Phenotype of a Homozygous CADASIL Patient in Comparison to 9 Age-Matched Heterozygous Patients With the Same R133C *Notch3* Mutation

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Background and Purpose—CADASIL is an autosomal dominant arteriopathy, characterized by multiple brain infarcts, cognitive decline, and finally dementia, which is caused by mutations in *Notch3* gene encoding a Notch3 receptor protein. We describe the clinical, neuropsychological, imaging, genetic, and skin biopsy findings in a CADASIL patient homozygous for the C475T mutation resulting in R133C amino acid substitution, in comparison to 9 age-matched heterozygous patients with the same mutation.

Methods—The patients were examined clinically and neuropsychologically and with MRI and positron emission tomography for assessment of cerebral blood flow. The gene defect was analyzed by sequencing the products of polymerase chain reaction of exons 3 and 4 of the *Notch3* gene. Dermal arteries were analyzed electron microscopically.

Results—The homozygous patient had his first-ever stroke at age 28 years. This is markedly earlier than the average, but the patient's heterozygous son had his first transient ischemic attack–like episode at the same age and another heterozygous patient had his first-ever stroke when only 2 years older. He was neuropsychologically more severely deteriorated than all but 1 of the heterozygous patients. These 2 patients had the most severe (confluent grade D) white matter MRI changes. Positron emission tomography showed markedly reduced cerebral blood flow. Skin biopsy revealed profuse deposits of granular osmiophilic material. The progression of disease in the homozygous case was, however, slower than in the most severely affected heterozygous patient.

Conclusions—Our homozygous patient's phenotype is within the clinical spectrum of CADASIL, although at its severe end. Thus, CADASIL may follow the classic definition of a dominant disease, according to which the heterozygous and homozygous patients are clinically indistinguishable. **(*Stroke*. 2001;32:1767-1774.)**

Key Words: CADASIL ■ dementia, vascular ■ homozygote ■ magnetic resonance imaging ■ neuropsychological tests ■ tomography, emission computed

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is an inherited generalized arteriopathy, the symptoms of which are almost exclusively neurological. Migraine with aura is a common early symptom. The first stroke most often appears at the age of 35 to 45 years.[1] Strokes are caused by small infarcts, which result from fibrosis and obliteration of the lumen related to destruction of the smooth muscle cells (SMC) in the walls of cerebral arteries. Recurrent infarcts, mainly in the cerebral white matter and deep gray matter, lead to cognitive decline and finally dementia.[2,3]

CADASIL is most often caused by missense point mutations of the *Notch3* gene.[4,5] Mutations either create or delete 1 cysteine residue, which most likely leads to structural transformation of the molecule and accumulation of ectodomains of the Notch3 protein in the arterial wall.[4,6,7] Thus far approximately 40 different point mutations and 3 deletions have been reported, each of which either abolishes 1 cysteine residue or introduces an extra cysteine residue.[5,7,8]

All patients reported thus far have been heterozygous. According to the classic definition of dominance, homozy-

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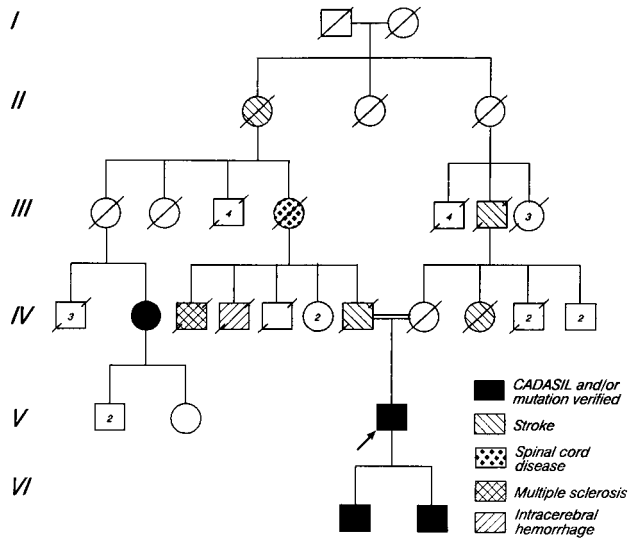


Figure 1. Pedigree of the family. The homozygous patient is marked with an arrow. The different, obviously erroneous, neurological diagnoses given to the members of the family, who most likely had CADASIL, are indicated by different markings.

gosity in an autosomal dominant disease should not aggravate the manifestation of disease (ie, homozygotes and heterozygotes are phenotypically indistinguishable), although aggravation has been described in some disease entities.[9]

