Apolipoprotein E genotype and rate of decline in probable Alzheimer's disease.

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Archives of neurology, 53(4)

0003-9942

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1996-04-01

10.1001/archneur.1996.00550040085017

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Peer reviewed
Apolipoprotein E Genotype and Rate of Decline in Probable Alzheimer’s Disease

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Background: The risk of Alzheimer’s disease (AD) appears to increase, and the age at onset to decrease, with the number of e4 alleles. If this relationship is due to increased rate of pathophysiological change, the presence of e4 would be expected to influence progression of disease, predicting a more rapid decline with increasing number of e4 alleles.

Objective: To determine if the frequency of the e4 allele of the apolipoprotein E (ApoE) gene affects the rate of clinical progression in AD.

Setting: Alzheimer’s Disease Research Center.

Subjects: One hundred one subjects meeting criteria of the National Institute of Neurological Disorders and Stroke for probable AD or of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) for definite AD; 78 of these subjects met the additional criterion of having a Mini-Mental State Examination score of at least 10 for analysis of rate of decline.

Measurements: The subjects’ characteristics and a neuropsychological battery, including the Mini-Mental State Examination, Spatial Delayed Recognition Span, Boston Naming Test, Category Fluency Test, and the Physical Capacity Subscale of the Psychogeriatric Dependency Rating Scale.

Design: The subjects were followed up longitudinally for approximately one decade. Medical histories were taken and physical and neurologic examinations and neuropsychological testing were performed every 6 months. Three and a half years of data were available for most tests and 5.5 for the Psychogeriatric Dependency Rating Scale; thereafter, patients were no longer testable. A general linear model analysis of variance was used to assess the influence of ApoE on demographic characteristics and baseline performances on neuropsychological measures. A random-effects regression model was used to predict change over time associated with presence of e4 on clinical and cognitive measures.

Results: The age at onset was greatest for the e4-heterozygous subjects and least for the e4-negative subjects. The heterozygous subjects declined more rapidly on the Mini-Mental State Examination and the Category Fluency Test than the subjects without the e4 allele or with e4 homozygosity. The homozygous subjects declined faster on only one subscale: the Physical Capacity subscale of the Psychogeriatric Dependency Rating Scale. Covarying for age at onset did not affect the results.

Conclusions: The ApoE genotype does not strongly influence the rate of decline in AD, implying that e4 might predispose to the development of the disease without accelerating its pathogenesis or progression. The effects of e4 on both age at onset and rate of decline need to be further investigated.

(Arch Neurol. 1996;53:345-350)

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The recent discovery of an overrepresentation of the e4 allele of the apolipoprotein E (ApoE) gene in Alzheimer’s disease (AD) has opened a whole new area of investigation and new hope for the discovery of at least one cause of AD. The gene coding for ApoE, a lipid transport protein, is located on chromosome 19 and has three alleles—e2, e4, and e3—the last being by far the most frequent. Almost 50% of sporadic cases of AD and more than 65% of late-onset familial cases carry the e4 allele, compared with approximately 20% in the normal population. The strength of this association, replicated by many groups, makes ApoE e4 the major genetic susceptibility factor thus far identified for AD. Furthermore, the risk of AD appears to increase, and the age at onset to decrease, with the number of e4 alleles carried by an individual.

It has been postulated that ApoE e4 plays a role in the pathogenesis of AD either by influencing the rate or amount of amyloid deposition in the brain or by promoting neurofibrillary tangle formation. Regardless of mechanism, ApoE allele e4 affects sporadic and late-onset fa-
SUBJECTS AND METHODS

SUBJECTS

Between November 1984 and March 1987, the ADRC enrolled for longitudinal study 209 patients who met the criteria of the National Institute of Neurological Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association for probable or possible AD. Medical history, neuropsychological evaluation, neurological and psychiatric examinations, and appropriate laboratory studies constituted the initial evaluation for entry into the ADRC. Exclusion criteria were current or past history of major mental illness, current alcohol or drug abuse, or central nervous system disorder (e.g., stroke, epilepsy, severe traumatic brain injury, or Parkinson’s disease). Extrapyramidal signs insufficient to diagnose Parkinson’s disease or marked behavioral disturbance did not exclude entry into the study. Procedures were fully explained to the patients and their guardians, and informed consent was obtained before enrollment. At each semiannual visit to the ADRC, interim histories were taken and neurologic examination and neuropsychological evaluations were repeated. This information was used to monitor each patient’s disease course and to determine whether clinical diagnoses should be reconsidered.

