Alzheimer's disease:

Interaction of apolipoprotein E genotype, family history of dementia, gender, education, ethnicity, and age of onset

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Article abstract—We evaluated 197 patients with predominantly late-onset Alzheimer's disease (AD) who belonged to several ethnic groups and analyzed the relationship of age of onset of AD to the presence or absence of several risk factors in this entire group of patients. The apolipoprotein E (apoE) ϵ4 allele frequency, which was 29% in all patients (compared with the reported population mean of 13.7%, $p < 0.001$, did not vary significantly between ethnic groups but declined significantly with increasing age. The apoE ϵ2 allele frequency was 3%, compared with the reported population mean of 7.4% ($p = 0.001$). The frequency of a positive family history of dementia in first-degree relatives (FH+) (overall 45%) did not vary significantly between ethnic groups. ApoE ϵ4-positive (ϵ4+) patients tended to have a higher FH+ rate (58%) than apoE ϵ4-negative (ϵ4−) patients (40%) ($p = 0.02$). When the potential risk factors of gender, education, FH+ status, and ϵ4+ status were examined together in a multiple linear-regression analysis, FH+ and ϵ4+ status (but not gender or education) were significant (they were both associated with an earlier age of onset of AD). In a post-hoc analysis, we found a reduced age of onset in women, but not men, who were both FH+ and ϵ4+. Additionally, those probands who were ϵ4+ were more likely to inherit the disease from their mothers than their fathers. The mechanism by which ϵ4+ and FH+ status operate as risk factors may be by their effect on the age of onset of AD.

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Epidemiologic studies suggest several known or potential risk factors for Alzheimer's disease (AD), including advanced age, a family history of dementia, female gender, and low educational level.[1-3] More recently, another important risk factor for AD was discovered, the apolipoprotein E (apoE) genotype. An association between late-onset AD and the apoE ϵ4 allele is now well established.[4-7] The risk for AD is increased two- to threefold for individuals heterozygous for the apoE ϵ4 allele and more than eightfold for individuals homozygous for this allele.[4]

One mechanism by which any factor may operate as a risk factor in a late-onset disease, such as AD, is by advancing forward the age of onset of the disease. For example, the mean age of onset of AD is earlier by several years in positive family history of dementia (FH+) patients than negative family history (FH−) patients.[8,9] The apoE ϵ4 allele also appears to reduce the mean age of onset of AD,[4] especially in subjects who are homozygous for the allele.[4,10,11]

There is no a priori reason to expect any specific interactions between suspected or known risk factors for AD. Patients who are FH+ for AD have a higher apoE ϵ4 allele frequency than those who are FH−. This does not necessarily mean that patients who are both FH+ and apo ϵ4+ are at a higher risk for developing AD than if they have only one of these risk factors. One way to explore this question is to examine the effect of each of these factors, individually and together, on the age of onset of AD.

In this study we evaluated the interaction between gender, ethnicity, education, a positive family history of dementia, and the presence of the apoE ϵ4 allele to age of onset in patients with AD. Our hypothesis was that ϵ4+ and FH+ patients would have an earlier age of onset than ϵ4− and FH− patients. We expected that the effects would be additive for these factors, so that those patients who were both ϵ4+ and FH+ would have earlier age of onset than those who had only one of these risk factors.

Because the longevity of women (and therefore, possibly, the average age of onset of AD in women) is greater than that of men, we expected that if female gender independently advances forward the age of onset of AD, it would not be demonstrable in this analysis. We did not expect education to have an effect on age of onset in this study because it appears to be a relatively weak risk factor,[2] and larger numbers of subjects would be required to demonstrate an effect.

Methods. Patients were evaluated at the Wien Center for Alzheimer's Disease and Memory Disorders (Miami

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Beach, FL). Phenotypic and genotypic data were collected for 197 patients. Patients were primarily late age at onset (mean age 75 ± 8 years) and diagnosed as having probable (n = 126) or possible (n = 71) AD, using established criteria.[12] The accuracy of a clinical diagnosis of possible or probable AD in this study is estimated to be 75 to 93%.[13-15] (Of all patients seen at this center who have come to autopsy [n = 61], the accuracy of the diagnosis of AD [probable or possible] has been 92%, with a sensitivity of 92% and a specificity [AD versus not AD] of 78%.)