In Finland, the first family with CADASIL was identified and published as hereditary multi-infarct dementia in 1987.[10] After the gene test became available, 15 new, apparently different families with approximately 100 patients or presymptomatic carriers of the gene defect have been identified in Finland. Fourteen of the 16 families identified in Finland carry the same C475T transition mutation of the *Notch3* gene, which leads to substitution of the 133 arginine by cysteine (R133C). In this report we describe the clinical and neuropsychological features as well as MRI, positron emission tomography (PET), and skin biopsy findings in a Finnish CADASIL patient homozygous for the R133C mutation. Findings are compared with those from an age-matched reference group of heterozygous CADASIL patients and his 2 heterozygous sons with the same mutation.

Subjects and Methods

Family History of the Homozygous Patient

In the patient's family, many members in several generations had suffered from neurological symptoms, which in the 1960s and 1970s were attributed to cerebrovascular disease or multiple sclerosis. The patient's father had died of stroke. Two paternal uncles had had a history of neurological diseases that were diagnosed as multiple sclerosis and intracerebral hemorrhage. The paternal grandmother had had a "spinal cord disease," and the great-grandmother had died of stroke. The patient's mother had died at the age of 31 years of tuberculosis and diabetes. She had not had any neurological symptoms. The maternal grandfather and 1 aunt had died of stroke. The patient has 2 sons. For details of the pedigree, see Figure 1.

Clinical History of the Homozygous Patient and His Sons

The male patient is at present aged 54 years. He has a history of migrainous headache. He had a mild stroke at the age of 28, which caused clumsiness of the right arm. The symptoms resolved within a couple of months and were assumed to have been caused by a minor intracerebral hemorrhage. A recurrent stroke occurred at the age of 36 years. The patient became depressed, was easily fatigued, and had insomnia. He was considered to be mentally slow but normally oriented and had no apparent memory deficit. A cranial CT scan revealed left-sided periventricular and internal capsular white matter hypodensities. At the age of 39 years he developed left-sided hemiparesis with aphasia and dysarthria. CT white matter changes had progressed and become bilateral. An old infarct was identified in the left capsula interna.

The right-sided motor and sensory disturbances were aggravated at the age of 47 years. Several small old infarcts and accentuated white matter changes were observed with CT. Carotid angiography was normal. Cognitive decline became clearly manifest around the age of 48 years, and the patient had to retire. The patient has been periodically treated with aspirin or warfarin but with no clinical effect. At the age of 52 years the patient was examined in detail for suspected CADASIL, as presented in Results.

The gene defect has been verified in both sons of the homozygous patient. The older son had no history of migraine until the age of 28 years, when he experienced an attack of migrainous headache with central facial paresis, visual disturbances, and dysarthria as aura lasting for 5 minutes. This attack was preceded over a 2-week period by several episodes of headache and vertigo that were each of 2 to 3