Patients were eligible for the present study if they were given the diagnosis of probable AD at study entry and at each subsequent semiannual evaluation, (2) met the criteria of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) for definite AD (if an autopsy was performed), and (3) had DNA available from fresh blood samples or frozen brain tissue. A total of 101 patients met the above criteria. Thirty-two percent were male and 90% were white. The average education of the subjects was 12.9 years, and 55% of the patients had a family history of dementia. The mean age at onset was 65.6 years, with an average illness duration of 4.1 years and a mean Mini-Mental State Examination (MMSE) score of 14.7 at entry. For analysis of the influence of ApoE genotype on rate of decline, the subjects had to meet the additional criterion of having an MMSE score of at least 10 at study entry. Seventy-eight patients (35% male and 88% white, with an average education of 13 years) met this additional criterion; 53% of these 78 patients had a family history of dementia. The mean age at onset was 66.1 years, with 3.6 years of illness and a mean MMSE score of 17.0 at entry.

PROCEDURES

Clinical and cognitive data collected during semiannual visits were used to define illness progression. The following measures had sufficient and necessary longitudinal data for assessing rate of decline: MMSE, Spatial Delayed Recognition Span, Boston Naming Test, Category Fluency Test (cities, animals, and foods), and Physical Capacity subscale of the Psychogeriatric Dependency Rating Scale (PGDRS). We did not consider several other measures. Longitudinal data on the Block Design subscale of the Wechsler Adult Intelligence Scale–Revised were not available because the test was given only at baseline and not administered to patients with a MMSE score under 15. Two other scales from the PGDRS also were not included in assessing the rate of illness progression. The Behavior Disorder scale was not used because scores do not increase monotonically across the illness; eg, behavioral disturbance would decrease with neuroleptic therapy and at end-stage of the illness.

Of the 101 patients with AD who were genotyped, 14 (13.9%) were homozygous for the ApoE ε4 allele, 56 (55.4%) were heterozygous (ε3/ε4 or ε2/ε4), and 31 (30.7%) had no ε4 alleles. The frequencies of the alleles are presented in Table 1. The baseline characteristics of the patients by number of ε4 alleles are listed in...
ness. The Orientation scale of the PGDRS was also not used because many patients were placed in nursing homes during the course of the study. The decision for institutional care often is based on families' social circumstances as much as on level of dementia. All the measures described above were used to compare baseline scores of groups of patients defined by ApoE genotype.

GENOMIC TESTING

Genomic DNA was extracted from white blood cells in living patients and from frozen or fixed brain tissue in autopsy cases. The ApoE genotyping was conducted according to the method of Hixson and Vernier. 33 Briefly, the DNA region of interest was amplified by polymerase chain reaction with primers F4 and F6 and then digested with the HhaI restriction enzyme. Digestion products were separated on 3% agarose gel (NuSieve, FMC Bioproducts, Rockland, Me), stained with ethidium bromide, and visualized and photographed under UV illumination. The pattern of migration of the digestion fragments is indicative of ApoE genotype.

STATISTICAL ANALYSIS

Random-effects regression models 34 were used to predict the change in clinical and cognitive measures associated with the presence of ApoE e4 over time. Each regression equation included a random intercept term for the individual's performance on the outcome variable at baseline, a covariate (ApoE genotype), visit number, and a term representing the interaction between the visit number and the covariate. A significant interaction term indicates that ApoE genotype significantly predicted the change in the outcome measure over time. The random-effects regression models were fit using SAS (Statistical Analysis System). 35 Separate equations were computed to assess the influence of ApoE genotype on rate of decline on each outcome variable.

