 *Liability classes used in linkage analysis*

	Genotype‡		
Phenotype	*NN*	*ND/DD*	Ratio*
Healthy (spouses)	0.0000	0.9800	50 : 1
Healthy†	0.0000	0.6000	5 : 2
Retinopathy†	0.0001	0.9000	1 : 9000
Raynaud's phenomenon/ migraine	0.5000	0.5000	1 : 1

*Ratio indicates the odds of being gene carrier.
†Family history and ophthalmological investigation.
‡Genotype is listed as homozygous normal (*NN*) and as heterozygous (*ND*) and homozygous (*DD*) gene carrier.

Migraine and Raynaud's phenomenon

Migraine was present in 65 of the 289 family members (22.5%) and in 12 (11.9%) of the 101 spouses (χ^2, $P \leqslant 0.01$). Age at onset of migraine ranged between 5 and 45 years in patients with retinopathy (median 13 years), and did not differ significantly from age at onset in spouses. Migraine was more frequent in female than in male family members (26.8 and 18.5%, respectively). Thirty-six family members had migraine without aura, seven had migraine with aura (not hemiplegic), nine sometimes had an attack with and sometimes without aura, one had only aura without migraine headache, and in 12 it was not known whether an aura occurred because information was obtained through relatives.

Raynaud's phenomenon was present in 50 family members (17.3%; 15.9% of the males, 18.8% of the females) and in four (4.0%) of the spouses (χ^2, $P \leqslant 0.01$). The combinations of vascular retinopathy, migraine and Raynaud's phenomenon are given in Table 3. A combination of all three symptoms

Table 2 *Candidate loci for genetic analysis of the family*

Disease	Locus	References
Stickler/Wagner syndrome	5q13–14, 12q13.11–q13	Ahmad *et al.*, 1991, 1993; Körkkö *et al.*, 1993; Brown *et al.*, 1995
CADASIL/familial hemiplegic migraine	19p13	Joutel *et al.*, 1993; Ophoff *et al.*, 1996
Hereditary haemorrhagic telangiectasia	3p22, 9q33–34, 12q	McAllister *et al.*, 1994; McDonald *et al.*, 1994; Shovlin *et al.*, 1994; Johnson *et al.*, 1995; Vincent *et al.*, 1995
Cerebral cavernous angiomas	7q	Kremer *et al.*, 1994
Transthyretin amyloidosis	18q11.2–q12.1	Sandgren *et al.*, 1990; Skinner *et al.*, 1992; Sandgren, 1995
Familial exudative vitreoretinopathy/ autosomal dominant neovascular inflammatory vitreoretinopathy	11q13–q23	Li *et al.*, 1992; Stone *et al.*, 1992; Muller *et al.*, 1994
Serotonin receptors		
5–HT-1A	5q11–q13	Kobilka *et al.*, 1987
5-HT-1B	6q13	Jin *et al.*, 1992
5-HT-1D	1p36.3–34.3	Libert *et al.*, 1991
5-HT-1E	6q14–q15	Levy *et al.*, 1992, 1994
5-HT-2A	13q14–q21	Sparkes *et al.*, 1991
5-HT-3	11q23.1–23.2	Weiss *et al.*, 1995
5-HT-7	10q21–q24	Gelernter *et al.*, 1995
Hereditary cerebral haemorrhage with amyloidosis, Dutch type	21q21.2	Broeckhoven *et al.*, 1990; Levy *et al.*, 1990
Cystoid macular dystrophy	7p	Kremer *et al.*, 1994
Facioscapulohumeral dystrophy	4q35	Wijmenga *et al.*, 1990