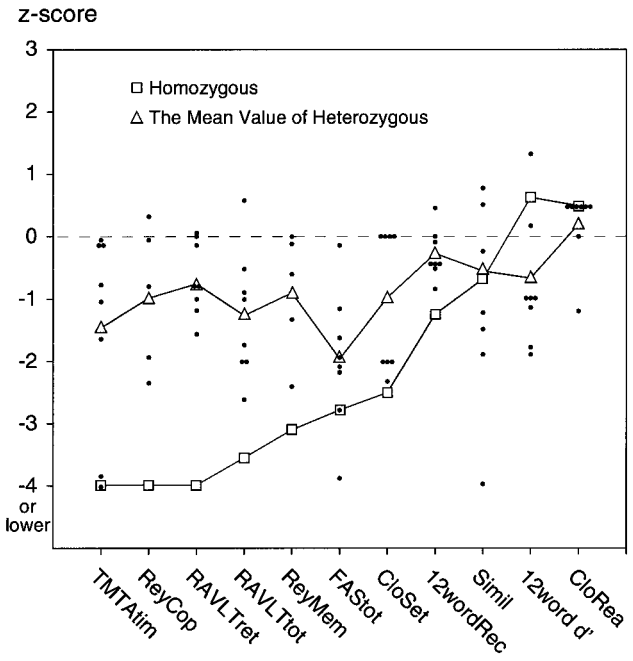


Figure 2. Cognitive performance of the homozygous patient at the age of 52 years compared with the heterozygous reference group at similar age (52±2 years). The individual test values of the heterozygous patients are indicated by a point. The homozygous patient has a clearly poorer performance in the majority of the tests. The difference is greatest (≥2 SDs) in a test of mental speed, as well as in tests demanding constructive ability and episodic memory, which all have a crucial impact on executive functions. The following neuropsychological tests were used: (1) executive functions: Trail Making Test A (TMTA-tim),[24] verbal fluency FAS (FAStot)[25]; (2) verbal abstraction: Wechsler Adult Intelligence Scale, Revised (WAIS-R) similarities (Simil)[26]; (3) visuospatial ability: Luria clock setting and reading (CloSet, CloRea),[27] Rey Osterrieth Complex Figure copying (ReyCop)[28]; (4) episodic memory: Rey Auditory Verbal Learning Test (RAVLT), 5-trial free recall (RAVLTtot) and 30-minute delayed recall (RAVLTret),[29] 12-word memory test with free recall (12wordRec) and recognition (12word d′),[30] and Rey Osterrieth Complex Figure immediate reproduction (ReyMem).

TABLE 1. Clinical Characteristics of Homozygous Patient and Heterozygous Reference Group

Patient (No.)	Sex/Age, y	First-Ever Stroke Age, y (No. of Strokes)	Motor Deficit	Mood Disorders	Dysarthria	Rankin Scale (0–6)
Homozygous	M/52	28 (6)	Slight to moderate	Depression	Severe	3
Heterozygous						
1	M/54	45 (5)	Severe	Depression	Severe	5
2	F/54	54 (1)	Slight	No	No	2
3	F/53	50 (4)	No	Depression	No	2
4	F/52	52 (1)	Slight	Depression	Slight	2
5	M/52	51 (1)	Slight	Bipolar mood disorder	No	2
6	M/51	. . . (0)	No	No	No	1
7	F/51	52 (1)	Slight	No	No	1
8	M/51	. . . (0)	Slight to moderate	Depression	Moderate	3
9	M/50	48 (3)	Slight	Depression	Slight	2

hours' duration. These symptoms may represent either transient ischemic attacks (TIAs) or severe migrainous aura. In a T2-weighted MRI 1.5 years earlier, minor periventricular hyperintensities were detectable. The younger son has a history of migraine with aura, but by the age of 19 years he has had no ischemic symptoms, although his MRI has shown minimal white matter abnormalities.

The Age-Matched Reference Group

As the reference group we selected all Finnish heterozygous CADASIL patients (9 in all; 4 women and 5 men) with genetically verified R133C, whose ages were ±2 years that of the homozygous patient and who were examined at an age (±2 years) similar to that of the homozygous patient. All patients were examined clinically and by MRI (n=7) or CT (n=2). All but 1 of the patients were tested neuropsychologically. The function of the patients was assessed with the Rankin Disability Scale. One heterozygous patient (No. 3) was also studied by PET, and her skin biopsy was examined by electron microscopy.

Neuropsychology

The cognitive performances of the homozygous patient and 8 heterozygous patients, examined at the age of 52±2 years, were compared with neuropsychological tests for executive and verbal functions, visuospatial ability, and episodic memory (for details, see Figure 2). Only a limited number of tests could be used in the comparison because of the moderate state of dementia in the homozygous patient (Mini-Mental State Examination score of 19). The heterozygous patient No. 1 had to be excluded from the neuropsychological reference group because he could no longer be tested at the corresponding age as a result of his rapidly developed dementia after the age of 45 years.

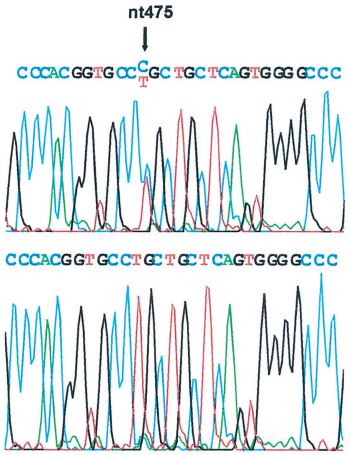


Figure 3. Sequencing results of the homozygous (bottom) and a heterozygous (top) CADASIL patient. The heterozygous patient has both C and T at nucleotide 475 (nt475), whereas the homozygous patient has mutated T in both alleles.

