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ApoE genotype in relation to AD and cholesterol

A study of 2,326 Chinese adults

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Article abstract—*Objective:* To calculate the frequencies of apolipoprotein E (apoE) alleles in a large Chinese community sample and to compare the serum cholesterol levels of ε2, ε3, and ε4 carriers. *Background:* In comparison with Western populations, a lower frequency of the apoE ε4 allele among the Chinese has been proposed as one factor for the lower prevalence of AD found in Chinese populations, but there are insufficient Chinese data on ε4 frequency that are based on large community samples. In addition, although Western studies have repeatedly found a lower cholesterol level in ε2 carriers and a higher cholesterol level in ε4 carriers in comparison with ε3 homozygotes, two Chinese studies have yielded inconsistent findings between them. *Methods:* During the incidence phase of an epidemiologic survey of several neurologic disorders in a Chinese community, the authors took blood samples from 2,326 participants to determine the apoE genotypes and to measure cholesterol levels. *Results:* The allelic frequencies of ε2, ε3, and ε4 were 11.8%, 76.4%, and 11.8% among 17 AD patients, and 7.8%, 84.1%, and 8.1% for the entire sample. The mean cholesterol level of the ε2 carriers was significantly lower, and that of the ε4 carriers significantly higher, than that of the ε3 homozygotes. *Conclusions:* The obtained ε4 rate of 8.1% is lower than most of the Western findings, and this may account in part for the lower prevalence of AD found among the Chinese. The associations between the apoE genotype and serum cholesterol level are similar between Chinese and white populations. Key words: Apolipoprotein E—Alzheimer's disease—Cholesterol—Chinese.

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The apolipoprotein E (apoE) gene exists in three major isoforms: the predominant ε3 and two mutant forms ε2 and ε4. The ε4 allele has been identified as a risk factor for AD.[1-7] In addition, the presence of ε2 has been associated with a lower, and that of ε4 with a higher, serum cholesterol level in comparison with the homozygotic ε3.[8-13]

Several studies have found a lower prevalence of AD among the Chinese[14-16] in comparison with Western populations.[17,18] The frequencies of the ε4 allele in Chinese populations range from 4.9 to 11.0%,[2-5,13,19] which are also lower than the range of 9.0 to 16.5% found in Western populations.[6,7,10,20-23] The lower frequency of ε4 among the Chinese has been proposed as one factor for their lower prevalence of AD.[15] However, previous studies on the distribution of the apoE

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genotype among the Chinese involved either hospital-based series[2,3,4,13,19] or a community sample of moderate size.[5] Therefore the findings could be either biased or unreliable. With regard to the association between the apoE genotype and serum cholesterol level, most of the data came from Western populations,[8-12] and two previous studies on the Chinese[13,24] have yielded inconsistent findings between them.

In the current study we calculated the frequencies of apoE alleles and compared the serum cholesterol levels of ε2, ε3, and ε4 carriers in a large community sample of 2,326 Chinese adults.

Methods. This study was conducted in Kinmen, an islet located west of Taiwan and off the southeastern coast of mainland China. All of its residents are Chinese.

A prevalence study of several neurologic disorders was conducted in 1993 and targeted all residents ≥50 years in age.[25] A total of 3,915 participants were examined for PD, essential tremor, stroke, TIAs, and migraine. A subset of 1,736 of the 3,915 participants was ≥65 years in age. These 1,736 participants were also examined for dementia, and 44 prevalent cases of dementia were found, including 35 patients with AD.[15]

An incidence study of the same disorders was conducted in 1996.[26] By that time, 258 of the original 3,915 participants had died, and 3,039 (83%) of the remaining 3,657 individuals were reexamined, including 2,326 (77% of 3,039) who consented to give blood samples for determination of apoE genotype and measurement of cholesterol level.

Among the subset of 1,692 (1,736 − 44) participants who were ≥65 years in age and who did not have dementia in 1993, 197 had died by 1996. Of the remaining 1,495 individuals, 1,197 (80%) were reexamined for dementia, including 938 (78% of 1,197) who also consented to give blood samples. Thus we obtained blood samples from 2,326 participants ≥53 years in age, including 938 from participants ≥68 years in age who were part of the 1,197 reexamined for dementia.

Blood was drawn from the participants who had fasted overnight. For each participant, a few drops of blood were deposited on filter paper and allowed to dry for use in the determination of the apoE genotype by PCR.[27] The remaining blood sample was centrifuged for 10 minutes at 1,500 *g* at room temperature, and the serum was then removed to measure the cholesterol level.

