

Apolipoprotein E $\epsilon 4$ and Age at Onset of Sporadic and Familial Alzheimer Disease in Caribbean Hispanics

Lucia Olarte, BS; Nicole Schupf, PhD; Joseph H. Lee, DPH; Ming-Xin Tang, PhD; Vincent Santana, MBA; Jennifer Williamson, MS; Prashanthi Maramreddy, PhD; Benjamin Tycko, MD, PhD; Richard Mayeux, MD, MSc

Background: The primary effect of the apolipoprotein E $\epsilon 4$ (APOE $\epsilon 4$) allele is on the age at onset of Alzheimer disease (AD).

Objective: To investigate whether the presence of the APOE $\epsilon 4$ allele can account for the earlier age at onset of familial AD (FAD) compared with sporadic AD (SAD).

Design: Population-based, case series ascertained in a prospective study of aging and dementia in Medicare recipients aged 65 years or older.

Setting: Clinics in northern Manhattan and in the Dominican Republic and Puerto Rico.

Participants: There were 680 Caribbean Hispanic subjects: 111 patients with FAD, with at least 1 family member with dementia; 163 patients with SAD; and 406 elderly persons without dementia or other illnesses.

Main Outcome Measure: Age at onset of dementia was examined in relation to frequency of APOE $\epsilon 4$. Sex,

education, and medical risk factors for stroke, hypertension, diabetes, and heart disease were examined as effect modifiers.

Results: The mean age at onset of AD was significantly lower in FAD than in SAD, and a statistically significant dose effect of the APOE $\epsilon 4$ allele was present for age at onset in FAD ($P = .001$) but not in SAD. The age at onset in patients homozygous for the APOE $\epsilon 4$ allele with FAD and SAD was similar. Compared with SAD, the major difference was younger age at onset in patients with FAD who were heterozygous for the APOE $\epsilon 4$ allele and those without an APOE $\epsilon 4$ allele.

Conclusions: Apolipoprotein E $\epsilon 4$ had a consistent lowering effect on age at onset of FAD, but this was attenuated in SAD. This suggests that among individuals with a family history of AD and the APOE $\epsilon 4$ allele, additional genetic or environmental factors may accelerate the onset of dementia.

Arch Neurol. 2006;63:1586-1590

THE $\epsilon 4$ ALLELE OF THE APOLIPOPROTEIN E gene (APOE $\epsilon 4$) is found with increased frequency among individuals with Alzheimer disease (AD) of both the late-onset sporadic (SAD) and late-onset familial (FAD) varieties.^{1,2} The APOE $\epsilon 4$ allele has been associated with acceleration of the development of AD³⁻⁵ and with a higher concentration of β -amyloid plaques in the brains of elderly persons with and without AD.^{6,7} Risk increases by nearly 2-fold for each APOE $\epsilon 4$ allele in both FAD and SAD and age at onset of AD decreases with increasing copies of the APOE $\epsilon 4$ allele.^{1,5,8-11}

The risk of AD was found to be 2 to 3 times higher among Caribbean Hispanics than in non-Hispanics living in New York City.^{12,13} In addition, risk of AD associated with the APOE $\epsilon 4$ allele has been found to vary among ethnic groups of African ancestry.¹³⁻¹⁸

In all populations, age at onset of FAD has been found to be earlier,¹⁹ and there is greater likelihood of carrying the APOE $\epsilon 4$ allele. In the present study, we investigated whether the presence of the APOE $\epsilon 4$ allele can account for the consistently lower age at onset among Caribbean Hispanics with FAD compared with SAD or whether other genetic or medical risk factors are involved in the earlier manifestation of symptoms.

METHODS

PARTICIPANTS AND SETTING

Sporadic and familial AD and elderly persons without dementia were identified from among individuals participating in a prospective study of aging and dementia in 4309 Medicare recipients aged 65 years or older residing in northern Manhattan (Washington Heights, Hamilton Heights, and Inwood). A stratified random

Author Affiliations are listed at the end of this article.

sample of 50% of all persons older than 65 years was obtained from the Health Care Finance Administration,¹³ which sent them a letter explaining that they had been selected to participate in a study of aging by investigators at Columbia University, New York, NY. The sampling procedures are described in detail elsewhere.¹³ Each participant underwent an in-person interview of general health and functional ability at enrollment in the study, followed by a standardized assessment including medical history, physical and neurologic examinations, and a battery of neuropsychologic tests.²⁰ Ethnic group was classified by participant self-report using the format of the 1990 US census.²¹ Participants were asked if they considered themselves white, black, or other ethnicity, and then were asked if they were Hispanic. Participants were recruited at 2 time points: January 7, 1992, to October 4, 1994, and November 8, 1999, to April 19, 2002. They have been followed up at approximately 18-month intervals, with similar assessments at each interval. The institutional review boards of Columbia University Medical Center and the New York Psychiatric Institute, New York, approved recruitment, informed consent, and study procedures.