Molecular Genetic Analyses

Genomic DNA was isolated from whole blood. Initial screening of the C475T (R133C) transition mutation was performed by polymerase chain reaction (PCR) amplification of exon 4 of the *Notch3* gene with primers N2AF (5′-TAGTCGGGGGTGTGGTCAGT) and N3AR (5′-CCTCTGACTCTCCTGAGTAG) and subsequent restriction endonuclease analysis with *Msp*A1I. Internal primers were also used to rule out the possibility that a primer binding site polymorphism prevents the amplification of the normal allele. Sequences of the forward and reverse primers were 5′-GGTCCCTCCAGGCCCTGACT and 5′-GGCAGGAGCAGAGGAAGCGTCCATCGGGCCCCACTGAGCTGC, respectively. The underlined T in the reverse primer denotes a deliberately introduced mismatch, which together with the C475T mutation creates a site for *Pst*I restriction endonuclease. ABI377 automated DNA sequencing was used to verify the results inferred from the restriction analyses. Uniparental isodisomy of chromosome 19, which was considered a remote possibility for the C475T homozygosity before consanguinity in the family was established by the genealogical survey, was ruled by searching for heterozygosity in the polymorphic CTG repeat region of the DMPK gene located on 19q13 by standard PCR/PAGE methods.

Imaging Studies

MRI and CT Studies

The homozygous patient and 7 reference patients were studied by MRI. The homozygous patient and heterozygous patient No. 3 were examined with 1.5-T SiemensMagnetom MR equipment. The MR study consisted of axial T2-weighted spin-echo 3120/90 (repetition time/echo time) images with slice thicknesses of 5 mm and T1-weighted sagittal 3-dimensional magnetization prepared rapid gradient echo 10/4 images with flip angle of 10 degrees and slice thickness of 1.5 mm. Four reference patients were imaged with 0.5-T Philips Gyroscan, and 2 patients were imaged with 1.0-T SiemensMagnetom. The studies consisted of at least T2- and proton density–weighted axial spin-echo images and T1-weighted coronal and sagittal images. Two patients were studied by using axial CT. MRI changes were assessed according to the semiquantitative rating scale of Scheltens et al[11,12] as well according to the classification of Chabriat et al for CADASIL.[13]

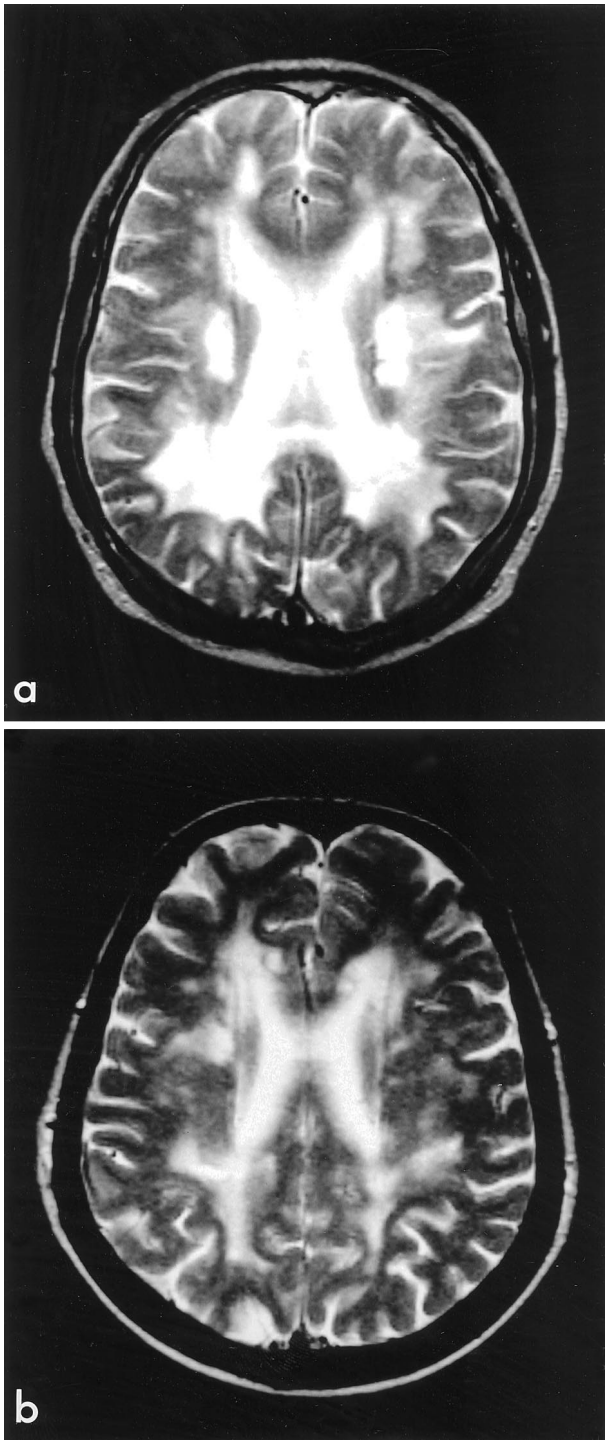


Figure 4. The confluent white matter hyperintensities in the homozygous patient's T2-weighted MRI (a) correspond to the most severe grade D, whereas the changes in the heterozygous reference patient No. 3 (b) of the same age were less severe (moderate=grade C).[13]

PET Procedure

Cerebral blood flow (CBF) was analyzed in the homozygous patient and 1 heterozygous patient (No. 3). In addition, 6 healthy volunteers (4 women, 2 men) with a mean age of 41.4±5.0 years were studied as controls. None of the controls had a history of either neurological or psychiatric disorders.