For the determination of dementia, neurologists interviewed and examined all 1,197 participants ≥68 years in age. The neurologists inquired about daily activities and made observations on alertness and attention, mood and affect, verbal abilities, and appropriateness of interview interactions. They also tested the participants' memories for common knowledge and for recent inputs, recognition and naming of common objects, temporal and spatial orientations, abstract thinking, and judgment. No reading, writing, or drawing was requested for this predominantly illiterate population. Whenever dementia was at all suspected, a reliable informant, typically a close family member, was also interviewed to inquire whether the participant had shown significant cognitive deterioration or personality change over the past 3 years. In addition, a neurologic history was taken and a neurologic examination of the participant was conducted. The diagnosis of dementia was made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised.[28] The diagnosis of probable AD was made for patients with insidious onset, progressive deterioration, and the absence of other plausible causes. Diagnosis was made by consensus among the neurologists. More details on the assessment and diagnosis have been reported elsewhere.[15]

Table 1 Distribution of the apoE genotype in the Chinese community sample

ApoE genotype	AD patients	Non-AD participants	All participants
Allelic combination			
ε2/ε2	0 (0.0)	11 (0.5)	11 (0.5)
ε2/ε3	4 (23.5)	320 (13.9)	324 (13.9)
ε2/ε4	0 (0.0)	15 (0.6)	15 (0.6)
ε3/ε3	10 (58.8)	1,628 (70.5)	1,638 (70.4)
ε3/ε4	2 (11.8)	311 (13.5)	313 (13.5)
ε4/ε4	1 (5.9)	24 (1.0)	25 (1.1)
Total	17 (100.0)	2,309 (100.0)	2,326 (100.0)
Allelic frequency			
ε2	4 (11.8)	357 (7.7)	361 (7.8)
ε3	26 (76.4)	3,887 (84.2)	3,913 (84.1)
ε4	4 (11.8)	374 (8.1)	378 (8.1)
Total	34 (100.0)	4,618 (100.0)	4,652 (100.0)

Values are n (%).

Results. From the original sample of 3,915 individuals who participated in the prevalence study, 3,039 participated in the incidence study, and 2,326 of the 3,039 also consented to give blood samples. This "blood sample" group included 1,188 men and 1,138 women, their age in 1993 ranged from 50 to 93 years (mean, 63.1 years; SD, 9.3 years), and their education ranged from 0 to 18 years (mean, 2.7 years; SD, 3.9 years). The remaining 1,589 (3,915 − 2,326) individuals included 258 who had died, 136 who had moved away or were untraceable, 446 who were unavailable for various reasons, 36 who declined to participate in the incidence study, and 713 who participated in the incidence study but declined to give blood samples. This "no blood sample" group included 776 men and 813 women, their age in 1993 ranged from 50 to 101 years (mean, 66.9 years; SD, 11.4 years), and their education ranged from 0 to 17 years (mean, 1.9 years; SD, 3.3 years). The two groups differed in age ($t = 11.00$, $p < 0.00$) and education ($t = 6.39$, $p < 0.00$), but not in men-to-women ratio (1.04 versus 0.95; $\chi^2 = 1.89$, $p > 0.10$).

Forty incident cases of dementia, including 30 cases of AD, were identified, yielding an incidence rate of 3.3% (40 of 1,197) for dementia, and 2.5% (30 of 1,197) for AD, over a 3-year interval. The 30 AD patients included 6 men and 24 women. Their age in 1996 ranged from 71 to 101 years (mean, 85.7 years; SD, 6.2 years). Their education ranged from 0 to 10 years (mean, 1.1 years; SD, 2.6 years). Seventeen of the 30 gave blood samples for apoE genotyping and measurement of cholesterol level, and 13 patients did not.

Table 2 Age-specific frequencies of the apoE ϵ4 allele

	Frequency of the apoE ϵ4 allele, %					
	AD patients		Non-AD participants		All participant	
Age group, y	n	ϵ4	n	ϵ4	n	
53–59	—*	—*	665	8.4	665	
60–67	—*	—*	723	7.3	723	
68–69	0	0.0	163	7.1	163	
70–79	1	0.0	530	9.7	531	
80–89	11	4.6	204	6.6	215	
90–101	5	30.0	24	6.3	29	
Total	17	11.8	2,309	8.1	2,326	

* Participants were not examined for AD.

These two subgroups did not differ in age, education, or gender.

