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APOE ε4 polymorphism and cognitive deficit among the very old Chinese veteran men without dementia

Che-Sheng Chu[a], Ti Lu[b], Shih-Jen Tsai[c,d], Cheng-Jee Hong[c,d], Heng-Liang Yeh[e], Albert C. Yang[c,d], Mu-En Liu[c,d,*]

[a] Department of Psychiatry, Puli Branch, Taichung Veterans General Hospital, Taichung, Taiwan
[b] Department of Psychiatry, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
[c] Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan
[d] School of Medicine, National Yang-Ming University, Taipei, Taiwan
[e] Taipei Veterans Home, Taipei, Taiwan

HIGHLIGHTS

- APOE ε4 alleles contributed detrimental effects on cognitive function in the very old Chinese male without dementia.
- Cognitive function impairment, especially executive abilities may be more profound among very elderly non-demented population.
- Asian population may be more vulnerable to the ε4 allele detrimental effect on cognition.

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ABSTRACT

Apolipoprotein E (APOE) gene polymorphism has been reported to be associated with cognitive dysfunction in healthy individuals, however the results were controversial in the very old elderly. The aim of this study is to assess the possible association of the APOE polymorphism with cognitive dysfunction in people aged 75 years and over. Four hundred and twenty-five aged Chinese veteran men without dementia were enrolled for APOE genotyping and neuropsychological tests including Mini-Mental Status Examination (MMSE), Digit Span Forward and Backward, and Cognitive Ability Screening Instrument Chinese language version (CASI C-2.0) were evaluated in these subjects. Among the elderly veterans, people who carry APOE ε4 were found to have worse performance on the total CASI scores, the abstraction/judgment subscores and the list-generating fluency subscores. This study suggests that the APOE ε4 alleles contributed detrimental effects on cognitive function in the very old veterans who do not have dementia.

1. Introduction

Population aging is now occurring across the industrialized countries. As in other developed countries, the percentage of the population aged 65 and older in Taiwan has continued to rise. The proportion of the elderly in Taiwan reached 7% in 1993 and 11% in 2010 and the percentage will peak 20% by the year 2025 [1]. Rapidly aging society was an issue need to be concerned. Populations with cognitive impairment are more vulnerable to medical and mental disability, and poor treatment adherence, especially in the older elderly veterans [2–4]. Therefore, the normal cognitive aging is important for elderly veterans.

Apolipoprotein E (APOE) is a plasma protein, which is recognized for its importance in lipids (e.g., cholesterol) transportation and neuronal repair [5]. The APOE gene is located on chromosome 19. There are three allelic forms, including ε2, ε3, and ε4 [5]. The ε4 allele has been considered as a well-demonstrated risk factor for Alzheimer's disease (AD), whereas the ε2 allele has been seen as a protective factor [6,7]. Literature reported an association between the APOE genotype and cognitive function in demented patients and revealed that APOE ε4 carriers were associated with poor global

Abbreviations: APOE, apolipoprotein E; CASI, Cognitive Abilities Screening Instrument; CDR, Clinical Dementia Rating Scale; DSB, Digit Span Backward; DSF, Digit Span Forward; MINI, Mini-International Neuropsychiatric Interview; MMSE, Mini-Mental Status Examination.

* Corresponding author at: Department of Psychiatry, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Road, Beitou District, Taipei City 11217, Taiwan, ROC. Tel.: +886 2 28757027; fax: +886 2 28757592.
E-mail address: liumuen@gmail.com (M.-E. Liu).

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cognitive function or greater cognitive decline [8]. Furthermore, there is growing evidence of relationship between APOE ε4 carriers and poorer cognitive performances in non-demented elders and suggests that APOE gene polymorphism plays a major role in normal cognitive aging [9,10].

For example, Risacher et al. recruited 209 elders with mild cognitive impairment (MCI) and 123 healthy controls across the United States and Canada, and found a deleterious effect of ε4 allele on cognitive function [10]. Additionally, Bretsky et al. included 965 non-demented elders from MacArthur Successful Aging Study and reported ε4 allele contributed an adverse impact on cognitive aging [9]. A meta-analysis and systemic review also revealed that the APOE ε4 carriers with older age were associated with poorer cognitive function between APOE ε4 and non-APOEε4 carriers in healthy aging [11]. However, others demonstrated that APOE ε4 alleles showed no impact on cognitive aging, especially in very old elders [12,13]. Moreover, most subjects recruited in previous meta-analysis report were older individuals, but not very old elders [11]. Therefore, the true impact of APOE on the very old elders may be neglected. In the current study, we examined the impact of APOE polymorphism on cognitive function in the very old healthy Chinese veterans.