PET scans were performed with the GE Advance PET scanner (General Electric Medical Systems) with the 2-dimensional scanning mode. The axial and transaxial spatial resolution of the reconstructed images was approximately 5 mm full width at half maximum. For CBF measurements, ^{15}O-labeled water was injected intravenously, and a parametric CBF image was obtained by an autoradiographic method[14] with 90-second integration time.

The regions of interest (ROIs) were identified and placed individually in the patients' and controls' MRI scans, which were matched with PET images.[15] ROIs were drawn on frontal, primary sensorimotor, and temporal cortical areas, hippocampus, putamen, cerebellum, and frontal and occipital white matter.

Statistical Analysis

The raw scores of the neuropsychological tests were converted to standard *Z* scores (mean=0, SD=1) to allow comparison between tests. Normal variation of performance is considered to be between *Z* scores of 1 and −1 (±1 SD). The mean values and SDs in the control groups in PET studies were calculated, and values were compared with the corresponding values for the homozygous patient. The values <2 SDs in the CBF analyses were considered significant.

The study was approved by the Joint Ethical Committee of Turku University Hospital and the University of Turku. All patients had given their informed consent.

Results

Clinical Findings

In the neurological examination at the age of 52 years, the homozygous patient was oriented in time and place. His speech was spastic and dysarthric, and his gait was spastic-atactic. He was unable to tandem walk or hop on either foot. Tests of coordination showed symmetric slowing in diadochokinesis, mild end-point dysmetria on finger-to-nose testing, and ataxia on heel-to-knee testing bilaterally. He had hyperreflexia of both upper and lower extremities, and the Achilles' reflexes were clonic on both sides. The plantar response was extensor bilaterally. There was no significant decrease in power or sensory functions of either upper or lower extremities. The cranial nerve status was normal. Masseter reflex was pathological. The main clinical symptoms in this patient and the age-matched reference group are given in Table 1. In the reference group the heterozygous patient No. 1 was neurologically more severely affected, whereas the condition of patient No. 8 was approximately similar to that of the homozygous patient.

The homozygous patient fulfilled the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* criteria of dementia[16] at the age of 48 years, at which age he also had to retire. Two patients in the reference group also fulfilled these criteria,[16] one (No. 1) being more severely affected than the homozygous patient.

Molecular Genetic Analyses

The *Msp*A1I restriction pattern of the patient was consistent with a homozygous mutation. Homozygosity of the C475T mutation was confirmed by DNA sequencing (Figure 3). Analysis of the polymorphic CTG repeat region in the DMPK gene at 19q13 disclosed heterozygosity, thus excluding uniparental isodisomy of chromosome 19.

Imaging

MRI Studies

In the homozygous patient's T2-weighted images, virtually the entire cerebral white matter was hyperintense, with nearly

TABLE 2. MRI Findings in Homozygous Patient and Age-Matched Reference Group Graded According to Classification of Chabriat et al[13] and Semiquantitative Rating Scale of Scheltens et al[11,12]

	Chabriat et al[13]	Scheltens et al[11,12]				
	(A–D)	PVH (0–6)	WMH (0–24)	BGH (0–24)	ITH (0–24)	Sum (0–78)
Homozygous	D	6	23 (6+6+6+5)	12 (3+4+1+4)	9 (2+1+5+1)	50
Heterozygous						
No. 1	(D)*	...	...	...	...	
No. 2	C	4	20 (6+5+3+6)	11 (3+2+3+3)	8 (1+3+4+0)	43
No. 3	C	4	21 (5+6+5+5)	9 (1+4+1+3)	6 (1+0+4+1)	40
No. 4	B	5	20 (6+5+4+5)	0 (0+0+0+0)	2 (1+0+1+0)	27
No. 5	(C)*	...	...	...	...	
No. 6	B	4	15 (5+4+1+5)	5 (0+4+1+0)	1 (1+0+0+0)	25
No. 7	C	5	21 (6+6+4+5)	11 (3+4+1+3)	4 (1+0+3+0)	41
No. 8	C	5	20 (6+6+3+5)	5 (0+3+0+2)	4 (1+0+3+0)	34
No. 9	C	5	20 (6+6+3+5)	7 (0+4+1+2)	10 (3+3+4+0)	42