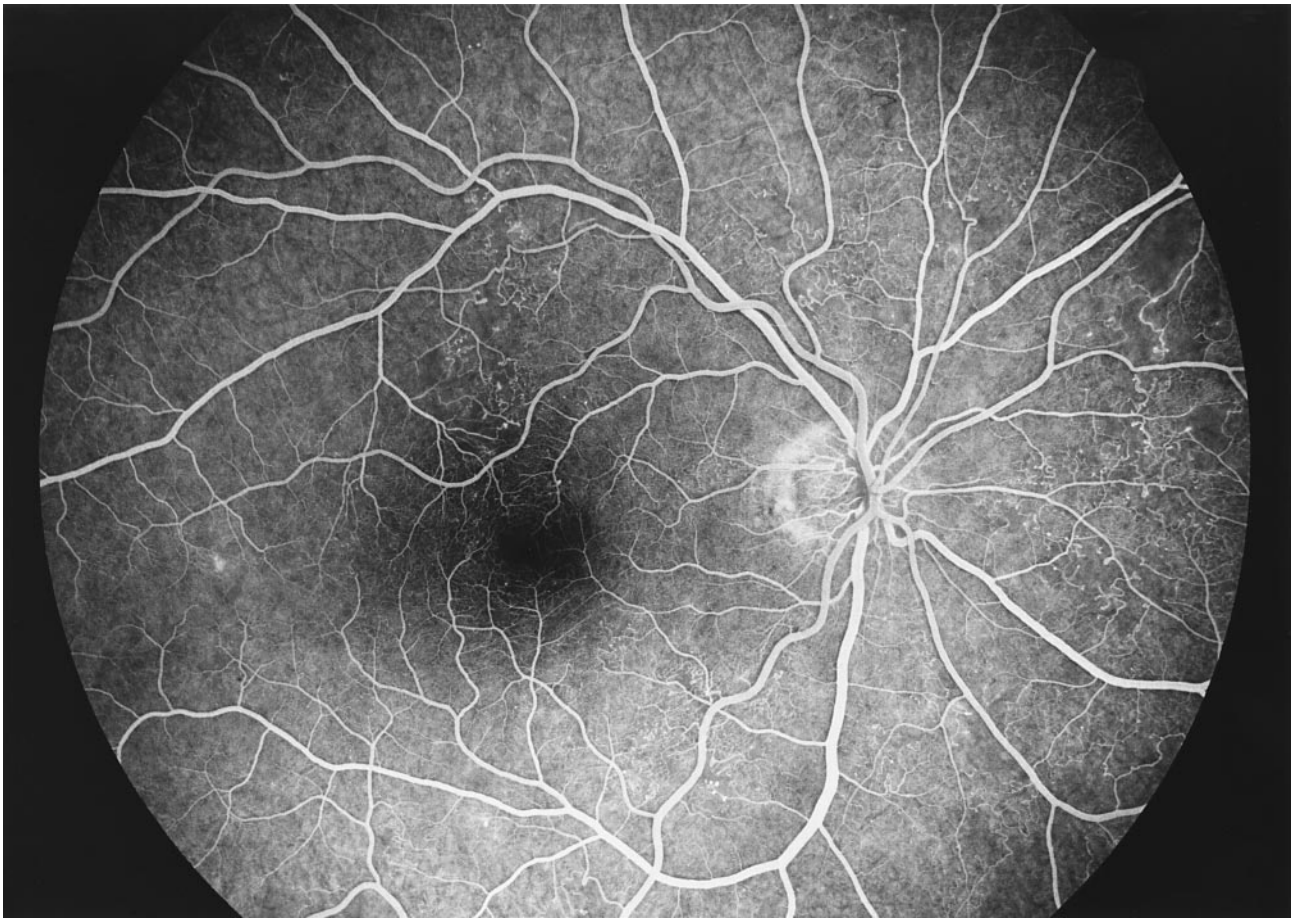

Fig. 2 Fluorescein angiogram of the right eye of a 45-year-old male with stage 2 hereditary vascular retinopathy showing microaneurysms, telangiectatic capillaries and avascular areas, especially located superior to the macula and nasally to the optic disc.

was found in 11 of the patients (II-8, II-11, II-12, II-13, III-14, III-15, III-17, III-73, III-77, III-81 and IV-32).

Neuropsychological examination and neuroimaging

In one patient (III-8) a clinical diagnosis of Pick's disease was made but unfortunately no neuropsychological examination was available. The patient died and no neuropathological investigation was obtained.

Comparison between family members and controls for the WMS

Of the 173 family members that were tested with the WMS, four (2.3%) had a significant memory decline, nine (5.2%) a possible decline, and eight (4.6%) could not be judged. In the control group (n = 46), one person (2.2%) had a significant memory decline, three (6.5%) a possible decline, and one (2.2%) could not be judged. No significant differences were found between family members and controls after correction for age.