2. Methods

2.1. Subjects

Five hundred and sixty-two ethnic Chinese men were recruited from residents of the Taiwan National Veterans Care Homes in Kaohsiung and Taipei. They had voluntarily applied for residency in these home care centers because they were living alone, in poor health, lacking family and social support, or physically handicapped. The majority were ambulatory, physically capable, and able to provide for their own daily needs with no assistance from others. Psychiatric evaluation was performed using the Mini-International Neuropsychiatric Interview (MINI) [14]. Cognitive functions were assessed with the Clinical Dementia Rating Scale (CDR), Mini-Mental Status Examination (MMSE), Digit Span Forward (DSF) and Backward (DSB), and Cognitive Abilities Screening Instrument Chinese language version (CASI C-2.0) [15]. The DSF and DSB evaluate attention and verbal working memory. The CASI, as a comprehensive neuropsychological test, contains nine domains, including long-term memory, short-term memory, attention, concentration/mental manipulation, orientation, abstraction/judgment, language, visual construction and list-generating fluency.

For an effective cognitive evaluation, spared visual and auditory acuity were required. Exclusion criteria included the following: (1) under 75 years old; (2) female gender; (3) present DSM-IV Axis I diagnoses; (4) chronic illness with medical control (i.e., malignancy, heart failure, lung disease, diabetes, etc.); (5) neurological disorders (i.e., stroke, Parkinson's disease, etc.); (6) subjects with CDR > 0.5; and (7) physically disabled and required a wheelchair, cane or other ambulatory equipment, or needed other assistance. Finally, 137 participants (24%) were excluded with the criteria. Four hundred and twenty-five aged men completed the examinations at clinics affiliated with the Veterans' Care Homes. These criteria worked together to provide a homogeneous group consisting of normal functioning, non-demented, aged ethnic Chinese men. Experiments were conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Kaohsiung Veterans General Hospital and Taipei Veterans General Hospital. Written informed consent was obtained from all subjects with adequate understanding of the study.

Table 1
Genotype distribution and corresponding allele frequency of APOE polymorphism.

Case numbers	Genotype distribution					
	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4
425	1 0.2%	72 16.9%	10 2.4%	284 66.8%	55 12.9%	3 0.7%

2.2. APOE genotyping

For APOE genotyping, DNA isolated from lymphocytes was amplified by polymerase chain reaction using an upstream primer (5′-TCCAAGGAGCTGCAGGCGGCGCA-3′) and a downstream primer (5′-ACAGAATTCGCCCCGGCCTGGTACACTGCCA-3′). Amplified gene fragments were digested with Cfo I and the fragments separated by electrophoresis on a 3% ethidium bromide-stained agarose gel. Allele assignment was based on the presence or absence of Cfo I cutting sites on the 56th and/or 194th base of the amplified gene fragment, as described by our previous work [16].

2.3. Statistics

Statistical analyses were performed using the SPSS 13.0 program (SPSS Inc., Chicago, IL). Normal distribution of variables was checked using the Kolmogorov–Smirnov test. We performed allele and genotype frequency and Hardy-Weinberg equilibrium tests for each APOE genotype. Chi-square tests were used to compare categorical variables between APOE ε4 carriers and non-carriers. Continuous variables were analyzed using the Student t test. In order to control the effects from non-genetic factors, a general linear model was used with age and years of education being entered as covariates. The criterion for significance was set at $P < 0.05$ for all of the tests. Data are presented as mean ± SD.

3. Results

Subjects were 425 ethnic Chinese elderly men with a mean age of 82.3 ± 4.6 (range = 75–101) years. The subjects had a mean duration of schooling of 5.1 ± 4.1 years. Mean MMSE and CASI scores were 25.4 ± 4.0 and 83.8 ± 9.7, respectively. The APOE genotype distribution for the 425 subjects was ε2/ε2 = 1, ε2/ε3 = 72, ε2/ε4 = 10, ε3/ε3 = 284, ε3/ε4 = 55 and ε4/ε4 = 3 (Table 1). The genotype distribution was in Hardy–Weinberg equilibrium. No significant differences were demonstrated for age ($P = 0.386$) or years of schooling ($P = 0.195$) among the ε4 carriers and non-ε4 carriers (Table 2). There were no significant differences in MMSE, DSF and DSB total scores between these two groups. For CASI performance, APOE ε4 carrier had the poor performance in CASI total scores, abstraction/judgment subscores, and list-generating fluency subscores, while compared with the non-ε4 carriers ($P < 0.001$). Using age and years of education as covariates, current positive results still existed (Table 2).

4. Discussion

We questioned whether the genetic effect of APOE ε4 could persist to the very old non-demented elders. This study enrolled non-demented Chinese veteran men with aged 75 years or over. There were associations between the APOE ε4 polymorphism and cognitive deficit measured by the CASI total score. For the nine domains of CASI, the subjects with the APOE ε4 allele performed poorly on the abstraction/judgment and list-generating fluency.

Our findings are in line with some previous reports, indicating that the APOE ε4 contributed the deleterious effect on cognitive