Original Research Article

Age-Related Association between Apolipoprotein E ε4 and Cognitive Function in Japanese Patients with Alzheimer's Disease

Tomoyuki Nagata[a, b]   Shunichiro Shinagawa[b]   Bolati Kuerban[c]
Nobuto Shibata[c]   Tohru Ohnuma[c]   Heii Arai[c]   Kazuhiko Nakayama[b]
Hisashi Yamada[a]

[a]Division of Molecular Genetics, Institute of DNA Medicine, and [b]Department of Psychiatry, Jikei University School of Medicine, and [c]Department of Psychiatry, Juntendo University School of Medicine, Tokyo, Japan

Key Words

Alzheimer's disease · Memory disorders · Apolipoprotein E · Working memory · Polymorphism

Abstract

Aims: In the present study, we investigated whether apolipoprotein E *(APOE)* polymorphisms influenced the cognitive function of Japanese patients with Alzheimer's disease (AD) at certain ages. *Methods:* Among 200 outpatients with dementia and amnestic mild cognitive impairment, 133 Japanese patients with AD were recruited and divided into two genotypic groups: *APOE* ε4 carriers and noncarriers. Then, we compared several neuropsychological test scores between the two genotypic groups for two different generations: 70s (70–79 years) and 80s (80–89 years). *Results:* The total Mini-Mental State Examination score (p < 0.05) and one of its subtest scores, the 3-stage command score (p < 0.01), were significantly lower for the ε4 carriers than for the noncarriers among patients in their 80s, but not among those in their 70s. The duration of illness differed significantly between the ε4 carriers and the noncarriers among subjects in their 80s but was not correlated with cognitive function. *Conclusion:* The present results suggest that *APOE* may significantly influence comparatively simple memory processing in certain generations of Japanese patients with AD.

Copyright © 2013 S. Karger AG, Basel

Tomoyuki Nagata
Division of Molecular Genetics, Institute of DNA Medicine
Jikei University School of Medicine, 3-25-8 Nishisimbashi
Minato-ku, Tokyo 105-8471 (Japan)
E-Mail t.nagata@jikei.ac.jp

KARGER

Nagata et al.: Age-Related Association between Apolipoprotein E ε4 and Cognitive Function in Japanese Patients with Alzheimer's Disease

Introduction

Apolipoprotein E *(APOE)*, phosphatidylinositol-binding clathrin assembly protein, and clusterin have been reported as candidate genes for Alzheimer's disease (AD) in a recent genome-wide study [1]. Among these candidate genes, *APOE* polymorphisms have been reported as being associated with a robust genetic risk of AD since the 1990s, and ε4 carriers are about three times more susceptible to AD than noncarriers [1, 2]. The relation between the *APOE* gene and the risk of AD has been investigated in populations all over the world, and a significant association between ε4 allele carriers and the manifestation of AD has been accepted. In Japan, a significant association between *APOE* ε4 carriers and the manifestation of AD has been reported in a large-scale study [3].

The *APOE* gene has functional roles: it influences onset age, induces morphological changes in the hippocampus, and causes neural vulnerability via cerebrovascular mechanisms [2, 4–9]. Regarding the influences on cognition, previous studies have reported that memory impairment or executive function is poorer in ε4 carriers than in noncarriers among patients with AD [6, 7, 10]. Moreover, from age-related viewpoints, the *APOE* gene tends to have a robust influence on the cognition of patients with AD who are in their 70s or 80s [2, 7, 11].

In Japan, while the *APOE* ε4 allele is associated with late-onset manifestation, a few reports have shown that it also influences cognitive function, neuroimaging, and neurobiological data [3, 8, 9, 12]. A previous report has shown a significant difference in memory decline among three genotypic groups classified according to ε4; however, the age of these three groups differed significantly [8]. Regarding clinical function in AD patients, cognitive impairment directly influences activities of daily living and might lead to subsequent behavioral and psychological problems (e.g. persecutory delusion and aberrant motor behavior) [13, 14]. Therefore, the investigation of risk factors of cognitive decline might have an impact on the prevention of subsequent problems.

