

No Association Between Apolipoprotein E ϵ 4 Allele and Rate of Decline in Alzheimer's Disease

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Objective: The relationship between number of apolipoprotein E ϵ 4 (APOE ϵ 4) alleles and the rate of cognitive decline in patients with Alzheimer's disease was examined. **Method:** Rate of decline in score on the Mini-Mental State was measured during the active phase of the decline curve between Mini-Mental State scores of 23 and 0. To characterize onset, the authors also estimated for each subject the age at which the Mini-Mental State score fell below 23 and obtained a retrospective report of age at onset from the caregiver. The number of APOE ϵ 4 alleles carried by each subject was determined from genomic DNA samples. The study included 86 subjects with probable Alzheimer's disease who had had at least two cognitive evaluations (a mean of 5.6 evaluations per subject over an average period of 3.6 years). **Results:** The results did not support an association between APOE ϵ 4 dosage and rate of cognitive decline. Age at onset and age at which the Mini-Mental State score fell below 23 were also not related to APOE ϵ 4 dosage. The APOE allele frequencies were similar to those in other studies of subjects with Alzheimer's disease, showing an enrichment of the ϵ 4 allele. **Conclusions:** Although the APOE ϵ 4 allele is a risk factor for Alzheimer's disease, there is no support of a strong association between APOE ϵ 4 dosage and rate of cognitive decline. The ϵ 4 allele did not predict age at onset. Methodological inconsistencies may account for discrepancies between these results and previous findings.

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Alzheimer's disease is characterized by heterogeneity in clinical presentation and disease progression. A variety of subtypes have been proposed on the basis of age at onset, degree of familiarity, and the

presence or absence of clinical features such as language disorder and parkinsonism (1-3). Yet the biological basis for clinical heterogeneity in Alzheimer's disease is unclear. One hypothesis is that genetic factors may contribute to clinical differences among subjects with Alzheimer's disease. Many studies have demonstrated that the apolipoprotein E ϵ 4 (APOE ϵ 4) allele is a genetic risk factor for both familial and sporadic Alzheimer's disease (4). It is estimated that up to 65% of the patients with Alzheimer's disease carry an ϵ 4 allele, compared to only 24% to 31% of control subjects (5). However, few studies have addressed the effect of APOE ϵ 4 on heterogeneity in the clinical phenotype in Alzheimer's disease.

An important dimension of clinical variation among subjects with Alzheimer's disease is the rate of decline (6). Rate of decline is the rate at which a patient's cognitive function decreases over time once the disease becomes manifest. Although patients and families often request information regarding the rate at which decline will occur,

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at present evidence supports great heterogeneity among patients with Alzheimer's disease and no adequate biological marker that can predict rate of decline.

In the present study we assessed whether the APOE $\epsilon 4$ allele is related to rate of change in cognition in Alzheimer's disease. Because the $\epsilon 4$ allele has been reported to result in an earlier age at onset of Alzheimer's disease (4), we hypothesized that it might also predispose to rapidity of decline. Unlike measures used in some studies of APOE and clinical progression of Alzheimer's disease (7, 8), our clinical measure was actual rate of change in cognitive status, not length of survival after disease onset. While survival after disease onset may be related to rate of cognitive decline, there is not a strong relationship, as patients live for variable amounts of time after reaching the end stage of the disease, after which no further measurable cognitive decline occurs.

METHOD

Subjects

A total of 33 women and 53 men with a clinical diagnosis of probable Alzheimer's disease were included in the study. All were part of a longitudinal study of Alzheimer's disease conducted at the Stanford/Veterans Affairs NIMH Clinical Research Center for the Study of Senile Dementia. The criteria for entry into the center were a clinical diagnosis of probable Alzheimer's disease according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (9) and an absence of active major medical problems. To determine the diagnosis of probable Alzheimer's disease, all subjects had a complete medical, psychiatric, neurologic, neuroimaging, and neuropsychological assessment. On the basis of these evaluations a consensus diagnosis was reached by an interdisciplinary team that included one to three physicians.