Because our statistical model assumes linear change, data on each measure were considered from study entry until a "floor" was achieved. For the MMSE, scores were no longer considered after the first score of 5. For the Physical Capacity subscale of the PGDRS, scores were no longer considered after the first score of 32 or more (maximum score is 36, indicating complete physical disability and total sensory impairment). For the Category Fluency Test, scores were no longer considered after the first total score of 2 (indicating zero items generated for one or two categories). For the Delayed Spatial Recognition Span, scores were no longer considered when the average of three trials was less than 1. There were no apparent floor constraints for the Boston Naming Test.

Thus, the data considered likely capture a phase of the disease during which decline is linear, even though decline across the entire illness may be nonlinear. 36 Furthermore, a previous investigation of a subset of ADRC patients that a linear model of decline provides the best fit to their longitudinal data on the MMSE. 37

Each subject had on average 6.3 observations for the MMSE (range, 1 to 14), 6.4 for the Delayed Spatial Recognition Span (range, 1 to 14), 6.1 for the Category Fluency Test (range, 1 to 15), 7.1 for the Boston Naming Test (range, 2 to 15), and 11.6 for the PGDRS Physical Capacity subscale (range, 2 to 18).

Finally, ApoE genotype was added to the multivariate model of predictors of decline in MMSE score in our previous study. 24 This was done to assess the predictive strength of ApoE genotype in relation to other predictor variables.

Table 2. At study entry, the three subgroups (e4/e4, e3/e4 or e2/e4, and no e4) were similar in all respects except for estimated age at onset of symptoms. Age at onset of symptoms was greatest among the group heterozygous for e4 (mean age, 67.2 years), followed by the group homozygous for e4 (mean age, 65.4 years) and the e4-negative group (mean age, 62.4 years). It is of note, however, that the mean age at onset was relatively early in all three patient groups.

Because the presence of ApoE e4 has been associated with late-onset familial and sporadic AD, but not early-onset familial AD, we also evaluated the characteristics of the three subgroups, excluding patients with disease onset before the age of 60 years 2 to eliminate potential early-onset familial cases. In these subjects, the age at onset was greatest among the group homozygous for e4 (70.5 years), followed by the group heterozygous for e4 (70.1 years) and the e4-negative group (68.6 years).

Seventy-eight of the 101 genotyped patients met criteria for the analysis on rate of decline. To determine whether these subjects differed from the rest of the cohort, we compared baseline characteristics. Since one criterion for this study was an MMSE score of 10 or more, these subjects had significantly higher MMSE scores at entry and had been ill for a shorter time (Table 3), suggesting that individuals who were eliminated from the analysis because of their low MMSE scores were similar except that more time had elapsed since the onset of the disease. Thus, they did not have a more rapid rate of decline.

Table 4 lists the rates of decline by ApoE genotype as estimated by random-effects regression models. Patients with one ApoE e4 allele declined more rapidly on the MMSE and the Category Fluency Test than those with no e4 alleles. Patients homozygous for e4 declined more rapidly on the Physical Capacity subscale of the PGDRS. Because the groups differed in terms of age at onset, and because earlier age at onset has been found to predict more rapid illness progression, we also performed random-effects regressions covarying for age at onset. The findings remained significant.

Presence of ApoE e4 was added to the final model of predictors of rate of MMSE decline derived in a previous study of this cohort through the use of backward stepwise multiple regression. 24 Variables in this model were handedness, education, family history of dementia, and performance on the Boston Naming Test, the Golfin Incomplete Figures Test, Block Design, the Benton Visual Retention Test, and the Responsive Naming Test. The equation was similar in the present sample, but not completely replicated. The ApoE variable was not significant when considered simultaneously with the variables previously found to predict rate of decline. Because a family history of dementia and ApoE genotype
could be related, we also examined the effects of $e4$ after eliminating family history from the model. Again, the presence of ApoE $e4$ did not predict rate of decline. The ApoE genotype did not emerge as a significant factor in this model when entered as a dichotomous variable (ie, $e4$ positive vs $e4$ negative) or a trichotomous variable (ie, no, one, or two $e4$ alleles).