PVH indicates periventricular hyperintensities (occipital and frontal caps, bands of lateral ventricles); WMH, white matter hyperintensities (frontal, parietal, occipital, temporal); BGH, basal ganglia hyperintensities (caudatum, putamen, pallidum, thalamus); ITH, infratentorial foci of hyperintensity (cerebellum, mesencephalon, pons, medulla); 0, no abnormalities; and 6, confluent abnormalities.

*Estimated degree of severity on the basis of CT scans.

maximal scores according to the semiquantitative rating scale of Scheltens et al[11,12] and with correspondence to grade D of the classification of Chabriat et al.[13] In T1-weighted MRI, there were large white matter infarcts (diameter >20 mm) bilaterally in capsula interna and pyramidal tract above the level of the lateral ventricles, frontal periventricular region, and parietal periventricular region. Smaller infarcts were detected in temporoparietal white matter, nucleus caudatus, putamen, and thalamus on both sides and in pons and left cerebellar white matter. These changes were more severe than the MRI lesions seen in 7 of the 9 reference patients, with only CT being available in 2 reference patients (Nos. 1 and 5) (Figure 4 and Table 2). In the heterozygous patient No. 1, who had a rapidly progressive CADASIL, the CT changes were equivalent to the MRI grade D level, whereas in patient No. 5 the CT changes were less severe. The results of the semiquantitative ratings of Scheltens et al[11,12] and Chabriat et al[13] are given in Table 2.

PET Studies

CBF in both the homozygous patient and the heterozygous patient (No. 3) was in all ROIs lower than in healthy control subjects. The decrease in the homozygous patient was significant (<2 SDs of the control value) in 17 of the 18 ROIs (Figure 5). In the white matter the CBF values were only 39% to 60% of the corresponding values of healthy controls. In cortical areas, cerebellum, hippocampus, and putamen, the CBF was reduced less but also significantly, to 57% to 78% of the control values.

Neuropsychological Results

The homozygous patient showed severely deteriorated performance in most of the tests (Figure 2). The results from 5 of the 11 tests were >2 SDs below normal variation of ±1 SD (*Z* score). The decline was most prominent (3 SDs below normal variation) in tasks measuring executive functions and in demanding constructional and episodic memory tasks. The impairment was primarily caused by poor organization and control of performance, as well as by poor attention. In the tests sensitive to these characteristics, the homozygous patient was clearly more deteriorated than the 8 reference patients tested. The heterozygous patient No. 1 could no longer be tested at the corresponding age because of his rapidly developed dementia after the age of 45 years. The