CLINICAL ASSESSMENT AND NEUROLOGIC DIAGNOSIS

All participants underwent structured neurologic and functional assessments by physicians, and a standardized battery of neuropsychologic tests²⁰ that included measures of memory, orientation, language, abstract reasoning, and visuospatial ability. The diagnosis of dementia was established based on all available information gathered from the initial and follow-up assessments and from medical records. Dementia was determined by consensus at a conference of physicians, neurologists, neuropsychologists, and psychiatrists. The diagnosis of dementia was determined according to the research criteria set forth by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease Related Disorders Association (NINCDS-ADRDA) for probable or possible AD,²² and the research criteria set forth by the National Institute of Neurological Disorders and Stroke and Association Internationale Pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) for vascular dementia.²³ Diagnosis of dementia required evidence of cognitive decline, including memory impairment, results of the battery of neuropsychologic tests, and evidence of impairment of social or occupational function (clinical dementia rating >1.0).²⁴

DEFINITIONS OF FAD AND SAD

Family medical history was ascertained by a physician at the initial visit and was verified by available family members. Once dementia status was determined by consensus, as described previously, patients with at least 1 first-degree relative with dementia were classified as having FAD and those without a family history of dementia were classified as having SAD. Additional patients with FAD came from an extension of the Washington Heights, Hamilton Heights, and Inwood communities to the Dominican Republic and Puerto Rico. Of the 111 patients with FAD, 9 (8.1%) participated while living in New York, 9 (8.1%) participated in Puerto Rico, and the remaining 93 (83.8%) participated in the Dominican Republic.

AGE AT ONSET OF DEMENTIA

During the assessment, participants were asked when they began to notice symptoms of memory loss, and this was confirmed by family members. The mean number of years be-

tween the reported age at onset and date of diagnosis was determined from all cases with known age at onset (650 patients [95.6%]). This value was then used to calculate age at onset for patients with missing values (30 [18.4%] of the 163 patients with SAD, 4.6% of all cases). The characteristics of these 30 patients did not differ from the overall population with SAD. Analyses were conducted including and excluding these 30 patients, without any difference in the outcome. Since the results were equivalent, the patients were included to enlarge the sample size.

APOE GENOTYPES

Blood samples were collected in tubes containing dipotassium plus EDTA at the initial assessment, and genomic DNA samples were prepared from peripheral white blood cells. Genotyping was carried out as described previously.¹⁶ Genotype was determined by a standard polymerase chain reaction–restriction fragment length polymorphism method using *Hha*I (*Cfo*I) digestion of a genomic polymerase chain reaction product spanning the polymorphic (cysteine/arginine) sites at codons 112 and 158. Acrylamide gel electrophoresis was used to assess and document the restriction fragment sizes.²⁵ Participants were classified as homozygous for the *APOE* ϵ 4 allele, heterozygous for the *APOE* ϵ 4 allele, or having no *APOE* ϵ 4 allele.

STATISTICAL ANALYSIS

The primary analysis compared age at onset of dementia by genotype in patients with SAD or FAD. We used χ^2 tests for categorical variables and analysis of variance for continuous variables to compare age, level of educational achievement, and the distribution of sex, genotype, and presence or absence of chronic medical conditions among patients with SAD or FAD and control subjects. We used a multivariable analysis of variance to examine the effect of the *APOE* ϵ 4 allele on age at onset of symptoms of dementia in patients with FAD or SAD compared with current age in the subjects without dementia, adjusting for sex, education, and history of stroke, hypertension, heart disease, and diabetes.

RESULTS

DEMOGRAPHIC DATA

Among the 929 participants of Caribbean Hispanic ancestry (21.6% of all participants), genotype and family medical history data were available for 680 individuals (73.2%). Of these 680 individuals, 274 (40.3%) had been diagnosed as having probable AD with symptoms manifesting after age 65 years. The remaining 406 individuals (59.7%) composed the comparison group of subjects without dementia and were similar in age and sex. Of the 274 patients with AD, 163 (59.5.9%) had SAD and 111 (40.5%) had FAD.