In AD, as in many dementia syndromes, clinical variability is the rule rather than the exception. Variations in age at onset, earliest symptoms, pattern of cognitive and functional impairment, presence of psychiatric and neurologic complications, and rate of decline are pronounced. Many researchers in the field have therefore suggested that AD is not a single disease but a clinical syndrome caused by many, possibly interacting, diseases with distinct pathogenetic mechanisms resulting in a relatively uniform histopathologic appearance.\(^{36,50}\)

Undoubtedly, the findings on ApoE in AD have suggested new perspectives in the search for causative factors and pathogenetic mechanisms. The role of other putative causative factors (eg, head injury,\(^{40-43}\) family history of Down's syndrome,\(^{34}\) maternal age at birth,\(^{45,46}\) exposure to toxins and metals,\(^{47,48}\) lack of education,\(^{49-52}\) and age\(^{53}\)) may need to be revisited in light of the ApoE genotype findings.

Several hypotheses on the mechanism of $e4$ as an etiologic agent in AD have been posed,\(^{1,2,15}\) but none is completely satisfactory at this point. If we believe that the clinical picture of AD is the result of a gradual accumulation of pathologic changes in the central nervous system (whatever these might be), we could hypothesize that a gene might continue operating over time, producing more and more of these changes and leading to increasing severity of disease. This would be particularly true for a genetic factor such as $e4$, which may have its greatest influence in long-lived individuals. If $e4$ causes earlier age at onset of AD by means of faster accumulation of histopathologic changes that lead to clinical symptoms, it might also result in a more rapid rate of decline. In addition, it could be hypothesized that this rate would be even faster in individuals homozygous for $e4$, consistent with the gene-dose effect and earlier age at onset.

**Table 1. Apolipoprotein E Allelic Frequency for 101 Patients With Alzheimer's Disease**

<table>
<thead>
<tr>
<th>Allele Type</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>$e2$</td>
<td>7</td>
<td>3.5</td>
</tr>
<tr>
<td>$e3$</td>
<td>111</td>
<td>54.9</td>
</tr>
<tr>
<td>$e4$</td>
<td>84</td>
<td>41.6</td>
</tr>
<tr>
<td>Total</td>
<td>202</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 2. Baseline Characteristics of 101 Patients With Alzheimer's Disease by Number of Apolipoprotein E (ApoE) $e4$ Alleles**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No ApoE $e4$ Allele (n=31)</th>
<th>One ApoE $e4$ Allele (n=56)</th>
<th>Two ApoE $e4$ Alleles (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>39</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Family history of dementia, %</td>
<td>43</td>
<td>58</td>
<td>64</td>
</tr>
<tr>
<td>White, %</td>
<td>87</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>Years of education</td>
<td>12.7 (4.1)</td>
<td>12.6 (4.2)</td>
<td>13.3 (2.9)</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>62.4 (8.8)</td>
<td>67.2 (7.7)</td>
<td>65.4 (10.7)</td>
</tr>
<tr>
<td>Years ill</td>
<td>4.0 (2.4)</td>
<td>4.2 (2.2)</td>
<td>4.4 (2.3)</td>
</tr>
<tr>
<td>MMSE</td>
<td>15.3 (5.8)</td>
<td>14.3 (6.2)</td>
<td>14.9 (3.8)</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>14.3 (8.7)</td>
<td>13.6 (8.8)</td>
<td>17.5 (7.5)</td>
</tr>
<tr>
<td>Category Fluency</td>
<td>14.4 (9.3)</td>
<td>14.6 (10.3)</td>
<td>17.9 (9.2)</td>
</tr>
<tr>
<td>Spatial Recognition Span</td>
<td>3.7 (2.3)</td>
<td>3.9 (2.3)</td>
<td>3.4 (2.0)</td>
</tr>
<tr>
<td>Block Design</td>
<td>4.2 (7.4)</td>
<td>7.0 (8.8)</td>
<td>3.7 (6.0)</td>
</tr>
<tr>
<td>PGDRS Physical Capacity</td>
<td>4.3 (5.4)</td>
<td>4.0 (3.8)</td>
<td>4.8 (3.7)</td>
</tr>
<tr>
<td>Behavior Disorder</td>
<td>4.0 (2.5)</td>
<td>2.8 (3.7)</td>
<td>4.0 (4.5)</td>
</tr>
<tr>
<td>Orientation</td>
<td>1.5 (1.7)</td>
<td>1.7 (1.5)</td>
<td>1.8 (1.8)</td>
</tr>
</tbody>
</table>

*Values other than percentages are expressed as mean (SD). MMSE indicates Mini-Mental State Examination; PGDRS, Psychogeriatric Dependency Rating Scale.

