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ORIGINAL COMMUNICATION

Population-specific spectrum of *NOTCH3* mutations, MRI features and founder effect of CADASIL in Chinese

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Abstract *Background and purpose* Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary disorder caused by *NOTCH3* mutations and characterized by recurrent subcortical infarctions, dementia and leukoencephalopathy. So far, most clinical, molecular and neuroimaging information has come from Caucasians. Therefore, we investigated the spectrum of *NOTCH3* mutations and MRI features in CADASIL patients of Chinese origin on Taiwan. *Methods* Mutational analysis of *NOTCH3* exons 2 to 23 by direct nucleotide sequencing was performed in patients with clinically suspected CADASIL. MRI findings were retrospectively evaluated and scored using a modified Schelten's scale. *Results* Nine different point mutations of *NOTCH3* were identified in 21 unrelated patients. Intriguingly, 47.6 % were in exon 11, and 19 % in each of exon 4 and 18. R544C was very common and present in all patients with a mutation in exon 11. Many patients with *NOTCH3* R544C share the same haplotype linked to the mutation using markers D19S929 and D19S411, which flank the *NOTCH3*. The sensitivity of T2-weighted MRI detecting anterior temporal abnormality was only 42.9 %. Furthermore, the neuroimaging evidence of intracerebral hemorrhage (ICH) was present in 23.8 % of the 21 patients. *Conclusions* A population-specific mutational spectrum of CADASIL was found in the Chinese patients on Taiwan. The Chinese patients carrying *NOTCH3* R544C may descend from a common ancestor. Anterior temporal hyperintensity on T2-weighted MRI may not be a sensitive marker for CADASIL. ICH is a relatively common manifestation of CADASIL in East Asians, especially in the presence of hypertension.

Key words CADASIL · NOTCH3 · leukoaraiosis

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL; MIM #125310) is an adult-onset, dominantly inherited disorder characterized by recurrent subcortical infarctions, dementia, and less frequently, migraine or psychiatric symptoms [1]. The pathological characteristic of CADASIL is a systemic vasculopathy with progressive degeneration of vascular smooth muscle cells, predominantly involving the small cerebral arteries [2]. Ultrastructural studies may demonstrate pathognomonic deposits of granular osmiophilic material (GOM) of unknown nature near the basement membrane of smooth muscle cells [3]. *NOTCH3* (MIM *600276) mutations have been identified as the genetic cause of CADASIL [4]. The gene encodes NOTCH3, a protein of 2,321 amino

acids. NOTCH3 is a member of the Notch family, which is involved in signaling events that control cell fate decisions during development [5]. It is a single-pass transmembrane receptor with a large extracellular domain containing 34 tandem epidermal growth factor-like (EGF-like) repeats [5]. There are 33 exons in *NOTCH3* and all mutations demonstrated to date in CADASIL occur in exons 2 to 23 encoding the EGF-like repeats. Most CADASIL-associated *NOTCH3* mutations in Caucasians result in a gain or loss of one cysteine residue within a given EGF-like repeat domain and with a strong clustering in exons 2 to 6 encoding the first five EGF-like repeats [6–8].

In clinical practice, family history might not always be positive because of mild symptoms in other family members or on account of de novo mutations [9]. To ascertain CADASIL, however, brain magnetic resonance imaging (MRI) is an indispensable tool. Typical MRI features in CADASIL include leukoaraiosis, presenting as diffuse T2-weighted hyperintensity of white matter, and focal and multiple lacunar infarcts [10]. Moderate to severe involvement of the anterior temporal poles on T2-weighted MRI was found, in Caucasians, to have high sensitivity and specificity for the diagnosis of CADASIL [7]. A Korean MRI study once demonstrated that 25 % of their symptomatic patients with CADASIL had primary intracerebral hemorrhage (ICH) [11], which previously had rarely been reported in Caucasians.