Comparison between patients with retinopathy and other family members for the WMS

In 14 patients with retinopathy the WMS was assessed; five of these 14 patients (35.7%) had a cognitive decline (significant or possible). In 116 family members without retinopathy, seven (6.0%) had a cognitive decline (significant or possible). In 43 family members no ophthalmologic examination was performed; one (2.3%) had a possible cognitive decline. Family members with retinopathy had (possible) cognitive decline more often than family members without retinopathy.

Extensive neuropsychological examination

In 12 patients with retinopathy and one family member without retinopathy (III-30) an extensive neuropsychological examination was performed. On the global cognitive deterioration scale, one patient (III-42) exhibited a mild and three patients (II-13, III-14 and III-30) a moderate cognitive decline. Two patients (III-15 and III-44) developed a significant discrepancy between verbal and performance IQ; III-15 also had memory problems. Patient III-17 showed memory problems but no intellectual problems and had

Table 3 *Distribution of vascular retinopathy (retinopathy), migraine and Raynaud's phenomenon among 289 family members*

	Retinopathy (n = 20)	Migraine (n = 65)	Raynaud's phenomenon (n = 50)
Retinopathy	–	14/65 (21.5%)	16/50 (32.0%)
Migraine	14/20 (70.0%)	–	27/50 (54.0%)
Raynaud's phenomenon	16/20 (80.0%)	27/65 (41.5%)	–
Migraine + Raynaud's phenomenon	11/20 (55.0%)	–	–

disturbances of graphic abilities. Patient III-42 had attention difficulty. Patient III-14 was disoriented in time and showed dyscalculia, and word fluency was reduced. The pattern of cognitive decline was not of the frontal lobe type.

Neuroimaging

An MRI was performed in seven patients with vascular retinopathy. In five patients (III-14, III-15, III-17, III-41 and III-42) small areas of high signal emission on the white matter were present in the T_2-weighted images, compatible with small areas of gliosis (Fig. 3). In two of them abnormalities were also found in the globus pallidus. Cerebral angiography was normal in one patient (III-44).

Other findings, including laboratory data

Additional diseases or causes of death were not significantly different between patients and controls: transient ischaemic attacks occurred in three (1.0%) family members and in two (2.0%) spouses; ischaemic heart disease in nine (3.1%) family members and in five (5.0%) spouses; epilepsy in three (1.0%) family members and in one (1.0%) spouse. Prinzmetal angina was not encountered in family members or in spouses. Seven family members were suffering from a hand tremor (III-8, III-19, IV-7, IV-10, IV-27, IV-69 and IV-71) and one patient had cerebellar ataxia (II-2). Some patients suffered from frequent nose bleeding, but there were no skin lesions suggestive of hereditary haemorrhagic telangiectasia, nor were there skin lesions indicating incontinentia pigmenti. Laboratory investigation showed no consistent abnormalities. Results of haematological and rheological investigations were normal. Muscle and skin biopsies performed in one patient (II-11) were normal. Clinical and laboratory investigations were not suggestive of systemic lupus erythematosus, Sjogren syndrome, scleroderma or other connective tissue diseases that could have caused Raynaud's phenomenon.

Genetic findings

The retinopathy, migraine, Raynaud's phenomenon and the combinations of these three were transmitted from both father and mother to offspring, and males and females were almost equally affected, indicating autosomal dominant inheritance. In the genetic linkage analysis a total of 185 microsatellite markers, uniformly distributed over the genome, was analysed. Each chromosome (except 21 and 22) was tested with at least three different markers. So far no lod scores higher than 3, the conventional criterion for the acceptance of linkage, have been obtained. Slightly positive lod scores ($0.5 \leqslant 1.0$) were found on chromosomes 1 (D1S413, CACNL1A3), 2 (D2S71), 4 (D4S189), 5 (D5S210), 6 (D6S105, D6S271), 8 (LPL), 10 (D10S189, D10S245), 11 (D11S439) and 15 (GABRB3). Higher lod scores ($1.0 \leqslant 2.1$) were found on chromosomes 1 (D1S412), 8 (D8S261), 11 (D11S528) and 15 (D15S111). However, all of these regions were excluded by nearby markers. It was not possible, however, to exclude the areas around D6S105, D6S271 and D10S189. The regions surrounding these markers need further analysis. Exclusion maps for the different chromosomes were compiled by combining the exclusion regions of the individual markers. Chromosomes 2, 5, 15 and 17 were completely excluded. Assuming a total chromosome length of 3699 cM, a total of 2780 cM could be excluded (Table 4).