*P < .05.

**Table 3. Baseline Characteristics of All 131 Patients From the Initial ADRC Cohort Not Included in the Analysis of Rate of Decline and the Subset of 78 Patients Meeting All Inclusion Criteria (MMSE Score at Entry of 10 or More), for Rate of Decline Analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Not Meeting Inclusion Criteria (n=131)</th>
<th>Patients Meeting Inclusion Criteria (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>42.0</td>
<td>34.6</td>
</tr>
<tr>
<td>Family history of dementia, %</td>
<td>45.9</td>
<td>53.3</td>
</tr>
<tr>
<td>White, %</td>
<td>86.3</td>
<td>88.5</td>
</tr>
<tr>
<td>Years of education</td>
<td>12.5 (3.3)</td>
<td>13.0 (4.0)</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>66.0 (8.2)</td>
<td>66.1 (8.6)</td>
</tr>
<tr>
<td>Years ill</td>
<td>4.3 (2.7)</td>
<td>3.6 (1.9)†</td>
</tr>
<tr>
<td>MMSE</td>
<td>13.2 (6.4)</td>
<td>17.0 (4.0)†</td>
</tr>
</tbody>
</table>

*Values other than percentages are expressed as mean (SD). ADRC indicates Alzheimer's Disease Research Center; MMSE, Mini-Mental State Examination.

†P < .05 when compared with rest of cohort.

‡P < .01 when compared with rest of cohort.

**Table 4. Rate of Decline on Neuropsychological Measures in Patients With Alzheimer's Disease by Number of Apolipoprotein E (ApoE) $e4$ Alleles**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No ApoE $e4$ Allele (n=25), Points</th>
<th>One ApoE $e4$ Allele (n=41), Points</th>
<th>Two ApoE $e4$ Alleles (n=12), Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>2.59 (P &lt; .001)</td>
<td>3.08 (P &lt; .001)</td>
<td>2.76 (P &lt; .001)</td>
</tr>
<tr>
<td>Spatial Recognition Span</td>
<td>0.70 (P &lt; .001)</td>
<td>0.85 (P &lt; .001)</td>
<td>0.62 (P &lt; .001)</td>
</tr>
<tr>
<td>Category Fluency</td>
<td>3.60 (P &lt; .001)</td>
<td>4.08 (P &lt; .001)</td>
<td>4.28 (P &lt; .001)</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>3.61 (P &lt; .001)</td>
<td>3.18 (P &lt; .001)</td>
<td>3.20 (P &lt; .001)</td>
</tr>
<tr>
<td>PGDRS Physical Capacity</td>
<td>4.02 (P &lt; .001)</td>
<td>4.04 (P &lt; .001)</td>
<td>4.59 (P &lt; .001)</td>
</tr>
</tbody>
</table>

*The rate of decline is expressed in points per year. MMSE indicates Mini-Mental State Examination; PGDRS, Psychogeriatric Dependency Rating Scale.

†P < .05 when compared with no ApoE $e4$.

‡P < .01 when compared with no ApoE $e4$.\(^{1,2,15}\)
Alternatively, ApoE could be influencing age at onset in AD by virtue of a mechanism other than progressive accumulation of lesions. For example, ApoE may interact at a given point in time with other etiologic factors (e.g., head trauma, other genes, and environmental factors), triggering a cascade of neurodegenerative effects that subsequently continue independently of ApoE genotype.