The mean age of the total sample was 77.6 years. Patients with FAD or SAD were older than unaffected subjects (**Table 1**). Patients with SAD or FAD and the controls did not differ in the proportion of women to men (Table 1), but mean years of education was significantly lower in patients with FAD or SAD compared with unaffected subjects (Table 1). The frequency of having 1 or more *APOE* ϵ 4 alleles was higher in patients with FAD compared with those with SAD, and the frequency of hav-

ing the APOE $\epsilon 4$ allele was also significantly higher among patients with SAD compared with unaffected control subjects (Table 1).

RELATION OF MEDICAL HISTORY AND FAD OR SAD

The frequency of a history of stroke, hypertension, heart disease, and diabetes in patients with FAD and SAD is given in Table 1. Head injury and seizure history were initially included in the analysis, but because they were infrequent findings these data were excluded. Patients with FAD were less likely to have a history of hypertension or diabetes than were elderly persons without dementia or those with SAD (Table 1). There was no significant difference in the frequency of heart disease or stroke between patients with FAD or SAD and elderly persons without dementia. The frequency of hypertension was lower in patients with FAD or SAD than in the unaffected subjects. The frequency of diabetes did not differ significantly between patients with SAD and unaffected subjects but was significantly lower in patients with FAD compared with control subjects ($P=.01$).

Table 1. Distribution of Genotype and Medical Risk Factors*

Variable	FAD (n = 111)	SAD (n = 163)	No Dementia (n = 406)
Sex			
Female	80 (72.1)	112 (68.7)	286 (70.4)
Male	31 (27.9)	51 (31.3)	120 (29.6)
Age, mean (SD), y	85.1 (6.4)	85.2 (6.9)	76.9 (5.6)
Educational achievement, mean (SD), y†	4.2 (4.1)	4.7 (4.1)	7.9 (4.4)
Genotype†			
-/-	49 (44.1)	113 (69.3)	308 (75.9)
$\epsilon 4/-$	51 (45.9)	45 (27.6)	91 (22.4)
$\epsilon 4/\epsilon 4$	11 (9.9)	5 (3.1)	7 (1.7)
Medical history			
Stroke	6 (5.4)	21 (12.9)	36 (8.9)
Hypertension†	48 (43.2)	96 (58.9)	255 (62.8)
Heart disease	18 (16.2)	33 (20.2)	86 (21.2)
Diabetes†	12 (10.8)	38 (23.3)	68 (16.7)

Abbreviations: FAD, familial Alzheimer disease; SAD, sporadic Alzheimer disease.

*Data are given as number (percentage) unless otherwise indicated.

† $P \leq .05$; all differences were statistically significant within this category.

RELATION OF GENOTYPE AND AGE AT ONSET AND AD CLASSIFICATION

Mean age at onset was compared in both groups of patients and by genotype. Overall, mean age at onset for FAD was lower than for SAD: 77.4 years (range, 70.9-78.8 years) vs 81.9 years (range, 75.0-82.5 years) ($P=.02$) (Table 2). Mean age at onset was also lower with increasing number of APOE $\epsilon 4$ alleles in both patient groups. The decrease in age at onset of AD with increasing number of APOE $\epsilon 4$ alleles was significant among patients with FAD ($P=.001$) but not those with SAD. Within strata defined by the absence or presence of the APOE $\epsilon 4$ allele, there continued to be a significantly lower age at onset among patients with FAD compared with those with SAD. Among those without an APOE $\epsilon 4$ allele, mean age at onset was 3.7 years earlier in FAD than in SAD ($P=.01$). Among those heterozygous for the APOE $\epsilon 4$ allele, mean age at onset was 5.6 years earlier in FAD than in SAD ($P<.001$). Among those homozygous for the APOE $\epsilon 4$ allele, mean age at onset was 4.1 years earlier in FAD than in SAD, but this difference failed to reach statistical significance, probably because of the small sample size.