The subjects or their caregivers had given written informed consent for clinical and biological studies of dementia. All subjects had been followed for at least 1 year in our center, and all had Mini-Mental State (10) scores of 15 or higher at entry into the center cohort. At the time of data analysis, 56 subjects were living and 30 were deceased. Of the deceased subjects, 28 of the 30 had been autopsied. Complete autopsy data, including full gross and microscopic neuropathologic findings, were available for 24 subjects. Preliminary neuropathologic reports were available for three additional subjects, and the remaining neuropathologic evaluation was in progress at the time of the data analysis. Of the 27 subjects with neuropathologic evaluations, 14 (52%) had a diagnosis of definite Alzheimer's disease, seven (26%) had a diagnosis of definite Alzheimer's disease with cortical Lewy bodies (one diagnosis was preliminary), two (7%) had a diagnosis of definite Alzheimer's disease with coexisting vascular changes, two (7%) had a diagnosis of definite Alzheimer's disease with coexisting Parkinson's disease, and two (7%) had a preliminary neuropathologic diagnosis of Lewy body dementia. Thus, on the basis of neuropathologic diagnosis, the predictive value of a positive clinical diagnosis of probable Alzheimer's disease was 93% for definite Alzheimer's disease alone or in combination.

Inclusion in our study group of subjects with coexisting Alzheimer's disease and Parkinson's disease neuropathology is justifiable since Gearring et al. (11) recently showed that the $\epsilon 4$ allele is overrepresented in this population, as it is in persons with pure Alzheimer's disease. Likewise, the frequency of the $\epsilon 4$ allele is higher than average in subjects with the Lewy body variant of Alzheimer's disease and in pure Lewy body disease (12-14). Hence, it is reasonable to hypothesize that APOE $\epsilon 4$ affects the rate of decline in these disease states just as it does in pure Alzheimer's disease. We did not require neuropathologic evaluation as part of the inclusion/exclusion criteria since the population of interest here are living patients with probable Alzheimer's disease.

Clinical Data

The Mini-Mental State was used to assess cognitive function. To determine rate of cognitive decline, we estimated slopes by using a linear regression of Mini-Mental State scores on age for each individual subject (15). Slopes were expressed as Mini-Mental State points per year. We restricted each patient's set of scores by analyzing only the portion of the data in which the Mini-Mental State declined from 23 to the first instance of a 0 score. In this way, the scores likely to be subject to ceiling or floor effects were excluded from the computation of the slope. In the present study group, 21 of the 86 patients scored 24 or above early in the course of their follow-ups, and these high scores were excluded from the slope fitting. Also, 21 of the 86 patients had one or more 0 scores after the initial 0, which were excluded. The subjects' follow-ups after exclusion of the high and low scores averaged 3.6 years in length ($SD=1.7$, range=1.0-7.9) and contained an average of 5.6 Mini-Mental State scores ($SD=2.5$, range=2-11). Nine of the 86 subjects had only two Mini-Mental State scores in the range used to calculate the slope of decline; all of the others had at least three.

Two indicators of age at onset were used in this study. One was the caregiver's report of the age when symptoms of dementia first became noticeable. The mean such age for the entire study group was 65.3 years ($SD=7.4$). Forty-four of the 86 subjects were classified as having early onsets (before or at 65 years of age; mean=59.3 years, $SD=4.1$), and 42 were classified as having late onsets (after age 65; mean=71.6 years, $SD=4.2$). The other measure was an estimate of the age at which the Mini-Mental State score fell below 23, which was calculated by using the y -intercept and slope parameters obtained from the linear regression. The mean value for this measure was 68.8 years ($SD=7.0$). The correlation between the two indicators was $r=0.84$.

Familiality was determined by using information obtained from caregivers or relatives at the time of initial evaluation. All information was reviewed, and if the data were incomplete or conflicting, family members were recontacted to clarify the history. By means of this method, 28 subjects were classified as having a family history of dementia, and 58 subjects were classified as having no identifiable family history.

