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Address correspondence and reprint requests to Dr. Dooneief, P & S Box #16, 630 West 168th Street, New York, NY 10032.

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ϵ4 Allele of apolipoprotein E increases risk of Alzheimer's disease in a Chinese population

Article abstract—We examined the apolipoprotein E genotype in 56 Chinese patients with late-onset sporadic Alzheimer's disease (AD) and 57 Chinese control subjects of similar age. The frequency of ϵ4 in the AD group was significantly higher than that in the control group (23.2% versus 7.9%, $p = 0.003$). The odds ratio for AD in individuals with either one or two ϵ4 was 2.96 (95% CI 1.11 to 8.03). The linear trend for AD in proportion to alleles of ϵ4 was also significant ($\chi^2 = 8.2$, $p = 0.004$). Our results support the association between ϵ4 and AD in the Chinese.

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C.J. Hong, MD; T.Y. Liu, PhD; H.-C. Liu, MD; S.J. Wang, MD; J.L. Fuh, MD; C.W. Chi, PhD; K.Y. Lee, MD; and C.B. Sim, MD

Studies have shown an increased frequency of the ϵ4 allele of apolipoprotein E (apoE) in late-onset sporadic Alzheimer's disease (AD).[1-3] However, the strength of association between ϵ4 and AD varies.[4] To better understand the relationship between ϵ4 and AD in the Chinese, we analyzed the genotype of apoE in Chinese AD patients and control subjects.

Methods. *Subjects.* The study was conducted at the Veterans General Hospital-Taipei, Taiwan, from 1994 to 1995. Fifty-six consecutively treated or admitted AD patients 65 years of age or older were included in this study. All the patients were identified by the neurologic clinics of Veterans General Hospital-Taipei and were diagnosed by a team of neurologists (H.C.L., S.J.W., and J.L.F.). The diagnosis of AD was made by consensus according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's and Related Disorders Association for probable AD.

All control subjects, older than 65 years old, were genetically unrelated to each other or to the patients. Twenty-three of 57 control subjects were spouses of the AD patients included in this study and 9 were spouses of patients with other neurologic diseases. Twenty-five others were individuals who presented themselves to this neurologic clinic with low back pain (n = 20) or headache (n = 5). Each control subject was given clinical, mental, and neurologic examinations and a Mini-Mental State Examination (MMSE) to rule out any insidious cognitive deficit.

Laboratory methods. DNA isolated from peripheral blood leukocytes was amplified by PCR along with an upstream primer: 5′-TCCAAGGAGCTGCAGGCGGCGCA-3′ and a downstream primer: 5′-ACAGAATTCGCCCCGGCCTGGTACACTGCCA-3′.[5] The PCR products were digested with CfoI, and the fragments were separated by electrophoresis on a 4% ethidium bromide-containing agarose gel. DNA fragments were visualized by ultraviolet illumination. ApoE genotypes for the patient and control groups were determined in a blinded fashion by scoring for a unique combination of fragment sizes, as described by Wenham et al.[5]

Statistical analysis. Allele frequencies for AD patients and control subjects were estimated by counting alleles and calculating sample proportions. Comparisons of genotype frequencies and allele frequencies were made using chi-square test. Chi square for linear trend of AD was calculated in proportion to the number of ϵ4 allele. Two-tailed Student's t test was used to compare quantitative data.

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Table 1 Age, sex, and the distribution of apoE genotypes and alleles in Chinese AD patients and control subjects

	AD patients (n = 56)	Control subjects (n = 57)
Age* (y)	74.5 ± 5.2†	73.2 ± 5.9
Sex (M/F)	36/20†	32/25
ε2/ε2	1 (1.8%)	0
ε2/ε3	1 (1.8%)	7 (12.3%)
ε2/ε4	0	1 (1.8%)
ε3/ε3	34 (60.7%)	41 (71.9%)
ε3/ε4	14 (25.0%)	8 (14.0%)
ε4/ε4	6 (10.7%)	0
ε2	3 (2.7%)†	8 (7.0%)
ε3	83 (74.1%)†	97 (85.1%)
ε4	26 (23.2%)‡	9 (7.9%)

* Mean ± SD.
† AD versus control subjects: not significant.
‡ AD versus control subjects: $p = 0.003$.

