

[CASE REPORT]

A Japanese Case of CADASIL with a Rare Mutation in Exon 24 of the *NOTCH3* Gene

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Abstract:

A 50-year-old man with a family history of stroke and depression slowly developed brain lesions. Magnetic resonance imaging revealed hyperintense lesions in the diffuse white matter, external capsules, and temporal poles on T2-weighted imaging. A heterozygous mutation c.3879C>G in exon 24 of the *NOTCH3* gene (p.Cys1293Trp) was detected, confirming a diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Exon 24 mutations are rather rare and this represents the first Japanese case of CADASIL.

Key words: autosomal dominant arteriopathy, leukoencephalopathy, CADASIL, *NOTCH3*, exon 24

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Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common form of hereditary cerebral angiopathy. The condition is caused by mutations in the *NOTCH3* gene on chromosome 19 (1, 2). Mutations of *NOTCH3* can occur in exons 2-24, but are most often reported in exons 3-6 (3, 4). To date, CADASIL due to mutations of exon 24 has only been reported in two Italian families (5, 6). We herein report the first Japanese CADASIL patient with a mutation in exon 24 of the *NOTCH3* gene.

Case Report

A 50-year-old man was admitted to our hospital to undergo further investigation of depression and slowly growing brain lesions that were identified by magnetic resonance imaging (MRI). T2-weighted brain MRI at 40 years of age showed areas of high intensity in the bilateral external capsules and diffuse white matter; however, the patient was asymptomatic. The patient became depressed; his depression was successfully treated by a psychiatrist at 49 years of age.

T2-weighted MRI showed new hyperintense lesions in the brainstem and the bilateral anterior temporal poles in addition to the previous lesions, while T2 star images demonstrated microbleeds in the bilateral basal ganglia and thalami at six months before he visited our hospital. His family history (Fig. 1) was notable for stroke in his father [at 43 years of age (II-1)] and his two brothers [at 62 (III-3) and 52 years of age (III-5), respectively; Fig. 1]. His medical history was only remarkable for untreated hypertension, which was diagnosed at 41 years of age. He was a never smoker and had no history of migraine.

His height was 171 cm and his weight was 74.3 kg. A general medical examination that included screening for carotid bruits was unremarkable except for hypertension (150/100 mmHg). A neurological examination revealed that his mental status and cognitive functions were normal (Mini-Mental State Examination, 30/30); his muscle strength, sensation, deep tendon reflexes, coordination, and gait were intact. The patient's laboratory data showed a normal complete blood count, chemistry, coagulation, lipid tests, and blood sugar. All of the following coagulation-related test results were within the normal ranges: protein S, protein C, total homocysteine, anti-DNA antibodies, anti-cardiolipin β 2-glycoprotein I complex antibodies, anti-cardiolipin antibod-

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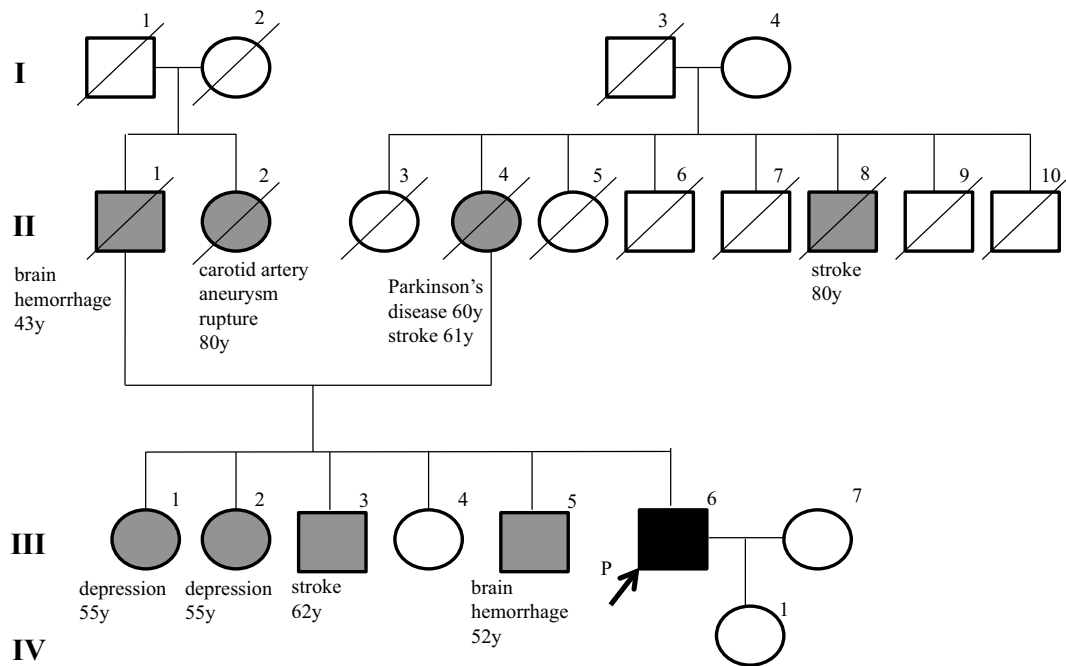