Apolipoprotein E Genotyping

Genomic DNA was obtained from frozen EDTA-containing whole blood or buccal mucosa cell samples from subjects living at the time of sampling ($N=69$), and from deceased subjects samples were obtained from frozen or paraffin-embedded brain tissue or archived frozen blood clots from serum separator tubes ($N=17$). DNA was extracted from whole blood samples or from blood clots by using the method of Lahiri and Nurnberger (16). Buccal mucosa samples were obtained by using a cytology brush, and DNA was extracted following the protocol of Richards et al. (17). DNA was extracted from frozen brain samples by using the TurboGen kit (Invitrogen, San Diego, Calif.) according to the manufacturer's instructions. DNA extraction from 5- and 8- μm paraffin-embedded brain sections that had been fixed in either methacarn or formalin was performed according to the protocol of Greer et al. (18).

APOE genotyping was performed according to the protocol of Hixson and Vernier (19). A negative control (no DNA template) was included with every batch of polymerase chain reactions. Restriction digestion products were visualized on ethidium bromide-stained gels. Genotypes were determined by two observers blind as to the clinical or neuropathologic diagnosis. To test for contamination of reagents with products of the polymerase chain reactions, we routinely performed 45 cycles with complete polymerase chain reaction reagents, but no template DNA, or polymerase chain reactions using blank samples of DNA extraction reagents as a template.

Statistical Analysis

One-way analyses of variance were performed with clinical variables (age at onset, age when Mini-Mental State score fell below 23, and rate of cognitive decline) as dependent variables and number of

$\epsilon 4$ alleles (zero, one, or two) as the classification factor. To determine differences in clinical variables between the groups with familial and nonfamilial disease and between the groups with early and late onsets, two-tailed *t* tests were used.

RESULTS

There were no significant differences among the groups with zero, one, and two APOE $\epsilon 4$ alleles in mean rate of cognitive decline ($F=0.34$, $df=2$, 83 , $p>0.05$). Excluding subjects with an early onset and a family history ($N=16$) did not alter the results ($F=0.29$, $df=2$, 67 , $p>0.05$). Likewise, there were no significant differences among APOE dosage groups in mean reported age at onset ($F=0.29$, $df=2$, 83 , $p>0.05$) or mean age when Mini-Mental State score fell below 23 ($F=0.93$, $df=2$, 83 , $p>0.05$). Means and standard deviations of the clinical measures for the three groups are presented in table 1.

The largest contrast for rate of decline was between the combined groups with zero and one $\epsilon 4$ alleles and the group with two $\epsilon 4$ alleles. This yielded a small effect size of 0.23 (two-tailed 95% confidence interval, -0.29 to 0.74). For the age at which Mini-Mental State score fell below 23, the largest contrast was between the group with zero $\epsilon 4$ alleles and the combined groups with one and two alleles; the effect size was 0.21 (confidence interval, -0.22 to 0.63). For age at onset as reported by the caregiver, the largest contrast was again between the combined groups with zero and one $\epsilon 4$ alleles and the group with two alleles (effect size, 0.17; confidence interval, -0.35 to 0.69). For these effect sizes, to achieve even 70% power to detect a significant difference with a 5% two-tailed test would require more than 300 subjects per group.

We found no significant differences in the clinical measures between subjects with and without a family history of dementia or between subjects with early and late onsets. The mean slope of cognitive decline (in Mini-Mental State points per year) for the early-onset subjects was -4.2 ($SD=2.0$), whereas the mean slope for the late-onset subjects was -3.9 ($SD=2.7$). This difference did not reach statistical significance ($t=0.53$, $df=84$, $p>0.05$). For the subjects without a family history of dementia, the mean

TABLE 1. Relation Between Number of APOE $\epsilon 4$ Alleles and Clinical Measures for Subjects With Alzheimer's Disease

Number of $\epsilon 4$ Alleles	N	Rate of Decline (Mini-Mental State points/year) ^a		Age at Onset Reported by Caregiver (years)		Age at Which Mini-Mental State Score Fell Below 23 (years) ^a	
		Mean	SD	Mean	SD	Mean	SD
0	36	-3.9	2.6	65.3	8.4	67.9	7.9
1	32	-4.0	2.5	65.9	7.1	70.1	6.4
2	18	-4.5	2.0	64.3	6.2	68.1	6.3
Total group	86	-4.1	2.4	65.3	7.5	68.8	7.0

^aDetermined by linear regression for each subject (see text).

slope of cognitive decline was -3.9 ($SD=2.4$), whereas for the subjects with a family history the mean slope was -4.3 ($SD=2.5$). This difference did not reach statistical significance ($t=0.68$, $df=84$, $p>0.05$).