ApoE = Apolipoprotein E; AD = Alzheimer's disease.

Results. The mean age and sex distribution of the AD patient ($p = 0.463$) and control ($p = 0.38$) populations were similar. The apoE genotype distribution and allele frequencies are given in table 1. The frequency of the ε4 allele in the AD patients was 23.2% versus 7.9% in control subjects, whereas that of ε2 was 2.7 versus 7.0% and that of ε3, 74.1 versus 85.1%. The allele frequencies (as calculated using the actual allele numbers) were significantly different between the AD patients and the control subjects ($\chi^2 = 11.6$, $df = 2$, $p = 0.003$). Comparison of genotype distribution between the AD and control populations showed a significant difference ($\chi^2 = 14.8$, $df = 5$, $p = 0.011$). If we compared the distribution of number of ε4 carriers (ε2/ε4, ε3/ε4, and ε4/ε4) and non-ε4 carriers (ε2/ε2, ε2/ε3, and ε3/ε3) between the AD and control populations, the difference remained ($\chi^2 = 5.9$, $df = 1$, $p = 0.015$).

Based on the ε4 carrier frequencies of AD patients, the odds of carrying at least one copy of the ε4 allele is threefold increased compared with control subjects (odds ratio = 2.96; 95% CI = 1.1 to 8.0).

There were six AD patients with ε4 homozygosity, whereas none was found in the control subjects. The linear trend of AD in proportion to alleles of ε4 was also significant ($\chi^2 = 8.2$, $p = 0.004$). The difference of the frequency of ε2 between the AD and control groups was not significant (2.7% versus 7.0%, $p = 0.13$).

Discussion. Our findings confirm the association between ε4 and AD and a significant trend of AD in proportion to the number of ε4 in a Chinese population. Although the odds ratios varies in different studies (table 2), more than 90 studies around the world have confirmed the association between ε4 and late-onset AD. Debate on apoE genotyping as an aid in differential diagnosis of AD has even been raised.[7]

The present data show that the frequency of ε4 in the control subjects was similar to the results of other studies of the Chinese (4.7 to 7.4%),[8,9] which were lower than those found in Whites and African-Americans.[4] Most epidemiologic studies from different Chinese populations found lower prevalence rates of dementia (including AD).[10] Whether the low frequency of ε4 reflects, in part, these findings deserves further investigation.

From the Neurological Institute (Drs. H.C. Liu, Wang, and Fuh), Departments of Psychiatry (Drs. Hong and Sim) and Medical Research (Drs. T.Y. Liu and Chi), Veterans General Hospital-Taipei & National Yang-Ming University School of Medicine, and Taipei Municipal Yang-Ming Hospital (Dr. Lee), Taiwan, China.

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Address correspondence and reprint requests to Dr. H.-C. Liu, the Neurological Institute, Veterans General Hospital-Taipei, Taipei, Taiwan, Republic of China.

Table 2 Frequencies of ε4 and odds ratio (OR) for AD associated with either homozygosity or heterozygosity for ε4 in different races and studies

	Control subjects			AD patients			
Publication	ε–/ε–*	ε4/ε–	ε4/ε4	ε–/ε–	ε4/ε–	ε4/ε4	OR
This study (n = 113) (Chinese)	48	9	0	36	14	6	3.0
Corder et al[1] (n = 234) (unidentified race)	74	63	2	19	55	21	4.6
Maestre et al.[4]							
African-American (n = 98)	32	23	2	20	16	5	1.3
Hispanic (n = 151)	70	18	2	36	21	4	2.4
White (102)	50	8	1	23	17	3	4.8
Kawamata et al.[6] (n = 89) (Japanese)	40	9	0	24	12	4	3.0

* Under the genotype, (ε–) indicates any isoform other than ε4 (i.e., ε2 or ε3).