The aims of the present study were to examine whether *APOE* ε4 influences cognitive function and to analyze its relation to the cognitive profiles of Japanese AD patients. Thus, we retrospectively compared two representative screening test scores, the Mini-Mental State Examination (MMSE) reflecting memory or attentional function and the Frontal Assessment Battery (FAB) reflecting executive function, among *APOE* ε4 carriers (homozygous and heterozygous) and noncarriers in two different generations (70s: 70–79 years old and 80s: 80–89 years old) that tend to be influenced by the *APOE* gene [7, 11, 15, 16].

Methods

Participants

Two hundred Japanese outpatients with dementia (AD: n = 133; dementia with Lewy bodies: n = 5; frontotemporal lobar degeneration: n = 8; subcortical vascular dementia or mixed-type dementia: n = 10, and idiopathic normal pressure hydrocephalus: n = 2) and amnestic mild cognitive impairment (A-MCI: n = 42) from among consecutive memory clinic outpatients visiting the Jikei University Hospitals (Tokyo or Kashiwa) participated in the present genomic study. One hundred and thirty-three consecutive Japanese patients with AD were recruited from among the above-mentioned patients. All AD patients were diagnosed as having probable AD based on the National Institute of Neurology and Communicative Disorder and Stroke/Alzheimer's Disease and Related Disorder Association (NINCDS/ADRDA) criteria [17]. Forty-two patients were diagnosed as having A-MCI according to the diagnostic criteria for MCI [18]. *APOE* genotypes for all patients with AD were identified at the Department of Psychiatry, Juntendo University School of Medicine, based on a method used in pre-

Nagata et al.: Age-Related Association between Apolipoprotein E ε4 and Cognitive Function in Japanese Patients with Alzheimer's Disease

vious reports [19, 20]. Next, we divided the 133 subjects into two groups according to whether they were ε4 carriers or noncarriers. Among the subjects' detailed demographic variables, behavioral and psychological symptoms were assessed based on information obtained from a structured interview with each patient's caregiver. The interviews were conducted by the same geriatric psychiatrists using the Behavioral Pathology in Alzheimer's disease (Behave-AD) scale [21]. To investigate neuropsychological characteristics, two representative screening tests, the MMSE (ranging from 0 to 30) reflecting memory or attentional function and the FAB (ranging from 0 to 18) reflecting executive function, were administered by a clinical psychologist [15, 16]. To determine the severity of each patient's dementia, the geriatric psychiatrists used the Clinical Dementia Rating-Sum of Boxes (CDR-SB: ranging from 0 to 18) based on information provided by each patient's caregiver [22]. The two geriatric psychiatrists and the clinical psychologist were experienced at performing neuropsychological and behavioral examinations, and the interrater validity of the scales was sustained by periodic discussions and exchanges of views. This study was approved by the Ethics Committees of the Jikei University School of Medicine (Tokyo and Kashiwa), and written informed consent was obtained from both the patients and their caregivers.

Comparison of FAB and MMSE Test Scores between the Two Groups according to Two Generations: 70s and 80s

The *APOE* gene tends to influence the cognition of patients with AD who are in their 70s or 80s [2, 7, 11]. Thus, we compared the MMSE and FAB scores between ε4 carriers and noncarriers according to two different generations: 70s and 80s.