APOE allele frequencies are given in table 2. The frequencies for the total study group are similar to those found in other studies of subjects with Alzheimer's disease, demonstrating that the frequency of the $\epsilon 4$ allele among persons with Alzheimer's disease is higher than population frequencies (20, 21). Table 2 also shows allele frequencies for the subjects subdivided by family history and age at onset. There were no significant differences in allele frequencies between subjects with and without a family history of dementia ($\chi^2=0.01$, $df=2$, $p>0.05$) or between the subjects with early and late onsets ($\chi^2=1.01$, $df=2$, $p>0.05$).

DISCUSSION

Our results do not support the hypothesis that there is an association between the APOE $\epsilon 4$ allele and rate of decline or age at onset among patients with probable Alzheimer's disease. The results of some studies are at variance with these (22, 23), whereas some previous findings are concordant (24, 25). Clearly, one cannot prove the null hypothesis with a statistically nonsignificant result. If, in fact, there was truly no association between rate of decline and $\epsilon 4$ dosage, 5% of well-done studies would show statistically significant associations. However, given publication bias related to statistical significance, the results of those 5% would be more likely to be published, creating a false impression of a positive association. Thus, it is important to exam-

TABLE 2. Relation of Frequency of Apolipoprotein E Alleles to Family History and Age at Onset for Subjects With Alzheimer's Disease

Allele	Total (N=86)	Family History				Age at Onset (years)				
		Positive (N=28)		Negative (N=58)		≤65 (N=44)		>65 (N=42)		
		Frequency	Number of Chromosomes	Frequency	Number of Chromosomes	Frequency	Number of Chromosomes	Frequency	Number of Chromosomes	
$\epsilon 2$	0.035	6	0.036	2	0.035	4	0.034	3	0.036	3
$\epsilon 3$	0.570	94	0.057	32	0.569	66	0.534	47	0.607	51
$\epsilon 4$	0.395	63	0.393	22	0.397	46	0.432	34	0.357	30

ine results more carefully than merely noting whether they are statistically significant and to examine effect sizes and their confidence intervals.

Variation among the conclusions of studies arises in a number of ways. There may be sampling differences. For example, Frisoni et al. (22) examined only 28 late-onset cases, whereas in the present study the full range of Alzheimer's disease cases was examined and there were more than three times as many subjects. There may also be measurement problems. Retrospective report of age at onset, for example, may be quite unreliable and may reflect confounding factors, such as whether the caregiver lives with the patient, the relationship between them, and the sensitivity of the caregiver to early signs and symptoms. The last is of particular importance, for sensitivity to early signs and symptoms may itself be related to previous experience with Alzheimer's disease in the family. In the present study, retrospective report of age at onset was used but was checked against a data-based measure of onset.

Ceiling and floor effects are a problem (26-29). In this study, we chose to exclude the upper, relatively flat portion of the decline curve and the flat end-stage portion. We selected an upper limit of a Mini-Mental State score of 23 because this value is frequently used as a clinical threshold for evidence of dementia (10), and evidence supports the most rapid decline for patient cohorts in which the initial Mini-Mental State scores average between 10 and 16 (27, 28, 30, 31). If such ceiling and floor effects are ignored, as they frequently are, the observed rates of decline may underestimate the true rate of decline, and the observed variance may overestimate the true variance. This may be, for example, why the rates of decline in this study were greater than those reported for a similar population by Dal Forno et al. (23), who used similar methods. Moreover, when the intercepts differ widely, any correlation between intercept and slope may result in spurious findings on slopes. Matching subjects at the intercept (Mini-Mental State score of 23 at time 0) addresses that problem.