The family history assessment used to classify patients as familial AD (FAD) was the protocol described by Duara et al.[8] At least two informants other than the patient were interviewed and differences in recollection were usually reconciled, or the most knowledgeable historian's family history was used. To be classified as FH+, in addition to the proband, at least one other first-degree relative was required to have a history of progressive dementia. The use of the above criteria for FAD is justified because this same criterion has been used by Farrer et al.[16,17] to define a major gene for AD.

The age of onset of AD was calculated from the patients' current age minus the average reported duration of disease, obtained from at least two knowledgeable family members.

ApoE ϵ genotypes were determined at the Center for Research in Neurodegenerative Diseases (University of Toronto, Toronto, Canada) using previously described methods.[7]

A multiple linear-regression analysis was performed with age of onset of AD as the dependent variable and with gender, education, FH+ status, and ϵ4+ status as the predictor variables. ApoE ϵ4 allele frequencies were compared in various subgroups of AD patients by chi-square analyses. The subgroups were divided by age, gender, ethnicity, and positive or negative family history of dementia. Furthermore, patients were grouped according to apoE genotype (ϵ4 allele positive or negative), and their current age, age of onset, and FH+ rates were compared between groups, using ANOVA or cross-tabulation analyses as appropriate. For all cross-tabulation analyses, Fisher's exact test was used. With regards to multiple comparisons, our major hypothesis in this study was the effect of apoE genotype, family history, gender, and education on age of onset. For this a priori hypothesis, criterion for significance was set at $p \leq 0.05$. However, given the number of exploratory contrasts for other measures, each p value was set at $p \leq 0.01$ for contrasts not part of our a priori hypothesis.

Results. The apoE ϵ4 allele frequency tended to be greater in patients diagnosed with probable (32%) than with possible AD (22%) ($p = 0.04$).

There was no difference among the four ethnic groups in gender ratio and positive family history, but age of onset was greater in Ashkenazi Jewish (mean 77 ± 7 years) than African-American (72 ± 8 years), Hispanic (72 ± 9 years), and white non-Hispanic non-Jewish patients (73 ± 9 years). Educational attainment was lowest in African-American (7 ± 4 years), intermediate in Hispanic (10 ± 5 years), and significantly higher in both Jewish Ashkenazi (12 ± 3 years) and white non-Hispanic non-Jewish (12 ± 3 years).

There was no difference in either apoE ϵ4 allele frequency (table 1) or apoE ϵ2 allele frequency (Jewish 2%, Hispanic 3%, non-Jewish non-Hispanic 5%, and African-American 3%) segregated by ethnic group. ApoE ϵ4 allele frequency in the entire patient group was 29%, which was significantly greater ($p < 0.001$) than 13.7%, as reported for normal subjects, 45 years and over, from the Framingham Offspring Study.[18] Further, the apoE ϵ2 allele frequency of 3% in the entire AD group was less than 7.4%, as reported in normal subjects,[18] even after controlling for the increased frequency of ϵ4 in the AD patient group. Explicitly, the ratio of apoE ϵ3 to apoE ϵ2 alleles was 22:1 in the AD group and 11:1 in the Framingham control group ($p < 0.008$). For all patients taken together, there was a significant age-associated decline in apoE ϵ4 allele frequency (see table 1).

Table 1 *ApoE ϵ4 allele frequency (%) by ethnicity and onset age*

	Onset Age			
Ethnicity	<70 yr	70–79 yr	≥80 yr	All ages
Jewish Ashkenazi (n = 100)	50	34	18	30
Hispanic (non-Jewish) (n = 46)	37	24	25	28
Non-Jewish, non-Hispanic caucasian (n = 30)	40	37	10	33
African-American (n = 19)	27	33	20	29
All subjects (n = 197*)	39	32	19	29

Values are percents. Fisher's exact tests showed a significant decline with age in allele frequency in all subjects ($p = 0.004$).

* Two subjects were Sephardic Jewish.