Discussion

Differential diagnosis of HVR

The autosomal dominant disorder described here is characterized by vascular retinopathy, Raynaud's phenomenon and migraine. For the differential diagnosis of this syndrome the eye disease is the key feature, because migraine and Raynaud's phenomenon are very common disorders in the general population.

Of the non-hereditary conditions with a vascular retinopathy, diabetes most strikingly resembles the HVR found in our family. In both disorders a microangiopathy (which may progress into a proliferative retinopathy) of the posterior pole and retinal periphery may be present. In our patients, however, glucose levels were normal. Other diseases that can be characterized by or are associated with retinal vascular occlusion have features that are distinctly different from HVR (e.g. hypertension, blood dyscrasia, vasculitides, connective tissue disorders, retinal venous occlusive disease, ocular ischaemic syndrome and Coats disease).

Several hereditary disorders must be considered in the differential diagnosis of HVR. Familial exudative vitreoretinopathy has much in common with the retinopathy of the family we studied. However, in this disorder non-perfusion is preferentially located in the temporal equatorial zone and the abnormalities are already present in early

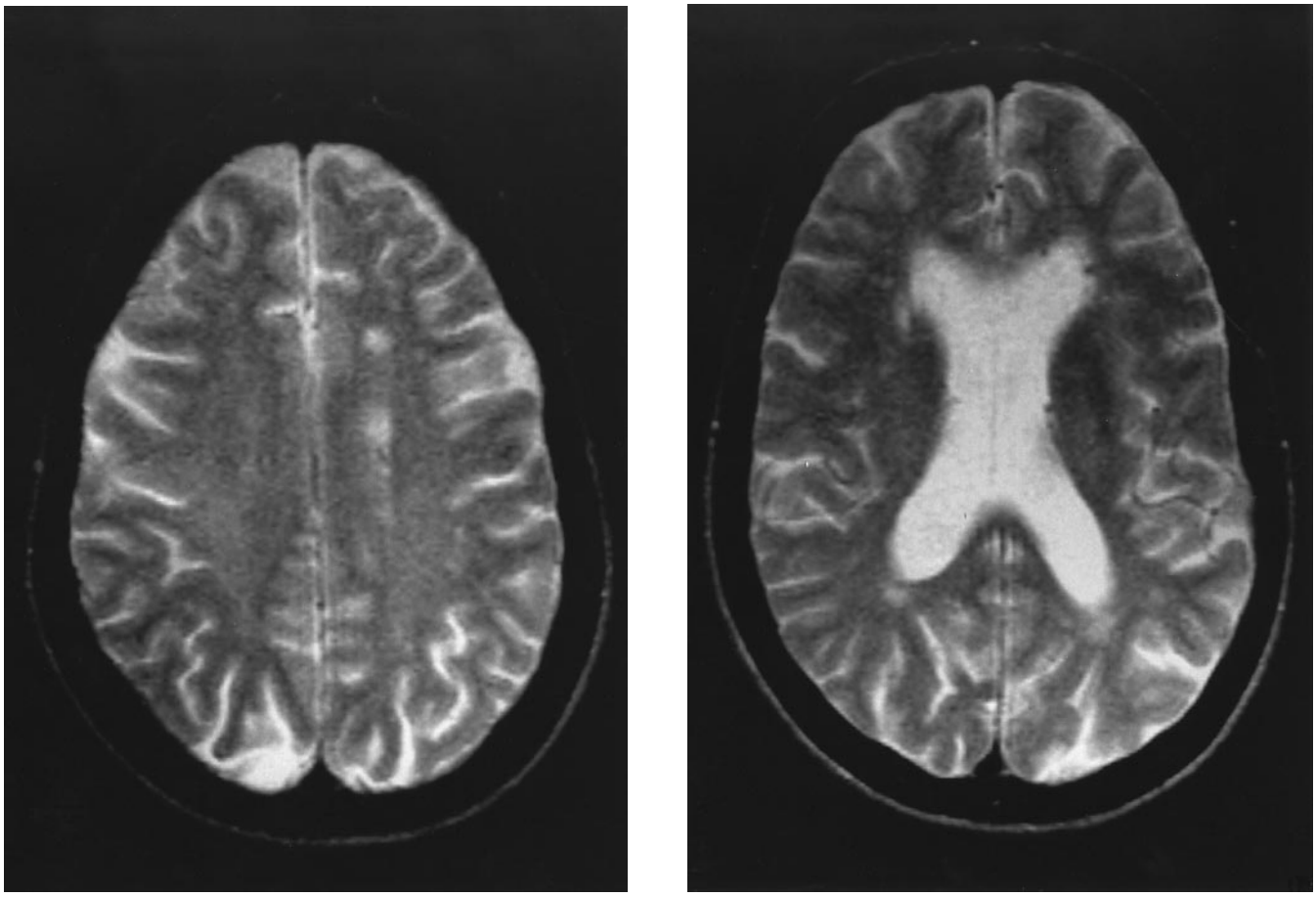

Fig. 3 T_2-weighted MRI images of a 53-year-old female patient showing small high signal-emitting lesions scattered throughout the white matter of both hemispheres.

Table 4 *Number of markers and exclusion percentage of genome*

Chromosome	Marker	Exclusion*	Chromosome	Marker	Exclusion*
1	11	58%	12	8	94%
2	19	100%	13	7	90%
3	5	57%	14	6	99%
4	9	74%	15	11	100%
5	19	100%	16	3	69%
6	12	84%	17	6	100%
7	6	80%	18	5	61%
8	9	99%	19	10	95%
9	9	86%	20	5	75%
10	8	34%	21	1	47%
11	16	93%	22	0	0%
			Total	185	75%

*Exclusion at lod score $\leqslant -2$, expressed as percentage of total chromosome length and total genome length (3699 cM) (Dib *et al.*, 1996).

childhood. The aberrant configuration of retinal vessels, ectopia of the macula, vitreous anomalies and retinal detachment were not observed in HVR in our family.

One family has been described with a syndrome consisting of retinal and choroidal ischaemic lesions, hyalinosis of the digestive tract and renal small vessels, intracerebral calcifications, subarachnoid haemorrhages due to aneurysmata, poikiloderma, and greying of the hair (Rambaud *et al.*, 1986; Effenterre van *et al.*, 1989). The tortuous arteriovenous shunt vessels with aneurysmal dilatation starting in the capillaries and spreading from the periphery to the posterior pole, the autosomal recessive pattern of