Statistical Analysis

SPSS 19.0J for Windows (SPSS Japan Inc.) was used for all statistical analyses. To control for type I errors, we used one-way ANOVA with a post hoc Tukey test for assessment of age of the participants in the present study, education years, duration of illness (in months; from age at onset until entry in the present study) as well as MMSE, Behave-AD, CDR-SB, and FAB scores and compared them between ε4 carriers and noncarriers. Seven MMSE subtest scores (with possible scores with a range of 0–5 for 'time orientation', 0–5 for 'place orientation', 0–3 for 'registration', 0–5 for 'attention and calculation', 0–3 for 'recall', 0–2 for 'naming', and 0–3 for '3-stage command') and six FAB subtest scores (with possible scores ranging from 0–3 for 'similarities', 'lexical fluency', 'motor series', 'conflicting instructions', 'go/no go', and 'prehension behavior') were assessed using the Mann-Whitney test. The sex ratio (female/male) and four other MMSE subtest scores (with possible scores with a range of 0–1 for 'repetition', 'reading', 'writing', and 'copying') were assessed using the χ^2 test. A p value <0.05 was considered statistically significant.

Results

Patient Characteristics

The *APOE* genotypes of 133 AD patients were examined: 66 subjects were found to be ε4 carriers (ε2/ε4: n = 3, ε3/ε4: n = 48, and ε4/ε4: n = 15) and 67 subjects to be noncarriers (ε2/ε3: n = 5 and ε3/ε3: n = 62). Among the demographic variables of all patients, only age at consultation was significantly lower among the ε4 carriers than among the noncarriers (F = 15.324; d.f. = 1; p < 0.001) (table 1). No significant differences in any other demographic variables were observed between the two genotypic groups in all AD patients (table 1). Regarding the age distribution of the patients in the present study, most of the subjects (88.7%) were in their 70s or 80s (50s: n = 2, 60s: n = 12, 70s: n = 56, 80s: n = 62, and 90s: n = 1).

Nagata et al.: Age-Related Association between Apolipoprotein E ε4 and Cognitive Function in Japanese Patients with Alzheimer's Disease

Table 1. Comparison of subject characteristics (mean ± SD) between *APOE* ε4 carriers and noncarriers in patients with AD (n = 133)

	Noncarriers (n = 67)	ε4 carriers (n = 66)[b]	χ^2 or F score	p value
Sex (male/female)	21/46	16/50	0.835[c]	0.361
Age, years	80.73±5.68	76.39±7.07	15.324	<0.001*
Duration of illness, months	29.76±18.99	35.80±25.07	2.459	0.119
Education, years	11.49±2.52	11.92±3.06	0.734	0.393
MMSE score	19.39±4.86	18.88±4.63	0.389	0.534
FAB score	11.02±3.5	10.68±3.76	0.243	0.623
Behave-AD score	7.43±5.01	8.05±5.95	0.413	0.521
CDR-SB[a]	6.88±3.11	6.78±2.96	0.036	0.849

Sex was analyzed using the χ^2 test. Other variables were analyzed using one-way ANOVA with post hoc tests (Tukey). [a] Ranging from 0 to 18. [b] Heterozygotes: 51, homozygotes: 15. [c] The χ^2 score is given. * p < 0.001.

Table 2. Comparison of subject characteristics (mean ± SD) between *APOE* ε4 carriers and noncarriers in patients with AD who were 70–79 years old (n = 56)

	Noncarriers (n = 24)	ε4 carriers (n = 32)[b]	χ^2 or F score	p value
Sex (male/female)	11/13	5/27	6.132[c]	0.013*
Age, years	76.29±2.94	76.25±1.98	0.004	0.95
Duration of illness, months	33.50±19.39	29.03±25.11	0.525	0.472
Education, years	12.08±2.04	11.97±3.18	0.024	0.878
MMSE score	18.13±6.11	19.72±4.43	1.250	0.269
FAB score	11.68±3.15	11.43±3.97	0.055	0.815
Behave-AD score	6.92±5.09	7.53±4.70	0.218	0.642
CDR-SB[a]	6.81±3.18	5.75±2.71	1.822	0.183

Sex was analyzed using the χ^2 test. Other variables were analyzed using one-way ANOVA with post hoc tests (Tukey). [a] Ranging from 0 to 18. [b] Heterozygotes: 26, homozygotes: 6. [c] The χ^2 score is given. * p < 0.05.