COMMENT

A family history of dementia and the presence of the APOE $\epsilon 4$ allele have been considered risk factors for AD.²⁶ A major putative effect of the APOE $\epsilon 4$ allele is the lowering of the age at onset of disease, a finding confirmed in this study. Our finding of lower age at onset of AD in patients with FAD compared with those with SAD is consistent with other investigations that have also shown a younger age at onset in FAD compared with SAD.^{3,4,9,19,27} This increased risk may be related, in part, to an increased frequency of the APOE $\epsilon 4$ allele. Regardless of genotype, age at onset of disease was consistently lower in FAD compared with SAD. The difference in mean age at onset between FAD and SAD was greater for patients with 1 or more APOE $\epsilon 4$ alleles (approximately 5 years) but was still apparent among patients with SAD or FAD without an APOE $\epsilon 4$ allele (approximately 3 years). Patients with FAD were more likely to carry an APOE $\epsilon 4$ allele than were those with SAD or control subjects without dementia. However, the finding of a significantly

Table 2. Relation of Genotype to Age at Onset of FAD and SAD*

	FAD		SAD	
	Unadjusted	Adjusted†	Unadjusted	Adjusted†
Age at onset, y	77.4 (6.7)	77.0 (8.0)	81.9 (6.7)	82.2 (12.9)
Genotype				
-/-	79.2 (7.4)	78.8 (6.4)	82.2 (6.7)	82.5 (6.3)
$\epsilon 4/-$	77.0 (5.5)	76.5 (6.3)	81.8 (6.5)	82.1 (6.3)
$\epsilon 4/\epsilon 4$	71.3 (3.8)	70.9 (6.3)	76.0 (7.5)	75.0 (6.3)

Abbreviations: FAD, familial Alzheimer disease; SAD, sporadic Alzheimer disease.

*Data are given as the mean (SD).

†Mean age at onset adjusted for gender, education, and history of medical risk factors (stroke, hypertension, heart disease, and diabetes).

‡ $P \leq .05$. Patients heterozygous for the APOE $\epsilon 4$ allele with FAD had a mean age at onset of disease 4.1 years earlier than in those with SAD, but this difference failed to reach statistical significance.

younger age at onset of AD in FAD compared with SAD, regardless of the presence or absence of an APOE $\epsilon 4$ allele, suggests that there are additional genetic or environmental factors in FAD in Caribbean Hispanics that may lead to a younger age at onset of disease.

The most parsimonious explanation for the lack of an APOE $\epsilon 4$ effect on age at onset in SAD is that other non-genetic factors may be involved. That is, patients with FAD may have inherited variants in genes other than those that lead to earlier onset of symptoms. Although no single candidate gene has been successfully confirmed, many genetic linkage studies suggest that there are additional putative loci predisposing to FAD.^{19,28-34} Whether these as yet unidentified genetic variants interact with each other or act independently remains to be determined. Alternatively, non-genetic risk factors might modify the effect of the APOE $\epsilon 4$ allele or age at onset of SAD. However, we found that the frequency of medical risk factors was similar between the control subjects and patients with SAD, whereas patients with FAD had fewer cardiovascular and cerebrovascular risk factors for dementia. Therefore, cardiovascular risk factors do not appear to explain this blunted effect on age at onset. It is possible that other nongenetic environmental factors could reduce the APOE $\epsilon 4$ effect. Regardless of the cause, our findings are consistent with the hypothesis that risk for FAD is more strongly influenced by genetic factors than is risk for SAD. Adjustment for the presence of cardiovascular and cerebrovascular risk factors did not modify the association between genotype and age at onset of AD in patients with FAD or SAD.

Although affected individuals were asked to state when symptoms of memory loss first appeared and age at onset was confirmed by available family members, our results may have been influenced by recall bias. The younger reported age at onset among patients with FAD may be related to a heightened sensitivity of memory loss among family members who have already witnessed disease onset and progression of disease. In SAD, the affected individual and family members may not be aware of the early signs of memory loss, which can lead to later reported age at onset. Patients may also exaggerate how long they have experienced memory loss, especially when it is years after symptoms began. This recall bias can result in a lower reported age at onset among patients with FAD compared with those with SAD.

We estimated the age at onset for 18.4% of patients who did not report age at onset. However, our reported age at onset for patients with FAD and SAD are consistent with prospective studies of incident AD that have also reported younger age at onset in patients with FAD compared with those with SAD.¹⁹

A strength of the study is that most of the patients with FAD or SAD came from the Washington Heights, Hamilton Heights, and Inwood communities of New York City. A few of the FAD cases included family members living in the Dominican Republic or Puerto Rico. Although all participants were of Hispanic descent, there may still be differences between geographic locations and traditions within the Hispanic community that may have acted as uncontrolled confounders.

