



# NEUROLOGY

Copyright © 1996 American Academy of Neurology Volume 47(2), August 1996, pp 444-448  
Apolipoprotein E genotype does not influence rates of cognitive decline in Alzheimer's disease  
[Articles]

Growdon, J.H. MD; Locascio, J.J. PhD; Corkin, S. PhD; Gomez-Isla, T. MD PhD; Hyman, B.T. MD PhD

From the Department of Neurology (Drs. Growdon, Locascio, Gomez-Isla, and Hyman), Massachusetts General Hospital and Harvard Medical School, Boston, and the Department of Brain & Cognitive Sciences and the Clinical Research Center (Drs. Locascio and Corkin), Massachusetts Institute of Technology, Cambridge, MA.

Supported by P50 AG05134 (J.H.G., J.J.L., T.G-I., B.T.H.), and EG12406 (B.T.H.). S.C. was supported by AG06605 and AGNS08117.

Received August 31, 1995. Accepted in final form December 1, 1995.

Address correspondence and reprint requests to Dr. John H. Growdon, Massachusetts General Hospital, WAC 830, Boston, MA 02114.

## Abstract

**Background:** Inheritance of the apolipoprotein E (apoE) epsilon 4 allele is a risk factor for developing Alzheimer's disease (AD) and is associated with a lower age of dementia onset. The purpose of this study was to determine whether apoE genotypes differentially influence the course of cognitive decline in AD dementia. **Methods:** We administered nine cognitive tests that assessed explicit memory, attention, language, visuospatial function, frontal-lobe function, and logical reasoning abilities to 66 probable AD patients every 6 to 24 months over a span of up to 5.5 years. We identified apoE genotype by a PCR-based method; there were 16 patients with epsilon 3/3, 34 with epsilon 3/4, and 16 with epsilon 4/4. Using regression statistical methods, we computed the change in performance for each test for each patient over time. We then analyzed the mean change in each test in patients grouped according to apoE genotype. **Results:** For the AD patients as a group, performance on all cognitive tests declined significantly over time, but the rate of decline did not vary significantly across apoE genotypes on any cognitive test. Specifically, the rate of cognitive decline was not faster in patients with an epsilon 4 allele than in those with epsilon 3/3. **Conclusions:** These results indicate that the mechanism placing individuals with an epsilon 4 allele at risk for developing AD does not influence the rate of cognitive decline. These observations imply that the influence of apoE epsilon 4 either precedes or occurs at an early point in the AD disease process.

A strong association exists between apolipoprotein E (apoE) genotypes and Alzheimer's disease (AD). The three common alleles of the apoE gene are epsilon 2, epsilon 3, and epsilon 4, with allele frequencies in the general population of approximately 0.08 for epsilon 2, 0.78 for epsilon 3, and 0.14 for epsilon 4. [1,2] The frequency of the epsilon 4 allele is increased three- to fourfold in late-onset familial and sporadic AD. [3-7] Further, among patients with AD, those with the epsilon 4 allele have a younger age at dementia onset than those with either the epsilon 2 or epsilon 3 alleles. [3,7] Some, [8,9] but not all, [10] studies found that the epsilon 2 allele is underrepresented in AD and may protect against developing AD, or at least delay its onset. [9] It is still uncertain, however, whether specific apoE genotypes influence any clinical aspects of AD other than age at dementia onset. In a previous study, [11] we found that AD patients' scores on a mental status examination and on an activities of daily living questionnaire were not related to the apoE genotype.

The purpose of the present study was to investigate whether the presence of different apoE alleles in AD affected specific cognitive functions or rates of cognitive decline differently. We sought to answer two questions. First, does the pattern of sparing and loss in specific cognitive functions differ across apoE alleles? Second, do AD patients grouped by apoE genotype differ in the rate of cognitive decline? The density of amyloid plaques in the brains of AD patients with an epsilon 4 allele is significantly greater than that in the brains of AD patients with other genotypes. [5,12] This finding raises the possibility that AD patients with an epsilon 4 allele have a more rapid rate of decline than AD patients with other genotypes. To address these questions, we identified the apoE genotype in 66 probable AD patients who annually took a set of tests that measured a broad range of cognitive functions.