Figure 1. Family tree. The proband is indicated by the arrow. Family members with cerebrovascular disorder or depression are indicated in gray.

ies, and lupus anticoagulant. Carotid ultrasound showed neither stenosis nor plaque formation. Echocardiography revealed no right-left shunt formation or thrombosis. A 24-hour Holter electrocardiogram was normal. Brain MRI demonstrated multiple hyperintense lesions in the subcortical white matter, basal ganglia, thalami, pons, external capsules, and temporal poles (Fig. 2). Brain single photon emission computed tomography using technetium-99m-hexamethylpropyleneamine oxime revealed intact blood flow without any hypoperfusion. The patient's clinical history and findings suggested the presence of CADASIL, and genetic testing was performed. A heterozygous mutation c.3,879C>G was detected in exon 24 [p.Cys1293Trp, 33rd epidermal growth factor (EGF)-like repeat] of the *NOTCH3* gene. We conclude that c.3,879C>G (p.Cys1293Trp) is a novel pathogenic mutation of CADASIL because of the following reasons. First, it is compatible with the characteristics of typical CADASIL mutations, that is, cysteine-related missense mutations in EGF-like repeats (4). Second, it was not previously reported in CADASIL (10). Third, it was not present in exome variation databases, including the Exome Aggregation Consortium (ExAC, <http://exac.broadinstitute.org>) and Human Genetic Variation Database (HGVD, <http://www.hgvd.genome.med.kyoto-u.ac.jp>)

Discussion

CADASIL is a hereditary autosomal-dominant cerebral arteriopathy that was proposed in 1993 (2). The typical clinical features of CADASIL include migraine with aura at approximately 30 years of age, followed by subcortical infarction and associated symptoms beginning at 40 years of age,

and concomitant cognitive decline starting at approximately 50 years of age (7). On brain MRI, T2-weighted and fluid attenuated inversion recovery (FLAIR) images revealed areas of hyperintensity in the bilateral subcortical white matter as well as subcortical lacunar lesions in the anterior temporal lobes. As the disease progressed, these lesions become confluent and spread to other areas, including the basal ganglia and external capsules (7, 8). Lesions of the temporal poles and external capsules are characteristic findings in CADASIL (9).

In 1996, *NOTCH3* was identified as the causative gene in CADASIL (1). The *NOTCH3* protein belongs to the Notch family and is a single transmembrane receptor that is implicated in the differentiation of stem cells. It is not yet clear how *NOTCH3* mutations result in the pathological changes seen in CADASIL; however, dysfunction due to abnormal protein aggregation around the vascular smooth muscle of the brain has been implicated (7). More than 200 mutations of exons 2-24 in *NOTCH3* have been reported (10), all of which manifest in the EGF-like repeats of the extracellular domain, and most of which are cysteine-related mutations (3). The mutations are most frequent in exons 3-6 (3, 4), while the mutation in exon 24, which encodes the 3' end of the EGF-like repeat, was previously identified in only two Italian families (5, 6).

Table summarizes the characteristics and clinical findings of these two families (Table). A 64-year-old man, the first case (6), had a chief complaint of parkinsonism for 4 years, followed by migraine without aura and cognitive decline; however, he did not have any history of transient ischemic attack (TIA), stroke-like attacks, or depression. He had a family history of cerebrovascular disease. Brain MRI