The multiple linear-regression analysis showed that the significant predictors of age of onset of AD were a FH+ status ($F = 4.7$, $p = 0.03$) and ϵ4+ status ($F = 4.1$, $p = 0.05$). There was no significant interaction between these two predictors of age of onset of AD, implying a simple additive effect for these two factors. There was no interaction between gender or education and FH+ or ϵ4+ status.

However, an examination of table 2 shows that in all subjects the age of onset was about 4 years earlier in ϵ4+ than in ϵ4− patients. This effect was not significant when it was studied in men separately but was highly significant in women, in whom the age of onset was significantly lower in those who were both FH+ and ϵ4+ than in those who were FH+ and ϵ4− ($p = 0.002$). This effect was not seen in FH− women. Family history status by itself influenced age of onset primarily in men and not in women, unless they were also ϵ4+.

A further breakdown of apoE genotype in the entire sample, according to the number of ϵ4 alleles, revealed mean ages of onset of 77 ± 8, 74 ± 8, and 69 ± 6 years ($p = 0.005$), corresponding to zero, one, and two ϵ4 alleles. Further breakdown of the ϵ4,4 genotype by gender and

Table 2 *Age of onset of AD by family history status and apoE genotype*

Feature	ε4−	ε4+	*p*
Number*	92	102	—
Age of onset (yr)			
FH+			
Men (n = 34)	73 ± 13	72 ± 9	0.80
Women (n = 59)	78 ± 8	71 ± 7	0.002
FH−			
Men (n = 25)	77 ± 8	75 ± 7	0.63
Women (n = 70)	77 ± 7	76 ± 6	0.42
All men	75 ± 10	73 ± 8	0.39
All women	78 ± 7	74 ± 7	0.002
All subjects	77 ± 9	73 ± 8	0.005

* Three subjects had ε2,4 genotype and were not included in the ε4− or ε4+ groups, and six subjects had insufficient data for a classification of family history.

family history was not attempted because of the small number of ε4 homozygous subjects (n = 11).

FH+ status tended to be more prevalent in those patients who were ε4+ (58%) than in those who were ε4− (40%) $p = 0.02$). This result was obtained primarily in men in whom ε4− patients had a significantly lower FH+ prevalence than ε4+ patients ($p = 0.01$), whereas ε4− and ε4+ women were not different in FH+ prevalence.

An analysis of the gender distribution of the secondary cases reveals a skewed distribution, with a significantly higher rate of affected mothers in those probands who were ε4+ (32 affected mothers) than those who were ε4− (12 affected mothers) ($p < 0.005$). A further analysis of the number of affected mothers compared with affected fathers shows a significant excess of affected mothers (32 mothers versus 12 fathers) only in those who were ε4+ ($p = 0.0009$). In probands who were ε4+, the mean survival age of the mothers (73 ± 18 years) was not different from the fathers (69 ± 16 years). We had sufficient data to perform these analyses within two major ethnic groups (Ashkenazi Jews and Hispanics). We found a significant excess of affected mothers of probands who were ε4+ compared with those who were ε4− among Ashkenazi Jews but not among Hispanics, who had an excess of affected female first-degree relatives regardless of apoE ε4 allele status.

Discussion. The prevalence of most risk factors for AD are remarkably similar across ethnic groups. Where there are differences, they can be explained by local demographic phenomena or differences among the ethnic groups. For example, the age of onset and the current age of Ashkenazi Jewish patients is higher than in the other ethnic groups because of local migration factors within the catchment area for most of our patients.[19] Educational differences between African-American and Hispanic patients versus the Ashkenazi Jewish and white non-Hispanic, non-Jewish patients are representative of national statistics for these ethnic groups. Family history of dementia is subject to great variability. It is difficult to quantify because it is dependent on several other factors, including educational level of the informant, family size, and longevity and the number of generations of the family that have lived (and died) in the United States. The untimely demise of many family members (e.g., Ashkenazi Jews affected by the Holocaust) may have a systematic effect on the presence of a positive family history of dementia in certain ethnic groups.