Comparison of Demographic Variables between ε4 Carriers and Noncarriers in Their 70s

We found a significant difference in the sex ratio (χ^2 = 6.132; d.f. = 1; p = 0.013) between ε4 carriers (male/female: 5/27) and noncarriers (male/female: 11/13), but no significant differences in any other demographic variables (table 2). To investigate whether the *APOE* genotypes (ε4 carriers or noncarriers) or the sex ratio (female/male) affected the MMSE or FAB scores, we performed a generalized linear model analysis (ANOVA). As a result, significant interactions between these two factors were not observed for the MMSE and FAB scores in a generalized linear model analysis (former: F = 1.719; d.f. = 1; p = 0.196, latter: F = 0.001; d.f. = 1; p = 0.971).

Comparison of Demographic Variables between ε4 Carriers and Noncarriers in Their 80s

The MMSE score was significantly lower (F = 5.757; d.f. = 1; p = 0.02) in the ε4 carriers than in the noncarriers, and the duration of illness (months) was significantly longer (F = 4.975; d.f. = 1; p = 0.029) in the ε4 carriers than in the noncarriers (table 3).

70

Dement Geriatr Cogn Disord Extra 2013;3:66–73

DOI: 10.1159/000348351 | © 2013 S. Karger AG, Basel
www.karger.com/dee

Nagata et al.: Age-Related Association between Apolipoprotein E ε4 and Cognitive Function in Japanese Patients with Alzheimer's Disease

Table 3. Comparison of subject characteristics (mean ± SD) between *APOE* ε4 carriers and noncarriers in patients with AD who were 80–89 years old (n = 62)

	Noncarriers (n = 41)	ε4 carriers (n = 21)[b]	χ² or F score	p value
Sex (male/female)	9/32	3/18	0.523[c]	0.473
Age, years	84.22±2.60	82.81±2.89	3.78	0.057
Duration of illness, months	28.44±18.78	41.52±26.98	4.975	0.029*
Education, years	11.02±2.68	11.38±3.15	0.218	0.642
MMSE score	19.98±4.02	17.29±4.47	5.757	0.02*
FAB score	10.58±3.69	9.35±3.66	1.358	0.249
Behave-AD score	7.88±5.07	10.29±7.65	2.199	0.143
CDR-SB[a]	7.05±3.13	8.52±3.01	3.163	0.08

Sex was analyzed using the χ² test. Other variables were analyzed using one-way ANOVA with post hoc tests (Tukey). [a] Ranging from 0 to 18. [b] Heterozygotes: 18, homozygotes: 3. [c] The χ² score is given. * p < 0.05.

MMSE Subtest Scores between ε4 Carriers and Noncarriers in Their 80s

Among the MMSE subtest scores, the 3-stage command score of the ε4 carriers was significantly lower than that of the noncarriers (Z = –3.007; d.f. = 1; p = 0.003) (table 4). To investigate the *APOE* genotypes (ε4 carriers or noncarriers) and the duration of illness (months) as covariates affecting the MMSE total and 3-stage command scores, we performed a generalized linear model analysis (ANCOVA). As a result, a significant interaction between these two factors was not observed for the MMSE total and 3-stage command scores (former: F = 0.016; d.f. = 1; p = 0.900, latter: F = 0.216; d.f. = 1; p = 0.644).

FAB Total and Subtest Scores between ε4 Carriers and Noncarriers in All AD Patients and Patients in Their 70s or 80s

No significant difference in the FAB total score was observed between the two genotypic groups among all AD patients or among the patients in their 70s or 80s (tables 1–3). Moreover, the six subtest scores were not significantly influenced by these genotypic groups among patients in their 70s or 80s (data not shown).