Although the APOE $\epsilon 4$ allele is more strongly related to FAD than to SAD, this genetic risk factor alone does

not explain the significantly earlier manifestation of AD in patients with FAD compared with those with SAD, which suggests that other genetic or environmental risk factors accelerate AD in patients with FAD.

Accepted for Publication: May 12, 2006.

Author Affiliations: Gertrude H. Sergievsky Center (Ms Olarte and Drs Schupf, Lee, Tang, Williamson, Tycko, Maramreddy, and Mayeux, and Mr Santana), Taub Institute for Research on Alzheimer's Disease and the Aging Brain (Ms Olarte and Drs Schupf, Lee, Williamson, Tycko, Maramreddy, and Mayeux, and Mr Santana), Departments of Neurology (Drs Tycko and Mayeux), Psychiatry (Dr Mayeux), and Pathology (Drs Schupf, Lee, and Mayeux), and Departments of Epidemiology (Drs Schupf, Lee, and Mayeux) and Biostatistics of the Mailman School of Public Health, Columbia University College of Physicians and Surgeons, New York, NY; Laboratory of Epidemiology, New York State Institute for Basic Research in Developmental Disabilities, Staten Island (Drs Schupf and Tang).

Correspondence: Richard Mayeux, MD, MSc, Gertrude H. Sergievsky Center, Columbia University College of Physicians and Surgeons, 630 W 168th St, New York, NY 10032 (rpm2@columbia.edu).

Author Contributions: *Study concept and design:* Olarte and Mayeux. *Acquisition of data:* Olarte, Santana, Williamson, Tycko, Maramreddy, and Mayeux. *Analysis and interpretation of data:* Olarte, Schupf, Lee, Tang, and Mayeux. *Drafting of the manuscript:* Olarte, Lee, Williamson, Maramreddy, and Mayeux. *Critical revision of the manuscript for important intellectual content:* Olarte, Schupf, Lee, Tang, Santana, Tycko, and Mayeux. *Statistical analysis:* Olarte, Schupf, Lee, Tang, and Mayeux. *Obtained funding:* Mayeux. *Administrative, technical, and material support:* Olarte, Santana, Williamson, Maramreddy, and Mayeux. *Study supervision:* Santana, Tycko, and Mayeux.

Financial Disclosure: None reported.

Funding/Support: This study was supported by grants PO1 AG07232 and P50 AG08702 from the National Institute on Aging, National Institutes of Health, and by the Charles S. Robertson Gift from the Banbury Fund.

REFERENCES

1. Lahiri DK, Sambamurti K, Bennett DA. Apolipoprotein gene and its interaction with the environmentally driven risk factors: molecular, genetic and epidemiological studies of Alzheimer's disease. *Neurobiol Aging*. 2004;25:651-660.
2. Cai X, Fallin D, Stanton J, et al. APOE is linked to Alzheimer's disease in a large pedigree. *Am J Med Genet*. 1997;74:365-369.
3. Corder E, Basun H, Lannfelt L, Viitanen M, Winblad B. Apolipoprotein E- $\epsilon 4$ gene dose. *Lancet*. 1995;346:967-968.
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. Mayeux R, Stern Y, Ottman R, et al. The apolipoprotein epsilon 4 allele in patients with Alzheimer's disease. *Ann Neurol*. 1993;34:752-754.
6. Hyman BT, Tanzi R. Molecular epidemiology of Alzheimer's disease. *N Engl J Med*. 1995;333:1283-1284.
7. Polvikoski T, Sulkava R, Haltia M, et al. Apolipoprotein E, dementia, and cortical deposition of beta-amyloid protein. *N Engl J Med*. 1995;333:1242-1247.
8. Emanuele E, Peros E, Tomaino C, et al. Apolipoprotein(a) null phenotype is re-