In this study we evaluated the importance of individual risk factors for AD by their effects on reducing the age of onset of the disease. The premise behind this form of analysis is that AD is an age-associated disease, the expression of which may be dependent on the length of time for which an individual is exposed to risk factors for the disease. Presumably, a potent risk factor would need a shorter exposure time than a weak risk factor, before the clinical onset of the disease. The strength of a risk factor would be judged, therefore, by the number of years by which that risk factor advanced forward the age of onset of the disease.

The merits of this type of analysis are that normal or disease control subjects are not required, as the patients serve as their own controls. The validity of case-control studies depends on the recruitment of appropriate control subjects. For a disease, such as AD, that is likely to be multifactorial and for which many of the risk factors are currently unknown, it is not really possible to define a true control group of normal subjects.

The problem with this type of analysis is that is does not account for risk factors that may not operate on the basis of duration of exposure to that risk factor. The risk factor may instead become activated through an interaction with other age-related physiologic or pathologic processes.

Nevertheless, in this study, via an age of onset analysis, we were able to confirm the now well-accepted finding that a family history of dementia and a positive apoE ε4 allele status confer significant risk for AD. We have also shown that the combined risks of being FH+ and ε4+ appear to be additive but not synergistic, that is, the presence of both risk factors does not result in an earlier age of onset than that predicted by a simple addition of the effect of each factor alone. Further, this study provides supportive evidence to several epidemiologic studies[1-3] that have found female gender to be a risk factor for AD.

Although the mean age of onset of AD in women in this study was not significantly different than in men, this in itself is an important finding, given the greater number of women in the general population above the age of 60 years. For example, in the catchment area for the patients in this study (south Florida), the ratio of women to men is 1.35:1 in the age group of 65+ years.[20] The ratio of women to men AD patients in this study is 2.1:1, which is significantly greater ($p < 0.001$) than in the catchment area general population. The higher number of women could

be related to recruitment biases inherent in a clinic population. Another possible reason for the higher number of women with AD may be related to an interaction between female gender and a known risk factor, the apoE ε4 allele, as discussed below.

Women who were ε4+ had a younger age of onset than women who were ε4− (see table 2). However, this effect was seen only in FH+ women. Conversely, the effect of FH+ status on age of onset was seen primarily in men, in whom ε4+ status had little additional influence. A likely explanation for the selective effects of ε4+ status is an interaction between female gender and the risk for AD conferred by the apoE ε4 allele. Because these results were not significant in the multiple-regression analysis, our conclusions need confirmation in a study with a larger number of patients. Indirect support for this conclusion comes from the preliminary report by Payami et al.,[21] who found that compared with those without the ε4 allele, age at onset of AD was earlier in women *but not men* heterozygous for the ε4 allele. However, earlier age of onset was found in both men and women homozygous for the ε4 allele. Payami et al.[21] suggested that women, because of their greater predilection toward AD, needed only one ε4 allele, whereas men required two ε4 alleles to reduce age of onset of AD. We did not have a sufficiently large number of subjects homozygous for the ε4 alleles to evaluate this possibility. Poirier et al.[22] also reported that the ε4/AD association was more pronounced in women than in men. In the recent report by Corder et al.,[23] however, there were no gender-specific effects reported for the risk conferred by the apoE ε4 allele.

The difference in apoE ε4 allele frequencies among cases with probable and with possible AD was expected, because the apoE ε4 allele is associated with AD, and patients with the greatest likelihood of having neuropathologically confirmed AD are cases with probable rather than possible AD.[13,24]

The allele frequency of apoE ε4 allele varies in different ethnic groups, with a mean of 13.5 ± 6% in all groups combined, the lowest frequency being reported in Chinese and Japanese (7.4 ± 0.8%) and highest frequencies among the Sudanese (29%),[25] the Dutch (30%),[26] and the Finnish (23 to 24%).[25] The weighted average ε4 allele frequency across different ethnic groups is about 15%.[25-28] Davignon et al.[28] reported no age nor gender effects on ε4 allele frequency in the general population. However, Rebeck et al.[29] demonstrated a decline in ε4 allele frequency with age, and Corder et al.[23] also reported that ε4 allele frequency declines in AD patients between the seventh and ninth decades. Furthermore, Sobel et al.[30] reported no association between the apoE ε4 allele and AD in centenarians in Finland. In this study, we also found the apoE ε4 allele frequency to decline significantly between the seventh and ninth decades in AD patients.