Discussion

As the results of the present study show, *APOE* ε4 significantly influenced the age at consultation in all AD patients (table 1). Furthermore, while *APOE* ε4 influenced the MMSE total and its subtest score, the 3-stage command score, among subjects in their 80s without any significant interaction with the duration of illness, such results were not observed in subjects in their 70s (tables 2–4). A previous study has reported that the onset age of AD in *APOE* ε4 carriers was younger than that in noncarriers, which might have influenced the significant differences in the age at consultation in all AD patients and the illness duration of the patients in their 80s between the two genetic groups in the present study [2].

Some previous studies have shown that *APOE* ε4 has a significant effect on memory retention, rather than on executive function, in other ethnicities or countries, and our results support these reports [6, 7, 10]. From a cross-sectional viewpoint, Caselli et al. [7] showed that age-related differences in memory decline among ε4 carriers and noncarriers increased with age. This could explain the present result, which indicates that a significant association

E X T R A
Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord Extra 2013;3:66–73

71

DOI: 10.1159/000348351

© 2013 S. Karger AG, Basel
www.karger.com/dee

Nagata et al.: Age-Related Association between Apolipoprotein E ε4 and Cognitive
Function in Japanese Patients with Alzheimer's Disease

Table 4. Comparison of MMSE subtest scores (mean ± SD) between *APOE* ε4 carriers and noncarriers in patients with AD who were 80–89 years old (n = 62)

MMSE subtests (ranges)	Noncarrier (n = 41)	ε4 carrier (n = 21)[a]	χ^2 score or M-W Z score	p value
Orientation to time (0–5)	2.34±1.67	1.71±1.42	–1.391	0.164
Orientation to place (0–5)	2.99±1.16	2.62±1.24	–1.305	0.192
Registration (0–3)	2.90±0.30	2.57±0.87	–1.616	0.106
Attention and calculation (0–5)	2.49±1.81	2.05±1.77	–0.939	0.348
Recall (0–3)	1.15±1.15	0.71±0.96	–1.412	0.158
Naming (0–2)	1.93±0.26	1.86±0.36	–0.871	0.384
Repetition (0–1)	0.88±0.33	0.76±0.44	1.385[b]	0.239
3-stage command (0–3)	2.95±0.22	2.57±0.75	–3.007	0.003*
Reading (0–1)	0.93±0.26	0.95±0.22	0.15[b]	0.698
Writing (0–1)	0.66±0.48	0.81±0.40	1.537[b]	0.215
Copying (0–1)	0.71±0.46	0.67±0.48	0.108[b]	0.742

M-W = Mann-Whitney test. [a] Heterozygotes: 18, homozygotes: 3. [b] The χ^2 score is given. * p < 0.01.

between *APOE* ε4 and cognitive function was found only in patients in their 80s, but not in those in their 70s. Wolk et al. [23] found that the *APOE* gene had double dissociable roles in memory and executive function through cortical morphometric evaluations performed in ε4 carriers and noncarriers with AD. Luczywek et al. [6] reported that *APOE* ε4 influences memory retention, rather than working memory, in patients with early-stage AD. However, we did not obtain similar results indicating a significant association between the *APOE* and FAB scores reflecting executive function.

Due to the effects of *APOE* ε4 on particular cognitive profiles, ε4 carriers with AD have been reported to have greater hippocampal cortical atrophy, possibly leading to memory impairments [4, 9, 23]. In a previous study evaluating the characteristics of the MMSE subtest using a factor analysis, the registration and 3-stage command tests were identified as involving immediate or simple memory processing, whereas recall was identified as involving complex memory processing [24, 25]. In the present study, a significant correlation was observed between the registration and the 3-stage command scores (Spearman correlation: ρ = 0.373, p = 0.003), but not between the recall and the 3-stage command scores (Spearman correlation: ρ = 0.105, p = 0.418) among patients in their 80s. Thus, *APOE* ε4 might influence these comparatively simple memory processing tasks in Japanese patients with AD who are in their 80s.