AD = Alzheimer's disease.

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Petechial hemorrhages accompanying lobar hemorrhage: Detection by gradient-echo MRI

Article abstract—Based on the pathologic observation that severe cerebral amyloid angiopathy is often accompanied by multiple petechial hemorrhages, we prospectively obtained gradient-echo MRI on 15 elderly patients with lobar hemorrhage on CT. Nine of the 15 demonstrated accompanying petechial hemorrhages restricted to the cortical or corticosubcortical regions. No similar lesions were present on gradient-echo MRI in 10 elderly control patients. These findings suggest that cerebral amyloid angiopathy might be neuroradiologically diagnosed and staged during life.

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Steven M. Greenberg, MD, PhD; Seth P. Finklestein, MD; and Pamela W. Schaefer, MD

A significant proportion of spontaneous lobar hemorrhage in the elderly is due to cerebral amyloid angiopathy (CAA).[1] CAA can cause petechial as well as large lobar hemorrhages.[2] Like the large lobar bleeds, the petechial hemorrhages are typically situated in cortical or corticosubcortical (C/CS) regions. They are generally not resolved on CT, but were detected by MRI in a few published cases of pathologically confirmed CAA.[3-5] The frequency of radiographically detectable petechial hemorrhages in patients with lobar hemorrhage, however, is unknown.

Petechial hemorrhages, if detectable in a significant proportion of patients, might aid in the diagnosis and staging of CAA during life. Although petechial bleeds can accompany hypertensive as well as CAA-related hemorrhage,[6] multiple bleeds restricted to C/CS territories are not characteristic of hypertensive disease and are therefore supportive of a clinical diagnosis of probable CAA.[7] Petechial hemorrhages may also be responsible for some clinical manifestations of CAA, such as recurrent episodes of spreading neurologic symptoms.[5]

We utilized the technique of gradient-echo MRI for detection of petechial hemorrhages. Gradient-echo MRI enhances the magnetic susceptibility (and resultant signal dropout) produced by chronic blood products, thus increasing sensitivity for hemorrhage.[8] We include a report of one patient in whom gradient-echo MRI detected a small bleed apparently causing recurrent neurologic spells.

Methods. Between July 1994 and June 1995, 23 patients over age 60 years presented to the Massachusetts General Hospital with primary lobar hemorrhage on CT. (This figure excludes patients with known causes of hemorrhage such as trauma, cerebral tumor, coagulopathy, or vascular malformation.) Of the 23 patients, 13 were prospectively evaluated using T_2-weighted and gradient-echo MRI. The 10 patients not evaluated by MRI consisted of 5 with terminal clinical state (1 with CAA at postmortem examination), 2 with diagnoses previously established by hematoma resection (both showing CAA in the pathologic tissue), and 3 whose treating physicians chose not to obtain MRI. An additional 2 patients (patients 1 and 10) were evaluated by MRI during this time period for hemorrhages that had occurred 1 to 2 years previously and were added to the series. Mean age of evaluated patients was 75.9 years (range, 65 to 90) and sex distribution was eight men and seven women. MRI evaluation was generally performed within 3 days of the lobar hemorrhage, except as noted. Controls consisted of 10 consecutive patients (7 men, 3 women) over the age of 60 years (mean 72.4, range 62 to 83) undergoing MRI for other indications.

CTs were performed without intravenous contrast on General Electric 9800 scanners. MRI was performed on a 1.5-T superconductive magnet (General Electric). Fast spin-echo T_2-weighted (TR 4,000–4,200/TE 96–104/NEX 1) and multiplanar gradient-echo (TR 749–750/TE 50/NEX

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