Although wide spectrum of mutations and MRI features of CADASIL have been described in Caucasians, there is still limited information in Chinese [12, 13]. Herein we report our observation on the population-specific mutational spectrum and MRI features of CADASIL in the Han Chinese on Taiwan.

Patients and methods

Patients

The study was approved by the Taichung Veterans General Hospital Institutional Review Board and written informed consent was obtained from all subjects who participated in the study. Thirty-nine patients with clinically suspected CADASIL were enrolled. The suggestive inclusion criteria were marked leukoaraiosis on the brain MRI and at least one of the following: young age at onset of repeated lacunar infarctions or transient ischemic attacks, cognitive decline, psychiatric disorders, or a family history of ischemic strokes. Patients with large vessel infarctions or significant major vessel stenosis, defined as more than 50 % narrowing of the lumen, were excluded. All patients were of Han Chinese in origin.

Molecular studies

Genomic DNA was extracted from peripheral blood samples. Exons 2–23 of *NOTCH3* were amplified using the self-designed intronic primers. The PCR products were directly sequenced for both sense- and antisense-strands using an automated fluorescent sequencing method on an ABI Prism 310 Genetic Analyzer (Applied Biosystems, Foster City, CA). The sequences of the PCR products were compared with the published human *NOTCH3* DNA sequences (gi: 42406306) to ascertain any sequence changes.

Haplotype analysis of the patients carrying NOTCH3 R544C

Haplotype analysis was performed to explore the possible founder effect of R544C [14] by using six polymorphic microsatellite markers flanking the *NOTCH3* gene: D19S840 and D19S929 are located telomeric to *NOTCH3*, while D19S411, D19S885, D19S930, and D19S410 are centromeric. These six markers cover a region of 7.54 Kosambi cM (KcM, sex-averaged). All the information on primer sequences and allele sizes of the markers was obtained from the National Center for Biotechnology Information (NCBI) database (http://www.ncbi.nlm.nih.gov/).

Neuroimaging

Brain MRI/MRI angiogram (MRA) were obtained on all patients and analyzed retrospectively. Original T2-weighted images were reviewed and leukoencephalopathy was graded, with the interpreters blinded to the clinical and genetic status of the patients, for the involvement of the anterior temporal poles and external capsules using the modified Schelten's scale [10, 15]. A score for each region was assigned according to the following scale: 0 = absent; 1 = up to five lesions of < 3 mm diameter; 2 = six or more lesions of < 3 mm; 3 = up to five lesions 4 to 10 mm in diameter; 4 = six or more lesions of 4 to 10 mm; 5 = one or more lesions > 10 mm in size; and 6 = confluent hyperintensity. Moderate or severe involvement of each region was defined as modified Schelten's scale ≥ 3 in one or both sides. In patients in whom no *NOTCH3* mutation were found, original MRIs were also reviewed, and these data were used to estimate the specificity of anterior temporal pole involvement on MRI in diagnosis of CADASIL in our population. Three observers (Y.C. Lee, M.H. Chang, and B.W. Soong) evaluated the neuroimages by mutual consent. The location and size of ICH, which is clearly recognizable on MRI or CT, were also recorded. Microbleeds were not surveyed because T2*-weighted gradient echo MRI, which is highly sensitive for visualizing microbleeds, was not performed in this study.

Results

General observations

NOTCH3 mutations were found in 21 (53 %) (16 men and 5 women; current age, 54.1 ± 12.2 years, range 34–79; age at onset of initial symptoms, 48.6 ± 13.8 years, range 20–77) out of 39 patients with clinically suspected CADASIL. Five of these subjects had been reported previously [13]. Cerebral infarction (CI) was the most common initial manifestation (11 patients; 52.4 %) with a mean age at onset of 47.6 ± 12.2 years (range 23–72). Other initial presentations were progressive gait disturbance in 4 (19.0 %), psychiatric problems in 2 (9.5 %), dementia in 1 (4.8 %), headache in 1 (4.8 %), epilepsy in 1 (4.8 %), and ICH in 1 (4.8 %). ICHs were found in 5 patients (23.8 %) from the MRI. Family history of CI or dementia was found in 12 patients (57.1 %). Hypertension and diabetes mellitus (DM) were found in 6 (28.6 %) and 2 (9.5 %) patients, respectively (Table 1).