## Methods.

### Subjects.

We examined 66 patients (37 women and 29 men) with a clinical diagnosis of probable AD. [13] These patients were part of a longitudinal behavioral study in which we analyzed the sensitivity and specificity of different cognitive tests in diagnosing, staging, and tracking the progression of AD. [14] Of the 123 AD patients in the longitudinal study, we could obtain apoE genotypes in 66; data from all 66 were included in the current study. Without knowledge of test-score performance, we performed apoE genotyping using blood or brain tissue by a polymerase chain reaction-based method. [5] There were 16 patients with apoE epsilon 3/3, 34 with apoE epsilon 3/4, and 16 with apoE epsilon 4/4 genotypes [Table 1](#). At the time of initial examination, the three groups did not differ significantly in gender distribution, age, age at AD onset, educational level, score on the Information, Concentration, Memory section of the Blessed Dementia Scale (IMC-BDS), [15] or score on the Activities of Daily Living (ADL) questionnaire. [16] In large AD population studies, the epsilon 4 allele was associated with lower age at dementia onset. [3,7] To observe this effect apparently requires a large sample size, however, because it

was not observed in our small sample or in another sample of 64 patients reported by Kurz et al. [17] There was a marginally significant increase in duration of illness ( $p = 0.057$ ) from the epsilon 3/3 group (mean 2.4 +/- 0.2 SEM years) to the epsilon 3/4 group (3.4 +/- 0.4 years) to the epsilon 4/4 group (4.1 +/- 0.7 years). Analyses of initial level of performance and rate of change were adjusted for duration of illness. Of the 66 patients, 11 have died. An autopsy was performed in 10, and the diagnosis of AD was confirmed neuropathologically in all ten.

## Graphic

[Table 1](#). Clinical characteristics of 66 AD patients according to apoE genotype (means and standard deviations)

---

### Cognitive tests.

Each patient completed nine cognitive tests [18-23] that assessed explicit memory, attention, language, visuospatial function, frontal-lobe function, and logical reasoning abilities. [14] All cognitive tests were scored on a numeric scale with high scores indicating proficiency and low scores impairment. The tests were administered on an annual basis. Twenty-seven patients had two examinations, 27 had three examinations, 7 had four examinations, 2 had five examinations, and 3 had six examinations. The mean interval between cognitive test sessions ranged from 0.8 +/- 0.2 SD to 1.2 +/- 0.5 years.

### Data analysis.

Using regression methods, we analyzed the rate of deterioration in performance for each cognitive test, for all patients as a group, and for each apoE genotype. Specifically, a separate regression analysis was conducted for each subject for each cognitive test where scores for the test were regressed on time since initial testing for that patient. The coefficient from each such regression was considered an estimate of rate of change for that patient for that cognitive test. The estimate was then used as the dependent variable score for that patient for that test and examined in relation to apoE groups and other covariates, such as age at onset, duration of illness, and initial test scores (analysis of covariance [ANCOVA]). This method is superior to computing rate as last minus first test score divided by time because it uses all available scores for an individual to estimate his or her rate of change. Not all cognitive tests could be conducted at all test sessions for each patient; only individuals with scores from at least two test sessions were included in any analysis for a given cognitive test. The number of patients in each analysis ranged from 63 (for Delayed Story Recall) to 32 (for Mental Rotation).

### Results.

#### Initial level of cognitive impairment.

Initial cognitive test scores were comparable across AD patients grouped according to apoE genotype [Table 2](#). On no cognitive test was there evidence, after adjusting for covariates and multiple significance tests, that having a specific allele relatively spared or worsened cognitive functions. This observation

indicates that apoE alleles do not exert differential effects on specific cognitive functions.

### Graphic

[Table 2](#). Apolipoprotein E genotype did not affect cognitive test scores at initial examination (initial score means and standard error of the means)

Rate of change in cognition.