In the current study, the ε4 allele frequency of 29% is lower than in many reports pertaining to AD patients (e.g., apoE ε4 allele frequency of 42 ± 6% in late-onset AD[5]), although higher by a factor of about two than the overall population mean apoE ε4 allele frequency. The likely explanation for this finding is that the average age of the patients in this study (78.6 years) is about 8 to 10 years greater than in most previously reported studies.[4-7,21-23]

Population studies of ε4 allele frequency in Hispanics have not been formally reported to our knowledge. In African-Americans, Hendrie et al.[27] reported an apoE ε4 allele frequency of 13.9% in control subjects (n = 54, mean age 78 years), which was significantly lower than the corresponding values of 29% in our African-American AD patients and 40.3% in their patient sample (n = 31). In Ashkenazi Jews, the apoE ε4 allele frequency is 15% in normal individuals (n = 86, mean age 76 years),[7] which is significantly lower than the corresponding value of 30% in our Jewish patients (mean age 78 years).

The ε2 allele frequencies in the current study (2 to 6%) are significantly lower ($p = 0.005$) than that for caucasians in general, who have a population mean ε2 allele frequency of 7.4%.[25,28] This is consistent with the conclusion in the recently reported study of Corder et al.,[23] who suggested that a protective effect from AD may be present for the apoE ε2 allele.

Finally, we found a clear preponderance of affected mothers in secondary cases of probands who were ε4+ compared with those who were ε4−. These findings were significant for Ashkenazi Jews, but we were unable to show any differential effect of ε4+ versus ε4− genotype on the gender ratio in the parents of Hispanic patients. The number of available subjects who were non-Jewish and non-Hispanic was too small for us to carry out such an analysis. A further analysis also showed that the number of affected mothers and sisters was significantly greater than fathers and brothers for probands who were ε4+. These last results could have occurred because women have a greater longevity than men. However, the survival age of fathers of ε4+ probands (69 ± 16 years) was not different from that of mothers of ε4+ probands (73 ± 18 years) in this study. We assume that those probands who were ε4+ (compared with those who were ε4−) have a greater (about twofold) preponderance of parents with at least one ε4 allele. Given simple Mendelian inheritance of the ε4 allele, mothers and fathers would be equally likely to have donated this ε4 allele. The number of mothers of probands who were ε4+ and affected with the disease, therefore, is out of proportion to what we expected. To explain this phenomenon, we suggest two possible explanations. First, some form of genetic imprinting occurs in the inheritance of the ε4 allele, with a resulting preference toward maternal-progeny than paternal-progeny inheritance. We suggested this hypothesis in a previous study[8] on the basis of the observation of the inheritance patterns in familial cases. Second, females who are both ε4+ and FH+ may be at a heightened risk for the develop-

ment of AD than are men with the same risk factors, as discussed previously.