Table 1 Clinical, molecular and neuroimaging features of CADASIL in Chinese

Patient/ sex	Age at onset (year)	Family history[a]	Risk factor	*NOTCH3* mutation		Manifestations[b]	MRI features of leukoencephalopathy or ICH			
				Exon	Amino acid changes		Age at MRI (year)	Anterior temporal WM changes[c]	External capsule WM changes[c]	ICH location/ largest diameter (cm)
1/F	55	N/A	DM	2	R54C	CI, dementia	73	+ (6,6)	+ (6,6)	
2/F	39	+	–	4	S118C	CI, dementia	54	+ (6,6)	+ (6,6)	
3/M	41	+	HTN	4	R133C	Progressive gait disturbance, CI, ICH[d]	43	+ (5,5)	+ (6,5)	Left thalamus/3.8[d]
4/M	41	+	–	4	R141C	CI	44	+ (5,5)	+ (5,5)	
5/M	50	+	–	4	R153C	Progressive gait disturbance	51	+ (6,6)	+ (5,5)	
6/F	23	–	–	6	R332C	CI, psychosis, dementia	34	+ (3,5)	+ (3,5)	
7/F	72	–	–	10	C504R	CI	79	– (0,0)	+ (3,5)	
8/M	58	+	–	11	R544C	Dementia	61	+ (5,5)	+ (6,5)	
9/F	56	–	HTN	11	R544C	ICH	56	– (0,0)	+ (6,6)	Right thalamus/1.9
10/M	52	+	HTN	11	R544C	CI, ICH	57	– (0,0)	+ (3,5)	Right posterior temporal/2.2 Right putamen/1.8
11/M	50	+	HTN	11	R544C	CI, ICH	56	– (0,0)	+ (5,5)	Left parietal lobe/2.7
12/M	34	+	HTN	11	R544C	Progressive gait disturbance, ICH[e]	35	– (0,0)	+ (5,5)	Right putamen/1.1
13/M	77	–	DM	11	R544C	Progressive gait disturbance, dementia	77	– (0,0)	+ (5,5)	
14/M	42	+	HTN	11	R544C	CI	42	– (1,1)	+ (5,5)	
15/M	46	+	–	11	R544C	CI, dementia	57	– (0,0)	+ (5,5)	
16/M	50	–	–	11	R544C	CI, progressive dysarthria,	52	– (0,0)	+ (5,5)	
17/M	49	+	–	11	R544C	Headache, depression, CI	54	– (0,0)	+ (5,3)	
18/M	65	–	–	18	C977S	Complex partial seizure	65	+ (6,6)	+ (5,5)	
19/M	46	–	–	18	C977S	Panic disorder, CI	46	+ (5,3)	– (2,2)	
20/M	20	–	–	18	C977S	Psychosis	46	– (0,0)	+ (4,4)	
21/M	54	+		18	C977S	CI	54	– (0,0)	+ (3,4)	

CI cerebral infarction; *ICH* intracerebral hemorrhage; *HTN* hypertension; *DM* diabetes mellitus; *WM* white mater; *N/A* not available

[a] Family history of cerebral infarctions or dementia

[b] In the order of appearance

[c] Positive was defined as leukoencephalopathy graded by modified Schelten's scale ≥ 3 on at least one side of the region on T2-weighted MRI. Original modified Schelten's scores of the left and right side were shown in the parentheses