- lated to a delayed age at onset of Alzheimer's disease. *Neurosci Lett*. 2004; 357:45-48.
9. Duara R, Barker WW, Lopez-Alberola R, et al. Alzheimer's disease: interaction of apolipoprotein E genotype, family history of dementia, gender, education, ethnicity, and age of onset. *Neurology*. 1996;46:1575-1579.
 10. Slooter AJ, Cruts M, Kalmijn S, et al. Risk estimates of dementia by apolipoprotein E genotypes from a population-based incidence study: the Rotterdam Study. *Arch Neurol*. 1998;55:964-968.
 11. Corder EH, Saunders AM, Risch NJ, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nat Genet*. 1994;7:180-184.
 12. Tang MX, Cross P, Andrews H, et al. Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in northern Manhattan. *Neurology*. 2001; 56:49-56.
 13. Tang MX, Stern Y, Marder K, et al. The *APOE*- ϵ 4 allele and the risk of Alzheimer disease among African Americans, whites, and Hispanics. *JAMA*. 1998;279: 751-755.
 14. Farrer LA, Cupples LA, Haines JL, et al; APOE and Alzheimer Disease Meta Analysis Consortium. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. *JAMA*. 1997; 278:1349-1356.
 15. Osuntokun BO, Sahota A, Ogunniyi AO, et al. Lack of an association between apolipoprotein E epsilon 4 and Alzheimer's disease in elderly Nigerians. *Ann Neurol*. 1995;38:463-465.
 16. Tang MX, Maestre G, Tsai WY, et al. Relative risk of Alzheimer disease and age at onset distributions, based on genotypes among elderly African Americans, Caucasians, and Hispanics in New York City. *Am J Hum Genet*. 1996;58:574-584.
 17. Maestre G, Ottman R, Stern Y, et al. Apolipoprotein E and Alzheimer's disease: ethnic variation in genotypic risks. *Ann Neurol*. 1995;37:254-259.
 18. 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.
 19. Duara R, Lopez-Alberola RF, Barker WW, et al. A comparison of familial and sporadic Alzheimer's disease. *Neurology*. 1993;43:1377-1384.
 20. Stern Y, Andrews H, Pittman J, et al. Diagnosis of dementia in a heterogeneous population: development of a neuropsychological paradigm-based diagnosis of dementia and quantified correction for the effects of education. *Arch Neurol*. 1992; 49:453-460.
 21. Census of Population and Housing. *Summary Tape File 1, Technical Documentation*. Washington, DC: Bureau of the Census; 1991.
 22. 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.
 23. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43:250-260.
 24. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982;140:566-572.
 25. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res*. 1990;31:545-548.
 26. Huang W, Qiu C, von Strauss E, Winblad B, Fratiglioni L. *APOE* genotype, family history of dementia, and Alzheimer disease risk: a 6-year follow-up study [published correction appears in *Arch Neurol*. 2005;62:453]. *Arch Neurol*. 2004; 61:1930-1934.
 27. Devi G, Ottman R, Tang M, et al. Influence of *APOE* genotype on familial aggregation of AD in an urban population. *Neurology*. 1999;53:789-794.
 28. Ertekin-Taner N, Graff-Radford N, Younkin LH, et al. Heritability of plasma amyloid beta in typical late-onset Alzheimer's disease pedigrees. *Genet Epidemiol*. 2001;21:19-30.
 29. Kehoe P, Wavrant-De Vrieze F, Crook R, et al. A full genome scan for late onset Alzheimer's disease. *Hum Mol Genet*. 1999;8:237-245.
 30. Papassotiropoulos A, Wollmer MA, Tsolaki M, et al. A cluster of cholesterol-related genes confers susceptibility for Alzheimer's disease. *J Clin Psychiatry*. 2005;66:940-947.
 31. Ray WJ, Ashall F, Goate AM. Molecular pathogenesis of sporadic and familial forms of Alzheimer's disease. *Mol Med Today*. 1998;4:151-157.
 32. Slifer MA, Martin ER, Bronson PG, et al. Lack of association between UBQLN1 and Alzheimer disease. *Am J Med Genet B Neuropsychiatr Genet*. 2006;141:208-213.
 33. St George-Hyslop PH. Molecular genetics of Alzheimer's disease. *Biol Psychiatry*. 2000;47:183-199.
 34. Walker LC, Pahnke J, Madauss M, et al. Apolipoprotein E4 promotes the early deposition of Abeta42 and then Abeta40 in the elderly. *Acta Neuropathol (Berl)*. 2000;100:36-42.

Announcement

Sign Up for Alerts—It's Free! *Archives of Neurology* offers the ability to automatically receive the table of contents of ARCHIVES when it is published online. This also allows you to link to individual articles and view the abstract. It makes keeping up-to-date even easier! Go to <http://pubs.ama-assn.org/misc/alerts.dtl> to sign up for this free service.