The present study has some limitations. First, since the sample size was comparatively small, we could not compare cognitive function among the three genotypic groups (homozygous for ε4, heterozygous for ε4, and noncarriers) or in younger subjects in their 50s or 60s. Therefore, some type I or type II errors might have occurred. For example, among subjects in their 80s, the mean score for 'recall' of the ε4 carriers was lower than that of the noncarriers, but the difference was not statistically significant (p = 0.158) (table 4). Furthermore, the statistical value (p = 0.02) in the MMSE total score comparison was comparatively small (table 3). However, the effect sizes or statistical values were almost the same as those in previous reports [7, 8, 10]. The statistical significance of the 3-stage command score (p = 0.003) might be reasonable if a p value of <0.05/11 (≑0.0045) is regarded as a significant difference according to the Bonferroni correction, since the MMSE scale has 11 subtest scores (table 4). Second, we did not observe a significant association between ε4 carriers and the

72

Dement Geriatr Cogn Disord Extra 2013;3:66–73

DOI: 10.1159/000348351 | © 2013 S. Karger AG, Basel
www.karger.com/dee

Nagata et al.: Age-Related Association between Apolipoprotein E ε4 and Cognitive Function in Japanese Patients with Alzheimer's Disease

FAB scores reflecting executive function (tables 1–3), as described in previous reports [10, 23]. We used representative screening tests that could be completed at bedside without requiring any tools or instruments, and we believe that the simplicity of these tests makes them valuable tools. However, the ranges of the subtest scores were comparatively small; thus, other batteries for evaluating executive function might provide useful information. Third, a significant difference in the sex ratio of the subjects in their 70s was observed in the present study, with a higher frequency of female ε4 carriers (table 2). However, Yasuno et al. [12] reported that the proportion of female elderly subjects with ε4 was comparatively high in Japan. Moreover, a significant interaction between the sex ratio and *APOE* ε4 was not shown for cognitive function in a generalized linear model analysis using ANOVA. Finally, among the subjects in their 80s, a significant difference in the duration of illness was shown, which might reflect differences in the age at consultation for AD among the two genotypic groups (table 3). However, a significant interaction of illness duration (in months) as a covariance was not shown for cognitive function in a generalized linear model analysis using ANCOVA.

In conclusion, despite some limitations, we found for the first time a significant effect of *APOE* ε4 on the MMSE score reflecting memory or attentional function (particularly for a simple memory processing task, the 3-stage command), rather than executive function, among Japanese AD patients in their 80s, which was a comparatively older generation. Our results support the findings of previous studies in other countries in addition to furthering the elucidation of the functional roles of the *APOE* gene [6, 7, 10]. Furthermore, defining the detailed associations between *APOE* gene diversity and cognitive behavior in patients with AD using an intermediate phenotype in studies involving neuroimaging or physiological methods in a normal elderly population will be an important task in the future.

Acknowledgement

References

1 Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskvina V, et al: Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet 2009;41:1088–1093.

2 Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA: Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261:921–923.

3 Ohara T, Ninomiya T, Hirakawa Y, Ashikawa K, Monji A, Kiyohara Y, Kanba S, Kubo M: Association study of susceptibility genes for late-onset Alzheimer's disease in the Japanese population. Psychiatr Genet 2012;22:290–293.

4 Lehtovirta M, Soininen H, Laakso MP, Partanen K, Helisalmi S, Mannermaa A, Ryynänen M, Kuikka J, Harti-kainen P, Riekkinen PJ Sr: SPECT and MRI analysis in Alzheimer's disease: relation to apolipoprotein E epsilon 4 allele. J Neurol Neurosurg Psychiatry 1996;60:644–649.

5 Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z, Holtzman DM, Betsholtz C, Armulik A, Sallstrom J, Berk BC, Zlokovic BV: Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. Nature 2012;485:512–516.