[d] Documented by a brain CT at age of 45 years

[e] Asymptomatic and uncovered on MRI

Spectrum of mutations

Nine different heterozygous point mutations of *NOTCH3* were identified (Table 1). In contrast to the pattern of distribution of mutations from exon 2 to 6 in Caucasians, the mutations in Chinese were predominantly located in exons 11 (47.6 %), 18 (19 %) and 4 (19 %). Four patients had different mutations in exon 4, and one patient each had mutations in exons 2, 6 and 10. C504R in exon 10 is a novel mutation. No similar nucleotide sequence variation could be found among 100 healthy elderly controls older than 80 years of age. *NOTCH3* mutations in exons 2 to 6, common among Caucasians, account for only 28.6 % of CADASIL in our population.

Haplotype analysis of the patients carrying NOTCH3 R544C

Twenty-four individuals from 10 unrelated families carrying *NOTCH3* R544C, including 8 patients and 9 unaffected individuals from 3 kindreds and 7 unrelated patients with *NOTCH3* R544C were haplotyped. The 10 families were assigned from A–J (Table 2). Three families (A–C) shared a common haplotype at loci D19S929 and D19S411 linked to the *NOTCH3* R544C (2-R544C-3). For patients D1 to J1, no samples from relatives were available for analysis. Although the phase of the haplotype could not be deduced with certainty in those patients, it is highly likely that they also have the common haplotype (2-R544C-3).

Neuroimaging

All the 21 patients with *NOTCH3* mutations had diffuse white matter hyperintensities on T2-weighted images. Among them, moderate to severe involvement of the anterior temporal lobes and external capsule was present in 9 (42.9 %) and 20 (95.2 %), respectively. There is no significant difference in age between patients with or without anterior temporal involvement ($p = 0.579$, 2-tailed t-test).

Six ICHs were found in five (23.8 %) patients with *NOTCH3* mutations (four on MRI and one on CT): two in the right putamen, one each in the left thalamus, right thalamus, left parietal lobe, and right posterior temporal lobe, with the largest diameters ranging from 1.1 to 3.8 cm. One patient had recurrent ICH (Fig. 1). All five patients had hypertension, and three were regularly taking aspirin 100 mg per day to prevent cerebral infarction around the time of ICH. No large vessel malformation or segmental intracranial stenosis suggestive of possible angiitis was found in any of the patients.

The neuroimaging studies of the ten patients with R544C in exon 11 revealed that only one had significant anterior temporal pole involvement and four had ICH. In contrast, among the six patients with mutations in exons 2 to 6, which are common in Caucasians with CADASIL, all had significant anterior temporal pole involvement and only one had ICH.

The initial clinical manifestations, MRI features and mutational spectrum of CADASIL in different studies were compared in Table 3.

Table 2 Haplotypes linked to R544C mutation in ten CADASIL kindreds

Locus	D19S840	D19S929	Notch3	D19S411	D19S885	D19S930	D19S410
Patient	4.34 KcM	0.00 KcM	0.00 KcM	0.00 KcM	2.13 KcM	1.07KcM	
A I-1	3	2	R544C	3	2	11	9
BI-1	6	2	R544C	3	2	6	8
BII-1	6	2	R544C	3	2	6	8
CI-5	2	2	R544C	3	3	1	6
CI-7	2	2	R544C	3	3	1	6
CI-9	2	2	R544C	3	3	1	6
CII-2	6	2	R544C	3	3	1	6
CII-3	2	2	R544C	3	3	1	6
D1	2/3	2	R544C	1/3	2/3	1/13	3/4
E1	2/6	1/2	R544C	3	3/4	6	5/8
F1	2/8	1/2	R544C	3	2/3	1	2/8
G1	2/7	1/2	R544C	3	2/3	1/2	2/9
H1	2	2/4	R544C	1/3	3/9	2/3	2/6
I1	2/3	1/2	R544C	1/3	2/3	1	2/9
J1	2/3	2/3	R544C	3/4	2/3	2/3	5/8