inheritance, an age of onset before 20 years of age, and the associated clinical features differentiate this syndrome from HVR.

Like HVR in our family, cerebroretinal vasculopathy (Grand *et al*., 1988; Gutmann *et al*., 1989; Jen *et al*., 1995) is characterized by microangiopathy of the posterior pole. In contrast to HVR, however, the retinal periphery is not affected. In addition, other features distinguish this syndrome from HVR: in a significant number of patients a cerebral frontal pseudotumour was found (Grand *et al*., 1988), and patients with cerebroretinal vasculopathy suffer from chronic daily headache rather than from attacks of migraine; they also show progressive cognitive deterioration and specific changes of cerebral vessels (fibrinoid necrosis) on pathological investigation, with extensive cerebral white matter lesions on MRI.

A minor degree of cerebral white matter change was found in some of the patients in our family but this was less extensive than that seen in cerebroretinal vasculopathy. Non-specific white matter changes on MRI are a frequent finding both in migraine patients (Pavese *et al*., 1994) and in normal subjects (Breteler *et al*., 1994). According to the neuropsychological examination, four family members (three with retinopathy, one without retinopathy) showed global cognitive deterioration, possibly consistent with global dementia. Some family members showed decline in specific functions indicative of focal cerebral dysfunction. Apart from the individual with the clinical diagnosis of Pick's disease, no indications of frontal lobe disease were found. Most patients, however, had no signs of cognitive decline.

On clinical grounds HVR can be distinguished from other hereditary diseases with vascular retinopathies such as facioscapulohumeral dystrophy (Gurwin *et al*., 1985; Fitzsimons *et al*., 1987), autosomal dominant peripheral retinal neovascularization (Gitter *et al*., 1978), autosomal dominant cystoid macular oedema (Deutman *et al*., 1976), hereditary central retinal angiopathy (Ehlers and Jensen, 1973), focal parafoveal retinal telangiectasia (Hutton *et al*., 1978), inherited retinal venous beading (Meredith, 1987; Stewart and Gitter, 1988; Piguet *et al*., 1994) and autosomal dominant retinal arteriolar tortuosity (Bartlett and Price, 1983; Wells and Kalina, 1985).