For all AD patients combined, test scores declined over time; the overall mean rate of change was in a negative direction (significantly less than 0 [ $p < 0.05$ ]) for each cognitive test. Although AD patients as a group deteriorated on all nine tests, for no cognitive test was there a significant difference in the mean rate of decline across the three apoE groups [Figure 1](#). In order to assess whether nonsignificant findings were actually due to small effects as opposed to insufficiently large sample sizes, we calculated the proportion of variance of rates for each cognitive test due to apoE group. The effect of apoE genotype was small and accounted for only 0.6 to 9.6% of the variance in rate of decline, depending upon the individual test. These calculations indicate that regardless of the number of patients examined, factors other than apoE genotype accounted for more than 90% of variability in rate of cognitive test score decline.

### Graphic

[Figure 1](#). Box-whisker plots displaying distributions of rate coefficients for AD patients grouped by apoE genotype, for the nine cognitive tests. In a box-whisker plot, the bottom edge of the box is at the 25th percentile, and the top edge of the box is at the 75th percentile, with whiskers extending as far as the data extend, up to 1.5 interquartile ranges from the box; more extreme values up to 3 interquartile ranges are indicated with a circle, and scores even more extreme with a solid circle. The central horizontal line represents the sample median. Scores on all tests declined significantly ( $p < 0.05$ ) over time, but rates did not differ across AD patients grouped by apoE genotype.

Additional analyses were adjusted by covariates, including the initial test score, duration of illness at the initial test date, age at onset of illness, and number of years during which the tests were administered (ANCOVA). None of these analyses revealed significant apoE effects. Further, there were no significant gender differences in mean rates of decline for any cognitive test nor any significant interaction between gender and apoE group.

Discussion.

The present study is the first to examine the clinical consequences of inheriting different apoE alleles on specific cognitive functions and their rates of decline in AD patients. We found that apoE genotype did not differentially affect the severity of impairment at baseline testing on any of nine cognitive tests, nor

the rate of decline in performance on those tests. The following discussion focuses first on the pattern of cognitive impairment, then on rate of cognitive decline.

We deliberately conducted a finer-grain analysis of cognitive function than an estimate based upon a mental status examination. In a separate study [14] we found that AD patients as a group were impaired on all nine of these tests compared with nondemented control subjects. The results also showed that measures of delayed recall were the most sensitive tests in distinguishing AD patients from control subjects, and that other tests, especially the Boston Naming and Verbal Fluency tests, were best for tracking the course of cognitive decline. Even with this broad spectrum of tests, our analyses revealed no differences among apoE groups in scores at baseline testing. This finding indicates that different patterns of sparing and loss of cognitive capacities in AD are not a function of apoE genotype. A more likely explanation for between-subject variability in test performance is differences in the distribution of neuronal loss. For example, studies in our laboratory have demonstrated that the presence and severity of visual deficits are variable in the AD population. [24-26] The heterogeneity of visual function likely reflects individual differences in the regional distribution of neuropathologic changes in extrastriate cortex. Anatomic evidence of variability among subjects in the density of neurofibrillary tangles in discrete cortical areas [27] is consistent with the irregular pattern of dysfunction.

Although the biological basis for the association between apoE and AD remains unknown, having an epsilon 4 allele increases the amount of amyloid deposited in the AD brain. [5,12] Under certain experimental conditions in animals, amyloid appears to be neurotoxic and can induce neuronal degeneration with neurofibrillary changes. [28,29] A similar effect may occur in AD [30] and could initiate or speed the dementia process. [31] We therefore questioned whether AD patients with an epsilon 4 allele have a more malignant course of cognitive deterioration than patients with other alleles. Our data rejected this possibility; all test scores declined significantly over time, but there were no differences in the rates of decline for any test according to apoE genotype. These data support and extend our previous finding [11] that apoE genotype did not influence rate of decline on global measures of dementia severity--the IMC of the BDS, and the ADL. In that study, we analyzed data from 153 AD patients who underwent biannual examinations over 31.8 months (SD +/- 18.7). Mean IMC-BDS scores worsened by 3.5 points per year and ADL scores by 10.6% per year for the group as a whole. Rates of change were similar for groups based upon apoE genotype. Our findings are also consonant with those of Kurz et al. [17] and Asada et al., [32] who found that rates of cognitive decline in AD did not differ between AD patients with and without an epsilon 4 allele.