The distributions of the apoE genotype of the 17 AD patients, the 2,309 non-AD participants, and the entire sample are summarized in table 1. The allelic frequencies of ϵ2, ϵ3, and ϵ4 were 11.8%, 76.4%, and 11.8% for the AD patients, 7.7%, 84.2%, and 8.1% for the non-AD participants, and 7.8%, 84.1%, and 8.1% for the entire sample. The difference between the allelic distribution of the AD group and that of the non-AD group was insignificant ($\chi^2 = 1.50$, $df = 2$, $p > 0.10$).

A subset of 921 non-AD participants were ≥68 years in age, and their allelic frequencies of ϵ2, ϵ3, and ϵ4 were 7.3%, 84.2%, and 8.5%. The difference in apoE allelic distribution between the AD group and this non-AD group (age, ≥68 years) was also insignificant ($\chi^7 = 1.58$, $df = 2$, $p > 0.10$).

A breakdown of the apoE4 frequency by age subgroup is presented in table 2. There was no difference among the six age groups in apoE4 frequency for the non-AD participants ($\chi^2 = 6.96$, $df = 5$, $p > 0.10$) or for all participants ($\chi^2 = 7.28$, $df = 5$, $p > 0.10$). Among the 17 AD participants, 10 of them were 71 to 84 years old and 7 of them were 87 to 95 years old. The apoE4 frequency was 5.0% for the younger group and 21.4% for the older group. The difference between these two groups was also insignificant ($\chi^2 = 2.14$, $df = 1$, $p > 0.10$).

A total of 2,326 participants gave blood samples, but the cholesterol level could not be measured for 29 of them (1.2%) because insufficient blood was drawn. Therefore, data on cholesterol level were obtained for 2,297 participants. To examine the association between the apoE genotype and serum cholesterol level, we classified the 2,297 subjects with cholesterol data into ϵ2 carriers (genotypes ϵ2/ϵ2 and ϵ2/ϵ3), ϵ3 homozygotes (ϵ3/ϵ3), and ϵ4 carriers (genotypes ϵ4/ϵ3 and ϵ4/ϵ4). Fifteen individuals with ϵ2/ϵ were excluded from this analysis. The results are shown in table 3. The mean cholesterol level of the ϵ2 carriers wa lower ($t = 5.09$, $p < 0.001$, one tailed) than that of the ϵ homozygotes. The mean cholesterol level of the ϵ4 carrier was higher ($t = 1.91$, $p < 0.05$, one-tailed test) than that o the ϵ3 homozygotes.

Table 3 Serum cholesterol level in relation to apoE genotype in the Chinese community sample

Allelic carrier	n	Age, y, mean (SD)	Cholesterol level, mg/dL, mean (SD)
ϵ2 (ϵ2/ϵ2 + ϵ2/ϵ3)	328	65.8 (9.6)	181.6 (34.9)
ϵ3 (ϵ3/ϵ3)	1,619	66.1 (9.2)	192.7 (36.2)
ϵ4 (ϵ3/ϵ4 + ϵ4/ϵ4)	335	66.0 (9.3)	196.9 (37.3)

Discussion. This study calculated the frequency o the apoE ϵ4 allele in a large Chinese sample of 2,326 community residents. Data were obtained from the incidence phase of a longitudinal study that had 3,915 original participants. The 2,326 participants who gave blood samples were, on average, slightly younger (by 3.8 years) and better educated (by 0.8 years) than the 1,589 individuals from whom no blood sample was obtained. However, there is no reason to expect that these differences would affect the genetically determined apoE ϵ4 frequency. Indeed, our results demonstrated that the apoE ϵ4 frequency did not change with age (see table 2).

Table 4 summarizes the apoE allelic frequencies from Western and Chinese community-based studies.[5-7,10,20-23] The ϵ4 frequencies found in the Chinese studies, including our finding of 8.1%, are lower than most of the findings from Western populations. The majority of the Western studies included AD patients in the calculation of ϵ4 frequency, but two of them did not.[7,22] In the current study, whether the 17 AD patients were included did not change the resulting ϵ4 frequency of 8.1% (see table 1). The age distribution of the participants in the current study is older than some Western studies and younger than others. Therefore, the obtained lower ϵ4 frequency of 8.1% seems unrelated to sampling differences.