References

1. Rocca WA, Hofman A, Brayne C, et al. Frequency and distribution of Alzheimer's disease in Europe: a collaborative study of 1980–1990 prevalence findings. Ann Neurol 1991;30:381–390.
2. Breteler, MMB, Claus JJ, van Duijn CM, Launer LJ, Hofman A. Epidemiology of Alzheimer's disease. Epidemiol Rev 1992; 14:59–81.
3. Brenner DE, Kukull WA, van Belle G, et al. Relationship between cigarette smoking and Alzheimer's disease in a population-based case-controlled study. Neurology 1993;43:293–300.
4. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261:921–923.
5. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele ϵ4 with late-onset familial and sporadic Alzheimer's disease. Neurology 1993;43:1467–1472.
6. Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: high-avidity binding to β-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci USA 1993;90:1977–1981.
7. Tsuda T, Lopez R, Rogaeva EA, et al. Are the associations between Alzheimer's disease and polymorphisms in the apolipoprotein E and the apolipoprotein CII genes due to linkage disequilibrium? Ann Neurol 1994;36:97–100.
8. Duara R, Lopez-Alberola RF, Barker WW, et al. A comparison of familial and sporadic Alzheimer's disease. Neurology 1993; 43:1377–1384.
9. Heston LL, Mastri AR, Anderson E, White J. Dementia of the Alzheimer type: clinical genetics, natural history, and associated conditions. Arch Gen Psychiatry 1981;31:1085–1090.
10. Lehtovirta M, Soininen H, Helisalmi S, et al. Clinical and neuropsychological characteristics in familial and sporadic Alzheimer's disease: relation to apolipoprotein E polymorphism. Neurology 1995;46:413–419.
11. Corder EH, Saunders AM, Strittmatter WJ, et al. Apolipoprotein E, survival in Alzheimer's disease patients, and the competing risks of death and Alzheimer's disease. Neurology 1995;45:1323–1328.
12. 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.
13. Molsa PK, Paljarvi L, Rinne JO, Rinne UK, Sako E. Validity of clinical diagnosis in dementia: a prospective clinicopathological study. J Neurol Neurosurg Psychiatry 1985;48: 1085–1090.
14. Wade JPH, Mirsen TR, Hachinski VC, Fisman M, Lau C, Merskey H. The clinical diagnosis of Alzheimer's disease. Arch Neurol 1987;44:24–29.
15. Duara R, Pascal S, Barker WW, Bruce J, Noremberg M. Neuropathological verification of probable and possible Alzheimer's disease (AD) [abstract]. Ann Neurol 1992;32:269.
16. Farrer LA, O'Sullivan DM, Cupples LA, Growdon JH, Myers RH. Assessment of genetic risk for Alzheimer's disease among first-degree relatives. Ann Neurol 1989;25:485–493.
17. Farrer LA, Myers RH, Connor L, Cupples LA, Growdon JH. Segregation analysis reveals evidence of a major gene for Alzheimer disease. Am J Hum Genet 1991;48:1026–1033.
18. Ordovas JM, Litwack-Klein L, Wilson PWF, Schaefer MM, Schaefer EJ. Apolipoprotein E isoform phenotyping methodology and population frequency with identification of apoE1 and apoE5 isoforms. J Lipid Res 1987;28:371–380.
19. Jewish Demographic Study of Dade County. Summary report. Miami, FL: Greater Miami Jewish Federation, 1994.
20. Florida Statistical Abstract. 1993. Gainesville, FL: University Press of Florida, 1993:26–27.
21. Payami H, Montee KR, Kaye JA, et al. Alzheimer's disease, apolipoprotein ϵ4, and gender. JAMA 1994;271:1316–1317.
22. Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S. Apolipoprotein E polymorphism and Alzheimer's disease. Lancet 1993;342:697–699.
23. Corder EH, Saunders AM, Risch NJ, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nature Genet 1994;7:180–184.
24. Galasko D, Hansen LA, Katzman R, et al. Clinical-neuropathological correlations in Alzheimer's disease and related dementias. Arch Neurol 1994;51:888–895.
25. Hallman DM, Boerwinkle E, Saha N, et al. The apolipoprotein E polymorphism: a comparison of allele frequencies and effects in nine populations. Am J Hum Genet 1991;49:338–349.
26. Smit M, de Knijff P, Rosseneu M, et al. Apolipoprotein E polymorphisms in The Netherlands and its effect on plasma lipid and apolipoprotein levels. Hum Genet 1988;80:287–292.
27. Hendrie HC, Hall KS, Hui S, et al. Apolipoprotein E genotypes and Alzheimer's disease in a community study of elderly African Americans. Ann Neurol 1995;37:118–120.
28. Davignon J, Gregg RE, Sing CF. Apolipoprotein E polymorphism and atherosclerosis. Atherosclerosis 1988;8:1–20.
29. Rebeck GW, Perls TT, West HL, Sodhi P, Lipsitz LA, Hyman BT. Reduced apolipoprotein ϵ4 allele frequency in the oldest old Alzheimer's patients and cognitively normal individuals. Neurology 1994;44:1513–1516.
30. Sobel E, Louhija J, Sulkava R, et al. Lack of association of apolipoprotein E allele ϵ4 with late-onset Alzheimer's disease among Finnish centenarians. Neurology 1995;45:903–907.

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