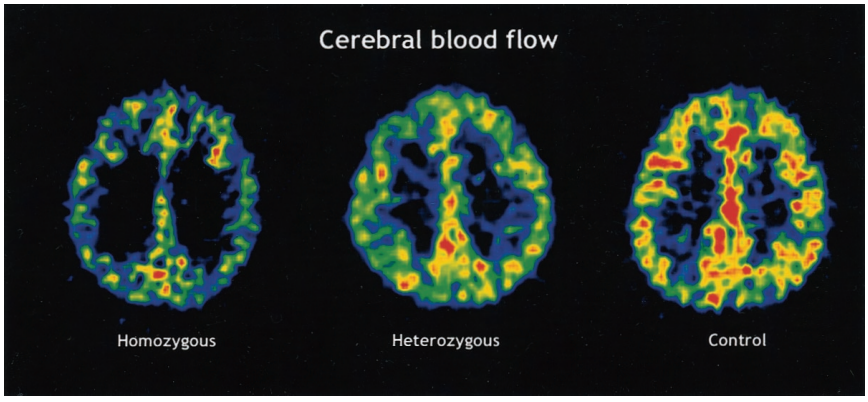
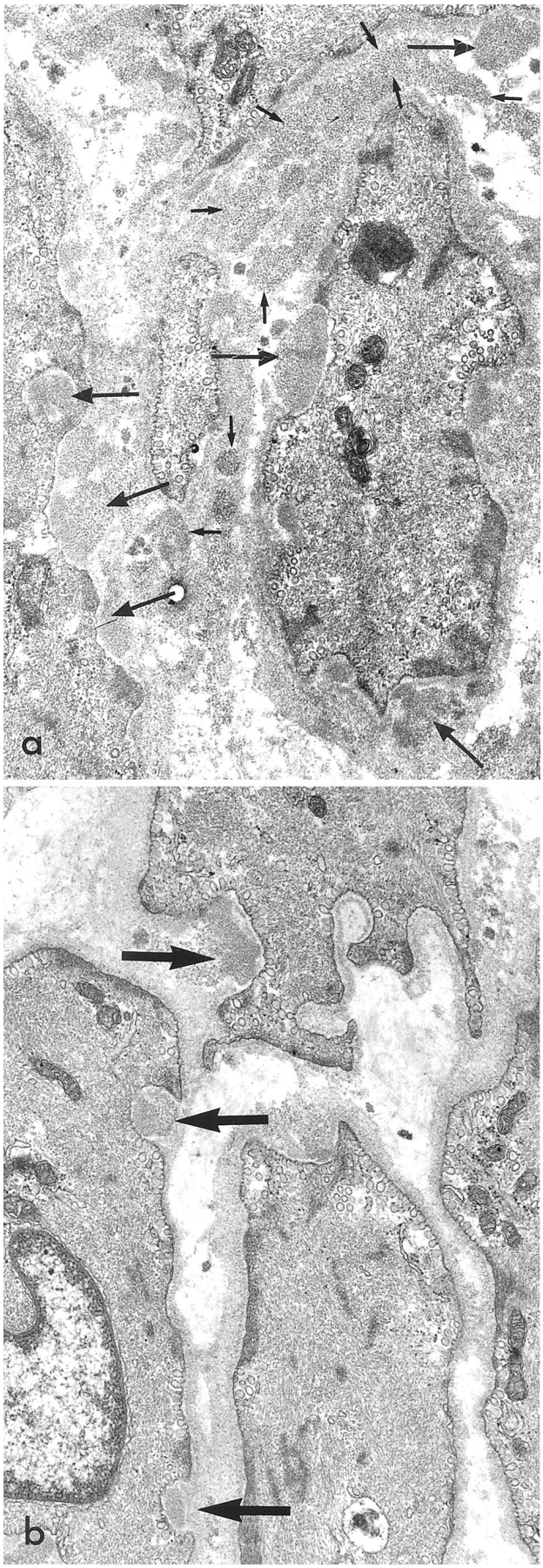


Figure 5. CBF images from left to right: the homozygous CADASIL patient, the heterozygous CADASIL patient No. 3, and a healthy male control. CBF has significantly decreased in almost all ROIs in both CADASIL patients, but the decrease is even greater in the homozygous patient.



homozygous patient and the reference group on average performed within normal variation in memory tests with support and tests based on well-established knowledge (Figure 2). However, in these tests there was a marked variation in the reference group, with 5 subjects having performances below the normal range. One reference patient had moderate aphasia, which explains his low performance (3 SDs below the normal range) in FAStot and Simil tests (see Figure 2) measuring verbal abilities.

Skin Biopsy

Electron microscopic analysis of the skin biopsy of the homozygous patient revealed abundant extracellular deposits of granular osmiophilic material (GOM) between the degenerative SMCs of deep dermal arteries. GOM deposits were located both in the indentations of the SMC surface and free between SMCs, often within irregularly thickened basal lamina. The amount of GOM in the homozygous patient was clearly greater than in the heterozygous patient No. 3, whose skin biopsy was available (Figure 6).

Discussion

The patient's homozygosity for the C475T (R133C) mutation of the *Notch3* gene suggested by the DNA restriction pattern was verified by sequencing, which also excluded the nearby silent polymorphism at nucleotide 474, which could lead to a similar restriction pattern. By using another pair of internal primers, we excluded the possibility that a primer binding site polymorphism could have prevented the amplification of normal alleles and thereby given a false indication of homozygosity.

Because the R133C mutation is common in Finland, the alternative that both parents of the homozygous patient had been heterozygous mutation carriers was the most likely explanation. The patient's father and several paternal and maternal relatives had suffered from neurological disorders, the clinical pictures of which were compatible with CADASIL, which was unknown at that time. The patient's mother died at the age of 31 years without identified neurological symptoms, but her death obviously occurred before CADASIL became manifest or her other diseases disguised her CADASIL. Finally, the genealogical analysis disclosed that the patient's parents had a common ancestor in generation I, and 1 paternal relative had genetically verified CADASIL in generation IV (Figure 1). The remote possibility of an uniparental isodisomy as the cause of homozygosity was also excluded. On these bases, the homozygosity of our patient was definitely verified.