Because apoE ϵ4 is a risk factor for AD, its frequency should be higher among AD patients than non-AD individuals. A trend consistent with this prediction was obtained in the current study (see table 1), but the difference was nonsignificant, perhaps because the number of AD patients was too small (n = 17). The current study excluded prevalent cases of AD, and many of the ϵ4 carriers in our sample

Table 4 The distribution of apoE alleles found in Western and Chinese community studies

Study population	n	Age, y, mean (SD)	Allelic % ε2	Allelic % ε3	Allelic % ε4	First author	Year published
American							
Rochester	507	26–63*	5.9	80.6	13.5	Reilly[10]	1991
Iowa	1,899	79.1 (0.1)	9.1	76.8	14.1	Hallman[19]	1991
Framingham	1,030	64.0 (5.7)	6.9	81.3	11.8	Myers[6]	1996
Boston	578	78.7 (6.1)	6.3	84.7	9.0	Evans[21]	1997
Finnish							
Rotterdam†	997	68.4 (7.7)	9.4	76.0	14.6	Slooter[22]	1998
Kuopio†	911	73.0 (0.1)	5.2	78.3	16.5	Kuusisto[7]	1994
Australian							
Canberra	638	80.4 (5.4)	6.3	80.8	12.9	Henderson[23]	1995
Chinese							
Shanghai	363	60–96*	8.6	80.4	11.0	Katzman[5]	1997
Kinmen	2,326	66.1 (9.3)	7.8	84.1	8.1	Liu	Current study

* The mean and SD values were not reported. The range (minimum to maximum) is shown instead.
† Based on non-AD individuals only.

were too young to become incident cases of AD. In the Shanghai study,[5] in which 65 AD patients were compared with 363 normal subjects, a significantly higher ε4 frequency in the AD group was obtained.

Many factors including differences in sampling, assessment tools, diagnostic criteria, and survival time can influence the prevalence rate for AD. Our finding of 8.1% of ε4 frequency in the large Chinese community sample does not imply that the lower prevalence rates of AD found in Chinese populations are fully attributable to genetic factors, but it does provide convergent evidence indicating that the lower apoE ε4 rate is one of the contributing factors.[15]

The association between the apoE genotype and serum cholesterol level has been well established for white populations.[8-12] Only two prior studies used all Chinese subjects,[13,24] and their findings were inconsistent. The current finding based on a much larger Chinese community sample confirms a lower cholesterol level in ε2 carriers and a higher cholesterol level in ε4 carriers. This finding suggests that the associations between the apoE genotype and cholesterol level are similar between the Chinese and the white populations.

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Cognitive impairments in patients with congenital nonprogressive cerebellar ataxia

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Article abstract—*Objective:* To report neuropsychologic functions and developmental problems of patients with congenital nonprogressive cerebellar ataxia. *Background:* Growing interest in cerebellar function has prompted closer attention to cognitive impairments in patients with cerebellar damage. *Methods:* The authors studied 11 patients with nonprogressive congenital ataxia (NPCA) with Wechsler's intelligence testing, with additional tests of attention, memory, language, visual perception, and frontal functions. *Results:* Seven of the 11 patients had an IQ of 60 to 92, with marked nonverbal deficits and subnormal to normal verbal performance (group A). Four patients had an IQ of 30 to 49 without pronounced profile asymmetry (group B). Four of the 7 group A patients had decreased alertness and sustained attention, but all had normal selective attention. Tests of frontal functions and memory yielded higher verbal scores than nonverbal scores. There was no deficit on the Aachener Naming Test (similar to the Boston Naming Test), because there were marked difficulties in the majority with visuoconstructive tasks and visual perception. Group B was significantly abnormal in almost all subtests, having a less prominent but similar profile. *Conclusion:* Patients with NPCA have significant cognitive deficits with an asymmetric profile and better verbal than nonverbal performance. Effects on nonverbal performance of longstanding deficits in visuospatial input during learning, the influence of impaired procedural learning, and asymmetric plasticity of the cerebral hemispheres may contribute to this uneven neuropsychological profile. Key words: Cerebellar ataxia—Cerebellum—Cognition—Child development.

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A growing interest in cerebellar function has directed closer attention to cognitive and affective changes in patients with cerebellar dysfunction.[1] Advances in functional imaging techniques provide the opportunity to analyze cerebellar activity during cognitive tasks.[2-4] Many studies have shown that the cerebellum seems to be important for visuospatial planning, organization and construction, speech, memory, motor and nonmotor skill acquisition, and in shifting attention between sensory modalities and in affecting regulation.[2-8] Acquired cerebellar lesions or generalized degenerative cerebellar changes in adulthood result in relatively mild neuropsychological deficits.[9-11] Children with acquired cerebellar lesions such as tumors have limited cognitive impairment.[12,13] However, children with congenital cerebellar dysfunction like cerebellar hypoplasia or Joubert's syndrome exhibit marked cognitive developmental delay with significant cognitive impairments in adult life.[14-16] There is only one report of more detailed neuropsychological assessment in children with nonprogressive ataxia and cerebellar hypoplasia.[15] We

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