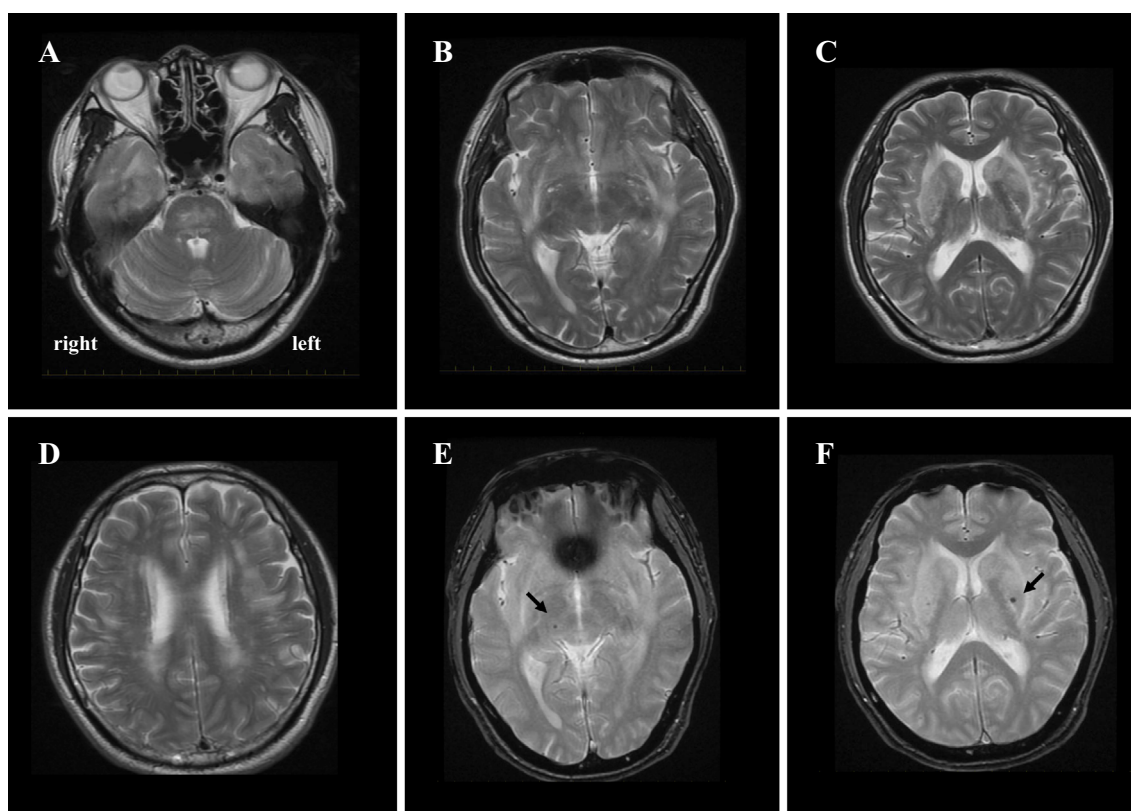


Figure 2. Axial cerebral MRI. A-D: T2-weighted images show diffuse and symmetric hyperintense lesions in the deep white matter, involving the brain stem, external capsules, and the anterior sections of the temporal lobes. E and F: T2-weighted images show a few microbleeds (arrows).

Table. Clinical Overview of Three Cases with a Mutation in Exon 24 of *NOTCH3*.

Age/Sex	Mutation of <i>NOTCH3</i> (EGF-like repeat)	Initial symptoms	Stroke	Migraine	Depression	Cognitive impairment	High-intensity lesion on brain MRI	Country (reference)
64/M	p.Cys1315Tyr (33rd)	Parkinsonism	-	+	-	+	Deep white matter External capsules	Italy (6)
73/F	p.Cys1298Phe (33rd)	Transient global amnesia	TIA	+	+	+	Deep white matter Brain stem Temporal poles Left external capsule	Italy (5)
50/M	p.Cys1293Trp (33rd)	Depression	-	-	+	-	Microbleeds in the right basal ganglia regions Deep white matter Brain stem Temporal poles Bilateral external capsule	Japan (present case)
							Microbleeds in the left thalamus	

EGF: epidermal growth factor, M: male, F: female, TIA: transient ischemic attack

showed typical findings of CADASIL. A genetic analysis revealed a mutation in exon 24 (p.Cys1315Tyr), which confirmed the diagnosis of CADASIL. The same mutation was subsequently identified in his brother and daughter. The late onset of disease and symptoms of parkinsonism are not typi-

cal of CADASIL.

The second case (5) was a 73-year-old woman who had episodic transient global amnesia (TGA) for 10 years. She also had migraine with aura, depression, TIA, and dementia. Brain MRI revealed the typical abnormal findings of CA-

DASIL. Her family history was positive for recurrent stroke, which occurred in her father. She was diagnosed with CADASIL after a mutation (p.Cys1298Phe) was identified in exon 24 of the *NOTCH3* gene. Her age at onset and recurrent TGA as a chief complaint are atypical clinical characteristics of CADASIL.

The brain MRI findings of both previous patients were typical of CADASIL, even though their age at the onset of disease and their clinical symptoms were not. In our patient, however, both the brain imaging findings and the clinical symptoms-such as the development of depression at 50 years of age-were typical of CADASIL.

The relationship between the genotype and phenotype of *NOTCH3* mutations has been thought to be weak (7, 11). Indeed, the clinical manifestations of our patient were typical of CADASIL while those of the abovementioned Italian families were not. Thus, the accumulation of further cases is needed to elucidate the genotype-phenotype correlations in patients with exon 24 mutations of the *NOTCH3* gene.

The authors state that they have no Conflict of Interest (COI).

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