Our findings conflict with those of Frisoni et al., [33] who reported that the rate of progression as judged by Mini-Mental State Examination (MMSE) scores and CDR ratings decreased significantly with increasing epsilon 4 gene dose. The study of Frisoni et al. differed from ours in several ways that could account for the divergent conclusions. First, their patients were on average more than a decade older than ours (80.7 vs. 68.7 years) and less well educated (5.1 vs. 14 years). Whether age, education, or other risk factors for AD interact with apoE status to influence rate of progression is unknown. Second, their study was a retrospective analysis of data, in which the baseline MMSE score was estimated by regression techniques; ours was a prospective study in which all test scores were based on actual

performance. We believe that analyses using actual test scores capture the true rate of progression more accurately than analyses that use estimates. Third, Frisoni et al. observed their patients for a mean duration of 1 year; we tested patients repeatedly for up to 5.5 years with a mean of 2 years. Because the course of AD in individual patients can be variable, long periods of observation are better than short periods for documenting the rate of progression. [34,35] Fourth, their report was based upon global measures of dementia severity, whereas our study measured specific cognitive functions.

In our study, apoE genotype did not exert an effect on cognition or rate of cognitive decline as measured by any of the nine tests, even on those language tests (i.e., naming and fluency) that are most sensitive to dementia progression. We conclude therefore that knowing the apoE genotype alone does not support predictions about the rate of cognitive decline in AD patients. This observation implies that the influence of apoE epsilon 4 either precedes or occurs at an early point in the AD disease process. ApoE epsilon 4 may be a risk factor for AD, but exerts no effect on cognition once the disease begins.

## REFERENCES

1. Mahley RW. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science* 1988;240:622-630. [\[Context Link\]](#)
2. 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. [\[Context Link\]](#)
3. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993;43:1467-1472. [\[Context Link\]](#)
4. Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S. Apolipoprotein E polymorphism and Alzheimer's disease. *Lancet* 1993;342:697-699. [\[Context Link\]](#)
5. Rebeck GW, Reiter JS, Strickland DK, Hyman BT. Apolipoprotein E in sporadic Alzheimer's disease: allelic variation and receptor interactions. *Neuron* 1993;11:575-580. [\[Context Link\]](#)
6. Tsai M-S, Tangalos EG, Petersen RC, et al. Apolipoprotein E: risk factor for Alzheimer's disease. *Am J Hum Genet* 1994;54:643-649. [\[Context Link\]](#)
7. 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. [\[Context Link\]](#)
8. Corder EH, Saunders AM, Risch NJ, et al. Apolipoprotein E type 2 allele decreases the risk of late-onset Alzheimer disease. *Nat Genet* 1994;7:180-184. [\[Context Link\]](#)

9. West HL, Rebeck GW, Hyman BT. Frequency of the apolipoprotein E epsilon 2 allele is diminished in sporadic Alzheimer disease. *Neurosci Lett* 1994;175:46-48. [\[Context Link\]](#)
10. van Duijn CM, de Knijff P, Wehnert A, et al. The apolipoprotein E epsilon 2 allele is associated with an increased risk of early-onset Alzheimer's disease and a reduced survival. *Ann Neurol* 1995;37:605-610. [\[Context Link\]](#)
11. Gomez-Isla T, West HL, Rebeck GW, et al. Clinical and pathological correlates of apolipoprotein E epsilon 4 in Alzheimer's disease. *Ann Neurol* 1996;39:62-70. [\[Context Link\]](#)
12. Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci USA* 1993;90:1977-1981. [\[Context Link\]](#)
13. 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. [\[Context Link\]](#)
14. Locascio J, Growdon JH, Corkin S. Cognitive test performance in detecting, staging, and tracking Alzheimer's disease. *Arch Neurol* 1995;52:1087-1099. [\[Context Link\]](#)
15. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry* 1968;114:797-811. [\[Context Link\]](#)
16. Weintraub S. The record of independent living: an informant-completed measure of activities of daily living and behavior in elderly patients with cognitive impairment. *Am J Alzheimer Care* 1986;1:35-39. [\[Context Link\]](#)
17. Kurz A, Egensperger R, Haupt M, et al. Apolipoprotein E allele epsilon 4, cognitive decline, and deterioration of everyday performance in Alzheimer's disease. *Neurology* 1996;47:440-443. [\[Context Link\]](#)
18. Randt CT, Brown ER, Osborne DP. A memory test for longitudinal measurement of mild to moderate deficits. *Clin Neuropsychology* 1980;2:184-194. [\[Context Link\]](#)
19. Benton AL. *The Revised Visual Retention Test*. New York: Psychological Corporation, 1974. [\[Context Link\]](#)