KcM Kosambi cM

Families are indicated with letters (A–J) and patients by numerical order. Alleles with an unknown phase are separated with a slash. Sex-averaged genetic distances of the markers are shown in the top row

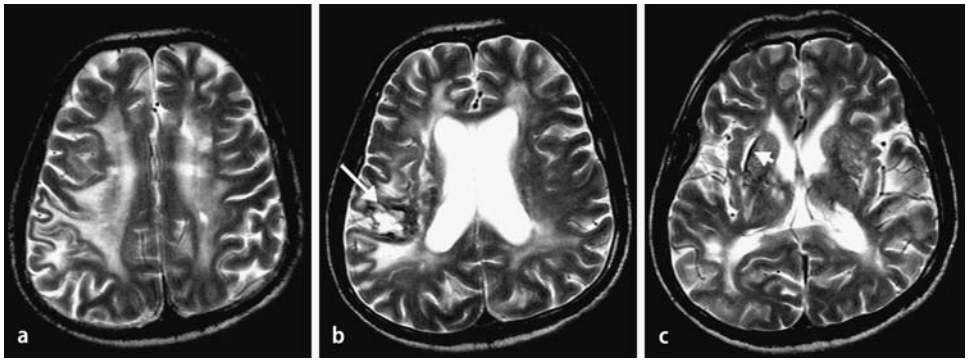

Fig. 1 T2-weighted magnetic resonance images from a 57-year-old patient with *NOTCH3* R554C showing diffuse white matter hyperintensities (**A**) and intracerebral hemorrhages in the right posterior temporal lobe (**B**) and putamen (**C**)

Table 3 Comparison of the mutational spectrum of NOTCH3, MRI features, and initial manifestations of CADASIL

Study	Number of patients (male/female)	Age of onset (± SD)	Mutational spectrum of *NOTCH3*	T2 weighted MRI features of diffuse WMA	Initial clinical manifestations				
					Ischemic events	Cognitive impairment	Psychiatric syndrome	Headaches	Seizures
This study	21 (16/5)	48.6 ± 13.8 (range 20–77)	Exon 2–6: 28.6 % Exon 10: 4.8 % Exon 11 (R544C): 47.6 % Exon 18 (C977S): 19 %	Anterior temporal: 42 % External capsule: 95.2 % ICH: 23.8 %	52.4 %	4.8 %	9.5 %	4.8 %	4.8 %
Markus et al., 2002 [11]	48 (25/23)	35.9 ± 14.6 (range 5–66)	Exon 2–6: 93.8 % Exon 8, Exon 18, Exon 22: 2.1 % each	Anterior temporal: 89 % External capsule: 93 % ICH: not specified	29.2 %	2.1 %	8.3 %	54.2 %	4.2 %
Desmond et al., 1999 [23]	105 (55/50)	36.7 ± 12.9 (range 10–59)	Not specified	Not specified	42.9 %	5.7 %	8.6 %	40 %	2.9 %
Choi et al., 2007 [7]	20 (9/11)	57.2 ± 10.2 (range 43–85)	Exon 2–6: 10 % (R75P) Exon 11: 85 % (R544C: 75 %)	Anterior temporal: 20 % External capsule: 90 % ICH: 25 %	55 %	15 %	0	10 %	0

SD standard deviation; *WMA* white matter abnormalities; *ICH* intracerebral hemorrhage

Discussion

Brute force genotyping of the *NOTCH3* gene is the best approach to confirm the diagnosis of CADASIL. However, it should be cautioned that genetic testing for CADASIL is associated with a significant portion of false negative results [8]. Cases with a high index of clinical suspicion should be further investigated by skin biopsy with ultra-structural studies if genetic testing is negative. In this series, nearly 50 % of clinically suspected cases were found not to have a mutation in exons 2 to 23. In Caucasians, skin biopsy was found to have a high specificity but fair sensitivity (45–75 %) [7, 16]. We have previously demonstrated a low sensitivity of skin biopsy in 5 cases of genetically proven CADASIL in our hands [13]. Conceivably, the sensitivity of skin biopsy could have been influenced by many factors, i. e., the depth, site and number of attempts of the procedure.