Neither Raynaud's phenomenon nor migraine has been associated with any of the syndromes mentioned above. There are, however, two other dominantly inherited syndromes affecting the retinal blood vessels which have been associated with migraine (but not with Raynaud's phenomenon). These are oculoleptomeningeal amyloidosis with amyloid angiopathy of the retinal and pia-arachnoid and meningeal vessels (Uitti *et al*., 1988), and hereditary cerebral haemorrhage with amyloidosis of the Dutch type (Haan *et al*., 1990*a*). The lack of vitreous opacities, which are frequently observed in ocular amyloidoses, and the absence of cerebral haemorrhages or amyloid polyneuropathy differentiate HVR from these amyloid diseases.

In one patient and her mother a combination of retinal telangiectasis and proliferation of retinal vessels was described (Schmidt and Soriano, 1993). Unlike HVR, the retinal periphery was unremarkable and Raynaud's phenomenon was not mentioned; migraine was reported only in a sister of the index patient.

In conclusion, the specific ocular findings of HVR differentiate this syndrome from all other hereditary retinopathies described so far.

Raynaud's phenomenon, migraine and HVR

Raynaud's phenomenon is a pathological vasomotor reaction of the digital blood vessels to cold exposure. It is usually classified into primary (Raynaud's disease) and secondary Raynaud's phenomenon, which has been associated mainly with connective tissue disorders. The absence of laboratory abnormalities and of signs and symptoms indicative of known underlying causes of secondary Raynaud's phenomenon makes it likely that the present family was suffering from primary Raynaud's phenomenon, which is a benign condition. In a recent large epidemiological survey, the population prevalence of Raynaud's phenomenon was 3.5%, with some preponderance of females (4.3%) over males (2.7%) (Weinrich *et al*., 1990). In colder climates the prevalence may be higher (Leppert *et al*., 1987). Although >50% of the first-degree family members of patients with Raynaud's phenomenon have also been found to be affected (Wollersheim and Thien, 1990; Planchon *et al*., 1994), environmental rather than genetic factors are considered to be involved. The clinical characteristics of the present family indicate that Raynaud's phenomenon can be part of a hereditary syndrome and suggest that there is a genetic relationship with migraine. This seems to confirm the findings in epidemiological surveys showing that the prevalence of migraine in patients with Raynaud's phenomenon is between 42 and 61% and in their first-degree relatives it is between 42 and 47% (Wollersheim and Thien, 1990; O'Keeffe *et al*., 1992, 1993; Planchon *et al*., 1994). Vice versa, Raynaud's phenomenon was found in 26% of patients with migraine (Zahavi *et al*., 1984). Prompted by the high prevalence of Raynaud's phenomenon and migraine in patients with Prinzmetal angina (Miller *et al*., 1981) and the co-occurrence of both disorders in patients with cerebral infarcts (Levy *et al*., 1984; Luthi *et al*., 1984; Geraud *et al*., 1986), a common underlying, possibly genetically determined, generalized vasospastic mechanism has been suggested.

In the present family, migraine and Raynaud's phenomenon are associated with a vascular retinopathy. Maurice Raynaud was the first to describe narrowing in the central artery of the retina in some of his Raynaud's phenomenon patients (Dunphy, 1932). Since then the association of Raynaud's phenomenon and retinal vascular abnormalities has been described in many more patients (Appelbaum and Lerner, 1926; Dunphy, 1932; Anderson and Gray, 1937), although in the recent literature no mention is made of this combination. One of the early patients described as having Raynaud's

phenomenon and 'retinal haemorrhages, exudates with overfilled veins and narrow arteries' suffered from migraine (Appelbaum and Lerner, 1926), but this may have been a spurious observation. Familial occurrence of Raynaud's phenomenon, retinopathy or migraine has never been mentioned in any of the reports on patients with Raynaud's phenomenon and retinal abnormalities. Vascular retinopathy has often been described in migraine (Coppeto *et al*., 1986), leading to designations such as 'retinal migraine', 'ocular migraine' and 'anterior visual pathway migraine'. None of these reports, however, mentions familial cases or an association with Raynaud's phenomenon.