20. Kaplan E, Goodglass H, Weintraub S. Boston Naming Test. Philadelphia: Lea & Febiger, 1983. [\[Context Link\]](#)
21. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol* 1935;18:643-662. [\[Context Link\]](#)
22. Golden CH, Hammeke TA, Purisch AD. Manual for the Luria-Nebraska Neuropsychological Battery. Los Angeles: Western Psychological Services, 1980. [\[Context Link\]](#)
23. Wechsler D. Wechsler Adult Intelligence Scale-Revised. New York: Psychological Corporation, 1981. [\[Context Link\]](#)
24. Cronin-Golomb A, Corkin S, Rizzo JF, Cohen J, Growdon JH, Banks KS. Visual dysfunction in Alzheimer's disease: relation to normal aging. *Ann Neurol* 1991;29:41-52. [\[Context Link\]](#)
25. Cronin-Golomb A, Sugiura R, Corkin S, Growdon JH. Incomplete achromatopsia in Alzheimer's disease. *Neurobiol Aging* 14:471-477, 1993. [\[Context Link\]](#)
26. Kurylo DD, Corkin S, Dolan RP, Rizzo JF, Parker SW, Growdon JH. Broadband visual capacities are not selectively impaired in Alzheimer's disease. *Neurobiol Aging* 1994;15:305-311. [\[Context Link\]](#)
27. Arnold SE, Hyman BT, Flory J, Damasio AD, Van Hoesen GW. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. *Cereb Cortex* 1991;1:1-6. [\[Context Link\]](#)
28. Yankner BA, Dawes LR, Fisher S, Villa-Komaroff L, Oster-Granite ML, Neve RL. Neurotoxicity of a fragment of the amyloid precursor associated with Alzheimer's disease. *Science* 1989;245:417-420. [\[Context Link\]](#)
29. Higgins LS, Rodems JM, Catalano R, Quon D, Cordell B. Early Alzheimer disease-like histopathology increases in frequency with age in mice transgenic for beta-APP751. *Proc Natl Acad Sci USA* 1995;92:4402-4406. [\[Context Link\]](#)
30. Smith MA, et al. Tau protein directly interacts with the amyloid beta-protein precursor: implications for Alzheimer's disease. *Nature Med* 1995;1:365-369. [\[Context Link\]](#)
31. Selkoe DJ. Alzheimer's disease: a central role for amyloid. *J Neuropathol Exp Neurol* 1994;53:438-447. [\[Context Link\]](#)
32. Asada T, Kariya T, Yamagata Z, Kinoshita T, Asaka A. ApoE epsilon 4 allele and cognitive decline

in patients with Alzheimer's disease. Neurology 1996;47:603. [\[Context Link\]](#)

33. Frisoni GB, Govoni S, Geroldi C, et al. Gene dose of the epsilon 4 allele of apolipoprotein E and disease progression in sporadic late-onset Alzheimer's disease. Ann Neurol 1995;37:596-604. [\[Context Link\]](#)

34. Huff FJ, Growdon JH, Corkin S, Rosen TJ. Age at onset and rate of progression of Alzheimer's disease. J Am Geriatric Soc 1987;35:27-30. [\[Context Link\]](#)

35. Morris JC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part IV. Rates of cognitive change in the longitudinal assessment of probable Alzheimer's disease. Neurology 1993;43:2457-2465. [\[Context Link\]](#)

---

*Accession Number: 00006114-199608000-00020*

Copyright (c) 2000-2006 [Ovid Technologies, Inc.](#)

Version: rel10.2.2, SourceID 1.11354.1.251