The present study was designed to deal with these methodological problems as well as is possible in a clinical setting, by using powerful analytic methods (32). Yet the overall result was that no statistically significant differences were found among subjects with differing numbers of $\epsilon 4$ alleles, and the sizes of the effects were at best small to moderate. Such small effects are unlikely to be of clinical significance, even if a larger study group could document them as statistically significant (33). Moreover, when we assessed previous studies, taking into account how each dealt with the methodological issues we have described, it appeared that the consensus of studies supports this overall assessment.

A lack of association between APOE genotype and rate of cognitive decline suggests that whereas the APOE $\epsilon 4$ allele increases the risk for developing Alzheimer's disease, it does not alter the rate at which clinical decline occurs. At first this seems surprising, since APOE $\epsilon 4$ dosage in Alzheimer's disease is correlated

with the number of neuritic plaques (25, 34, 35). Yet the number of plaques may not be correlated with the degree of cognitive impairment (36, 37). Therefore, the lack of association between APOE genotype and rate of decline is not necessarily at odds with previously reported associations between APOE genotype and neuropathologic data.

It is possible that some of our subjects with early-onset familial disease could carry presenilin 1 mutations (38). Because APOE $\epsilon 4$ has not been demonstrated to affect phenotype in presenilin-linked cases (39, 40), we performed a separate analysis of the effect of $\epsilon 4$ dosage on rate of decline after excluding the early-onset familial cases. However, the results of this analysis were the same as for the full study group.

Certain clinical features of Alzheimer's disease, such as extrapyramidal signs and psychiatric symptoms, have been shown to be associated with rate of cognitive decline (41, 42). These clinical features may be the result of the same underlying biological process that determines rate of overall cognitive decline, or the presence of emerging neuropsychiatric symptoms may actually be causative in the decrease in cognitive function. Patients with chronic concurrent medical conditions may also decline rapidly (43). Factors such as quality of daily care, nutrition, stability of living situation, coping skills of caregivers, and nursing home placement may also influence the rate of cognitive change in demented patients.

We found no association between APOE genotype and age at onset in Alzheimer's disease when using onset data obtained from caregivers and other ancillary sources. This finding is in agreement with the results of several other studies that included cases of sporadic Alzheimer's disease (7, 44-46). Further, a novel indicator for an important early milestone in the disease, the age at which the Mini-Mental State score declines past 23, also showed no relationship to $\epsilon 4$ dosage in the present study.

There has been debate recently over the role of APOE genotyping in diagnosis or prognosis in Alzheimer's disease (47, 48). Our results suggest that the APOE genotype is not useful in providing information on the rate at which a patient will decline once the disease is diagnosed. Additional studies will be required to clarify which dimensions of clinical variation in Alzheimer's disease, if any, are related to the APOE $\epsilon 4$ allele.

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Information on APA Periodicals at the 1997 Annual Meeting

The American Journal of Psychiatry and *Psychiatric Services* will be located in the APA Periodicals Exhibit in the APA Resource Center (Exhibit Halls A/B, Ground Level, Convention Center). Hours of operation: Saturday, May 17, 12 noon-6:00 p.m.; Sunday, May 18, 7:30 a.m.-6:00 p.m.; and Monday, May 19, through Wednesday, May 21, 10:00 a.m.-6:00 p.m.

Staff of both journals will be available to answer authors' questions and to receive papers submitted for publication. Each journal publishes only original material not published elsewhere in any form and not being considered for publication elsewhere. Five copies and a disk are required for *The American Journal of Psychiatry*; six copies are required for *Psychiatric Services*.

Persons who wish to contact editors or reporters of *Psychiatric News* should inquire at the APA Staff Office, located in Room 15B, Mezzanine Level, Convention Center, where an editor can be paged. They also may leave written announcements, suggestions for articles, or letters to the editor for the newspaper's consideration.