Our study represents one of the largest investigations of ApoE and rate of decline in AD. The size of the sample, together with the extended (10-year) follow-up of patients, is unique. In this study, ApoE genotype did not relate significantly to clinical characteristics of patients at baseline, and only very small trends for more severe disease could be identified from the MMSE and the Category Fluency Test. The scores of the patients with one ApoE ε4 allele declined more rapidly on the MMSE and the Category Fluency Test than did those of the patients with no ε4 alleles. On the other hand, this effect was not found in patients with two “doses” of the implicated gene. In these patients, rate of change in physical capacity was more rapid than in subjects without an ε4 allele, but was not significantly different in the heterozygous individuals. Although these findings are statistically significant, the differences between the groups in rate of decline were not consistent or large and there was no gene-dose effect. Furthermore, ApoE ε4 was not a significant factor when included in a multivariate model with other variables previously found to predict rate of decline in this cohort. Thus, other variables, such as family history of dementia or pattern of cognitive impairment, appear to account for more of the variance in the rate of decline in MMSE scores in AD than does ApoE genotype.

The results of this study are far from excluding the possibility of an effect of ε4 on rate of decline. In a disease often spanning decades, a 10-year follow-up period might not represent a sufficiently long interval to detect a small effect that is dispersed over the course of time or perhaps evident at the earliest stages of the disease. It is possible, therefore, that ε4 has a small but consistent effect that our period of study did not allow us to detect. In support of this hypothesis, our measures of global cognitive and functional impairment, probably most sensitive to overall decline, did show a small but significant relationship to ApoE genotype.

Although we could not demonstrate a gene-dose effect, there were only a small number of ε4 homozygous individuals in our sample, limiting our statistical power. Study of a much larger sample of homozygous patients would be necessary to arrive at a more definitive conclusion.

Study of the baseline characteristics of our patients did not confirm earlier age at onset with increasing doses of ε4. In fact, we found a trend in the opposite direction. In particular, the group of patients heterozygous for ε4 had an older age at onset, while the youngest age at onset was seen in patients with no ε4 alleles. This trend remained after patients with symptom onset before the age of 60 years were eliminated. The cutoff point of 60 years of age was chosen so that we could compare our results with those of the seminal study in which gene-dose effects of ε4 on age at onset were first demonstrated. We note, however, that the finding of an effect of ε4 on age at onset has not been universally replicated. Indeed, the results of at least two other studies, those of Duara et al and, most notably, Corder et al (1995), fail to confirm this finding.

Several methodological limitations of our study are acknowledged. First, our sample comes from a referral-based population through geriatric neurology and neuropsychiatry clinics. It was mainly composed of whites with a higher-than-average education who also tend to have more dedicated spouses or caregivers than do patients in population-based studies. In addition, while many studies use the date of diagnosis of dementia to define the onset of disease, we used the time of onset of symptoms, as established retrospectively with highly reliable methods, as our disease-onset date. This way to determine age at onset might also contribute to the younger ages of our subjects compared with the subjects of other studies.

Except for mean age at onset, our sample appeared to be typical of AD cohorts, including the frequency of the ApoE ε4 allele. Our cohort did not include more cases with a family history of dementia than other studies; therefore, it is unlikely that earlier age at onset is the result of “contamination” with a high number of early-onset familial AD cases, in which other genetic causes may be implicated.

In summary, the effect of ε4 on both age at onset and rate of decline needs further investigation. If replicated, the overall finding of minimal effect on clinical progression might suggest that the presence of ε4 affects development of AD by mechanisms other than the progressive accumulation of histopathologic lesions. Significant methodological difficulties in the longitudinal study of AD complicate the evaluation of rate of decline. We look forward to additional studies of ε4 and clinical variability in AD, which will contribute to our understanding of possible pathogenetic mechanisms related to this recent exciting genetic discovery.

Accepted for publication December 16, 1995.

This study was supported in part by grants AG08325 and AG05146 from the National Institute on Aging, Bethesda, Md, and by grants from the Alzheimer's Association (Dr Troncoso), the Charles A. Dana Foundation, New York, NY, and the Develbiss Fund, Baltimore, Md.

The authors sincerely thank Pamela Talalay, PhD, for her editorial advice.

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ARCH NEUROL/VOL. 53, APR 1996
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