Pathophysiology of Raynaud's phenomenon and migraine

Although the exact pathophysiology of Raynaud's phenomenon has not yet been unravelled there is consensus that vasospastic mechanisms are involved (Cleophas and Niemeyer, 1993). At least fifty aetiological theories have been postulated, the most recent of them concerning dysregulation of the neuroendothelial control of vascular tone caused by imbalance of vasoconstrictive and vasodilating mediators (Kahaleh and Matucci-Cerinic, 1995). There are several mediators of vasoconstriction (e.g. neuropeptide Y, noradrenaline, endothelin, thromboxane A2) or vasodilation (e.g. somatostatin, prostaglandin E2, prostacyclin, histamine, nitric oxide, substance P, calcitonin gene-related peptide). One of the most recent hypotheses focuses on a deficiency of the very powerful vasodilator, calcitonin gene-related peptide (Anonymous, 1995). Interestingly, endothelium-derived vasodilating mediators such as nitric oxide and vasoconstrictive mediators such as endothelin-I have been implicated in vascular ophthalmic complications in a number of acquired diseases, such as diabetes and hypertension (Haeffliger *et al*., 1994). Theoretically, similar dysregulation of vascular tone can play a role in migraine (Goadsby *et al*., 1990; Haeffliger *et al*., 1994; Raynaud *et al*., 1994). The combination of Raynaud's phenomenon, migraine and vascular retinopathy in the family described here suggests a genetically determined disturbance of the regulation of vascular tone. Some questions, however, remain to be answered. First, the absence of ischaemic heart disease such as Prinzmetal angina in our family is remarkable (Miller *et al*., 1981). Second, it is not clear why dysregulation of vascular tone produces paroxysmal symptoms (Raynaud's phenomenon and migraine) on the one hand and permanent vascular damage (retinopathy) on the other.

Genetic considerations

Non-vascular hereditary ocular disorders have been mapped to many chromosomal loci. For example, the investigation of retinitis pigmentosa and retinal dystrophies has led to the discovery of an increasing number of responsible genes (Rosenfeld *et al*., 1994). On the other hand, only a limited number of hereditary vascular ocular diseases have been mapped. Familial exudative vitreoretinopathy and familial neovascular inflammatory vitreoretinopathy have been linked to the same region on chromosome 11q, but as yet there is no evidence that the two disorders are allelic. In HVR we excluded this chromosome 11 locus as well as the loci for autosomal dominant cystoid macular dystrophy (7p) (Kremer *et al*., 1994) and Wagner disease (5q13–14) (Brown *et al*., 1995). All other vascular eye diseases that have been mapped are X-linked (Norrie disease and the X-linked form of familial exudative vitreoretinopathy) and provide no candidate loci for the present family.

After exclusion of candidate loci, we continued the genetic analysis as a genome-wide search. Genetic linkage analysis was conducted with the highest odds for being a gene carrier for the most distinct phenotype, the retinopathy. A lod score of 4.19 at $\theta = 0$ should be possible with the highly informative microsatellite markers that are available. High-resolution linkage maps based on microsatellite markers have facilitated linkage mapping of a large number of gene defects (Wijmenga *et al*., 1990; Heutink *et al*., 1992; Nancarrow *et al*., 1992). Because of their relatively high informativeness these markers frequently allow us to exclude large areas of the genome (Deutekom van *et al*., 1994).

A lod score of $\geqslant 3$ was found with none of the 185 markers, and most of the slightly positive lod scores were excluded by one or more neighbouring markers. Only the areas around the markers D6S105, D6S271 and D10S189 need further analysis before linkage can be excluded. The marker (D11S528) with the highest lod score (2.1) proved to be uninformative because almost all subjects had the same allele. Neighbouring markers also excluded the area around this marker. Of the autosomal genome, 75% was excluded in this study, and thus further investigation is needed to elucidate the genetics of this rare disease.

Several conclusions can be drawn from this family. First, genetic factors are involved in Raynaud's phenomenon. Secondly, the genetic linkage of migraine, vascular retinopathy and Raynaud's phenomenon supports a vascular aetiology of this disorder. Finding the gene for this family may help to elucidate the genetic background of migraine and of vascular disorders in general.

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