The homozygous patient's elder son experienced his first episode of either TIA or severe migrainous aura at the age of 28 years, at which age the father suffered from his first stroke. The homozygous patient is the youngest with first-ever stroke among those Finnish CADASIL patients with the same R133C mutation, whose mean age at first-ever stroke is 46

Figure 6. The number of GOM deposits (arrows) in the homozygous CADASIL patient's dermal artery (a) is greater than in the heterozygous patient's similarly processed skin biopsy (b). Electron micrograph, ×20 000.

years.[10] This mean age is very similar to those reported from elsewhere, eg, 49.3 years among French patients[2] and 46.1 years among German-Austrian patients,[3] although the age at the first-ever stroke in CADASIL is highly variable. Among the Finnish heterozygous R133C patients, 1 patient had a stroke at 30 and another at 32 years of age. Similarly, Dichgans et al[3] reported a patient with the first-ever stroke at the age of 30 years. Yet, there is marked phenotypic variation both intrafamilially and between the Finnish families with the same mutation as well as between families with different genotypes.[3,17] The reasons for such great variation are still unknown.

Our homozygous patient's disease falls within the phenotypic spectrum of the Finnish R133C CADASIL patients, although at its severe end. Similarly, the homozygous patient's neurological deficits and the degree of cognitive decline, particularly in executive functions, were more severe than in most age-matched heterozygous reference patients. However, 1 reference patient (No. 1) was more severely affected than the homozygous patient. The pace of progression in this patient was markedly more rapid than in the homozygous patient, to which alcohol abuse may have contributed. Moderate dementia developed within 26 years in the homozygous patient. In contrast, in the heterozygous patient No. 1 severe dementia developed within 9 years from the first-ever stroke. This is the same as the mean interval reported in the literature.[2] However, since longitudinal studies on the progression of disease are lacking, it is unknown whether early onset is associated with a more rapid or slower progression.

In MRI studies the findings were either the most severe or the second most severe in the homozygous patient when compared with the 7 heterozygous reference patients with MRI examination available (Table 2). In PET studies CBF was markedly decreased in all brain regions, especially in the white matter, as also described by Chabriat et al.[18] The decrease in CBF was somewhat greater in the homozygous patient than in the heterozygous patient No. 3. However, since only 2 CADASIL patients' PET results, as well as GOM accumulation in dermal arteries, are compared, no definite conclusions can be drawn, although these results also appear to correspond to the severe end of the spectrum.

In general, in a dominantly inherited disease the mutation may implement its pathological effect by either loss or gain of function, ie, a single functional allele cannot maintain the required function (haploinsufficiency) or accentuated function has a toxic effect. During development Notch receptors (4 in mammals) control cellular differentiation by regulating gene transcription.[19] The function of the normal Notch3 protein in adults is unknown, as is the exact mechanism by which the mutated Notch3 molecule causes CADASIL.

If CADASIL is due to loss of Notch3 function, the fact that the double dose of gene defect does not appear to aggravate the symptoms indicates that either the mutated Notch3 receptors retain some of their function or other (Notch?) molecules can compensate for the loss. On the other hand, it was recently demonstrated that vascular SMCs, which in CADASIL become degenerated, are the only cells expressing *Notch3*. Ectodomains of the mutated Notch3 protein accumulate around SMCs,[7] and these might sop up the ligands and thereby turn down Notch3 signaling.[20] Accordingly, more abundant accumulation might occur in a homozygous patient. The profusion of GOM in the homozygous patient agrees with this possibility, even though GOM and ectodomains were not shown to be identical.[7] The mechanism by which a toxic gain of function might cause CADASIL is still completely open.

The classic definition of dominance states that homozygotes and heterozygotes are phenotypically indistinguishable. However, in many dominantly inherited diseases the course is more severe in homozygotes.[9] Such neurological diseases include, for example, Charcot-Marie-Tooth 1A disease, spinocerebellar ataxia (SCA) type 3 (Machado-Joseph disease), and probably dentato-rubro-pallido-luysial atrophy as well as SCA types 1, 2, and 6. However, in Huntington disease[21,22] and in familial (Lys200) Creutzfeldt-Jakob disease,[23] homozygosity has no significant effect on the severity of the disease. Our homozygous patient's phenotype falls at the severe end of the clinical spectrum in CADASIL, and furthermore, his older heterozygous son's phenotype may be of similar severity. Thus, these findings suggest that CADASIL belongs to the latter group, since the homozygosity does not appear to aggravate the symptoms. Of course, more homozygous patients should be found and examined before definite conclusions can be made.

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