In Caucasians, *NOTCH3* mutations were initially demonstrated to cluster in exons 2 to 6, with the highest frequency in exon 4 [6, 8]. However, more recent studies have uncovered a wider array of spectrum. In a Dutch series of 39 families, *NOTCH3* mutations in exon 4 remained very common (53.8 %), but mutations in exon 11 came second in the frequency (15.3 %) [17]. Among 28 Italian patients with CADASIL, *NOTCH3* mutations resided most frequently in exon 11 (21.4 %), followed by exon 3 and 4 (both 17.8 %) [18]. In 17 Korean families with CADASIL, 15 had R544C and 2 had R578C mutations, both in exon 11 [11]. In the Chinese, R544C in exon 11 alone accounts for 47.6 % of the mutations. The occurrence of this rare mutation in ten apparently unrelated pedigrees and the occurrence of a common haloptype linked to *NOTCH3* R544C both potentially suggest the existence of a founder effect, which actually might not be rare in CADASIL given its late age at onset and lack of a negative impact on fertility. Several CADASIL founder mutations have previously been reported, e.g. R133C in Finnish families [14], R544C in Koreans [11] and R607C in Italians [18].

In Caucasians, significant leukoaraiosis in the ante-

rior temporal poles on T2-weighted MRI has been regarded as a useful marker for CADASIL, with a sensitivity of 89 % [7]. However, this does not seem to be the case in Chinese, given the lower sensitivity of 42.9 %. In this series, all the six patients with *NOTCH3* mutations in exons 2 to 6 had significant anterior temporal abnormality on the MRI, while of the 10 patients with R544C in exon 11, only one had anterior temporal hyperintensities. In the Korean series, infrequent involvement (four out of 20) of the anterior temporal poles in patients with R544C in exon 11 was also observed [11]. Although the underlying mechanisms leading to distinctively different MRI features in patients with different *NOTCH3* mutations remain elusive, variable functional perturbations caused by the NOTCH3 mutations in exons 2 to 6 and exon 11 have been demonstrated in a cell expression study [19], in which it was shown that the *NOTCH3* C542Y mutant exhibited a significant reduction in Jagged1-induced transcriptional activity, whereas R90C and C212S had normal signaling activities [19].

Although hypertension is a well-known risk factor for ICH, cerebral hemorrhage is disproportionately very common in our series. Five of the 6 patients with hypertension had ICH, whereas none of the 15 patients without hypertension had ICH. Among the five patients with both CADASIL and ICH, four had R544C in exon 11. Intriguingly, in a Korean study, among the five patients with CADASIL and hypertension, three had R544C. Given the small case number of these two series, it is still too early to speculate that patients with R544C are particularly liable to ICH if they also have hypertension. At the least, the findings in this study strongly argue for a stringent control of hypertension in patients with CADASIL [22]. It has been proposed that underlying arteriovenous malformation (AVM), arterial aneurysm or Notch pathway alteration might be the possible causes of ICH in CADASIL [20]. In this series, none of the 21 patients was found, by the MRA, to have AVM or primary angiitis of the central nervous system [21].

Our study demonstrates that Chinese with CADASIL have a distinct mutational spectrum and anterior temporal hyperintensity on MRI might not be a sensitive marker for CADASIL in the Asians. In other words, the absence of anterior temporal abnormality should not be a reliable criterion for the exclusion of CADASIL, particularly for those subjects with *NOTCH3* mutations outside exons 2 to 6. Finally, more ICH might occur in those Asians with CADASIL in the presence of hypertension, which necessitates a more stringent control of hypertension.

Conflict of interest The authors report no conflicts of interest.

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