6 Luczywek E, Nowicka A, Pfeffer A, Czyzewski K, Styczyńska M, Lałowski M, Barcikowska M: Cognitive deficits and polymorphism of apolipoprotein E in Alzheimer's disease. Dement Geriatr Cogn Disord 2002;13:171–177.

7 Caselli RJ, Dueck AC, Osborne D, Sabbagh MN, Connor DJ, Ahern GL, Baxter LC, Rapcsak SZ, Shi J, Woodruff BK, Locke DE, Snyder CH, Alexander GE, Rademakers R, Reiman EM: Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. N Engl J Med 2009;361:255–263.

8 Hirono N, Hashimoto M, Yasuda M, Kazui H, Mori E: Accelerated memory decline in Alzheimer's disease with apolipoprotein epsilon4 allele. J Neuropsychiatry Clin Neurosci 2003;15:354–358.

9 Mori E, Lee K, Yasuda M, Hashimoto M, Kazui H, Hirono N, Matsui M: Accelerated hippocampal atrophy in Alzheimer's disease with apolipoprotein E epsilon4 allele. Ann Neurol 2002;51:209–214.

10 Caselli RJ, Dueck AC, Locke DE, Hoffman-Snyder CR, Woodruff BK, Rapcsak SZ, Reiman EM: Longitudinal modeling of frontal cognition in APOE ε4 homozygotes, heterozygotes, and noncarriers. Neurology 2011;76: 1383–1388.

11 Schiepers OJ, Harris SE, Gow AJ, Pattie A, Brett CE, Starr JM, Deary IJ: APOE E4 status predicts age-related cognitive decline in the ninth decade: longitudinal follow-up of the Lothian Birth Cohort 1921. Mol Psychiatry 2012;17:315–324.

12 Yasuno F, Tanimukai S, Sasaki M, Hidaka S, Ikejima C, Yamashita F, Kodama C, Mizukami K, Michikawa M, Asada T: Association between cognitive function and plasma lipids of the elderly after controlling for apolipoprotein E genotype. Am J Geriatr Psychiatry 2012;20:574–583.

13 Martyr A, Clare L: Executive function and activities of daily living in Alzheimer's disease: a correlational meta-analysis. Dement Geriatr Cogn Disord 2012;33:189–203.

14 Nagata T, Shinagawa S, Ochiai Y, Kada H, Kasahara H, Nukariya K, Nakayama K: Relationship of frontal lobe dysfunction and aberrant motor behaviors in patients with Alzheimer's disease. Int Psychogeriatr 2010;22: 463–469.

15 Dubois B, Slachevsky A, Litvan I, Pillon B: The FAB: a Frontal Assessment Battery at bedside. Neurology 2000; 55:1621–1626.

16 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.

17 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.

18 Petersen RC, Doody R, Kurz A: Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985–1992.

19 Wenham PR, Newton CR, Price WH: Analysis of apolipoprotein E genotypes by the Amplification Refractory Mutation System. Clin Chem 1991;37:241–244.

20 Shibata N, Ohnuma T, Baba H, Higashi S, Nishioka K, Arai H: Genetic association between SORL1 polymorphisms and Alzheimer's disease in a Japanese population. Dement Geriatr Cogn Disord 2008;26:161–164.

21 Reisberg B, Borenstein J, Salob SP, Ferris SH, Franssen E, Georgotas A: Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. J Clin Psychiatry 1987;48(suppl):9–15.

22 Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL: A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566–572.

23 Wolk DA, Dickerson BC; Alzheimer's Disease Neuroimaging Initiative: Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimer's disease. Proc Natl Acad Sci USA 2010;107:10256–10261.

24 Buckner RL: Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuron 2004;44:195–208.

25 Ideno Y, Takayama M, Hayashi K, Takagi H, Sugai Y: Evaluation of a Japanese version of the Mini-Mental State Examination in elderly persons. Geriatr Gerontol Int 2012;12:310–316.