Apolipoprotein E, survival in Alzheimer's disease patients, and the competing risks of death and Alzheimer's disease

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Article abstract—The apolipoprotein E (APOE) ε4 allele carries an increased risk of a patient developing Alzheimer's disease (AD) while the ε2 allele carries a decreased risk. We compared survival from the onset of AD in subjects with different numbers of ε4 alleles and evaluated changes in genotypic frequencies with age. Two subject groups were investigated: unrelated AD case and control subjects, and affected and unaffected members from 74 multiplex AD families. In both subject groups, survival from onset decreased with increasing onset age, was longer in women, and was unrelated to ε4 gene dose. The ε2/ε3 genotype became more common with age ($p = 0.004$). The ε4 allele decreased in frequency with age in all patient groups but, unexpectedly, remained unchanged in control subjects. We conclude that the progression of AD is not strongly related to ε4 gene dose, that the higher prevalence of AD in women may involve the longer survival of affected women, and that AD and death are competing risks involving APOE that change over time.

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Apolipoprotein E (APOE) genotype is a major risk factor for late-onset (onset of clinical symptoms after age 60) familial and sporadic Alzheimer's disease (AD). APOE has three major allelic variants, ε2 (8%), ε3 (77%), and ε4 (15%),[1] that encode the three isoforms of apolipoprotein E (apoE), a 34-kilodalton protein that mediates the clearance of several plasma lipoproteins.[2] ApoE isoforms differ by single amino acid substitutions at positions 112 and 158: ε3 (cys_{112}, arg_{158}), ε4 ($cys_{112} \rightarrow arg$), and ε2 ($arg_{158} \rightarrow cys$).

The ε4 allele confers substantial risk of AD in a dose-related fashion[3-13] while the ε2 allele is apparently protective.[14-19] Risk involving ε4 and protection involving ε2 are strong before age 70 and diminish with age.[15] More than 80% of late-onset AD may be attributable to APOE genotypes other than the lowest-risk ε2/ε3 genotype, implicating APOE as the most important biologic risk factor related to AD that has been identified to date.[15] Several studies indicate that the risk of AD in relation to APOE genotype may be modified by other factors, including serum cholesterol level[20] and head trauma.[21] However, there are no studies, in relation to APOE genotype, of the progression of AD from the onset of clinical symptoms until death.

Several studies[22-26] indicate that selective mortality in the general population involves APOE genotype. This mortality follows the same pattern of risk found for AD: the ε2 allele is protective while the ε4 allele confers risk. Schächter et al[22] found that the

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frequency of ε2 is doubled and the frequency of ε4 is halved in French centenarians compared with control subjects less than 70 years of age. Louhija[23] found similar changes in Finnish centenarians. Smaller shifts in allele frequencies were found at earlier ages by Davignon et al[24] in octogenarians and by Cauley et al,[25] who compared younger (age 42 to 50) and older (age 65 to 90) women. Eggertsen et al[26] evaluated 407 Swedish individuals and found that the frequency of the ε4 allele decreases with age; the ε4 frequency is 20.3% overall and 14.7% in those older than age 60. The extent to which risks of death from AD versus other causes (possibly mediated by cardiovascular disease[26-29]) operate simultaneously, thereby constituting dependent competing risks, has not been described.

Here we compare the duration of AD from onset of symptoms until death in subjects with different numbers of APOE ε4 alleles and describe changes with age in APOE genotypic frequencies in AD patients and unaffected subjects.

Methods. *Patients.* Two subject groups were evaluated: unrelated autopsy-confirmed AD case (n = 103) and cognitively intact control (n = 236) subjects, and affected (n = 158) and unaffected (n = 220) members of 74 multiplex AD families. All participants were older than 60 years of age when examined and found to be normal or at the onset of the clinical symptoms of AD. Standard established diagnostic criteria were used by all the contributing centers in assigning clinical status to AD patients.[30,31] The age at onset of obvious memory problems, obtained from spouses and relatives, served to identify the age at onset of AD. The clinical staff did not know the patient's APOE genotype. Informed consent was obtained from each subject or, when necessary, the legal guardian. APOE genotyping was carried out using amplification by polymerase chain reaction.[4]

All the unrelated autopsy-confirmed AD cases were from subjects ascertained at the Joseph and Kathleen Bryan Alzheimer's Disease Research Center (ADRC). Control subjects were derived from two sources and combined: 92 subjects in the Duke Established Populations for Epidemiologic Studies of the Elderly (age greater than 65 years)[32] and 144 unaffected spouses of AD patients at the Joseph and Kathleen Bryan ADRC. Familial AD cases and their families were ascertained through patients with diagnosed AD (ie, the probands) at the Joseph and Kathleen Bryan ADRC, the Massachusetts General Hospital ADRC, The Neuropsychiatric Institute and Hospital at the University of California at Los Angeles, and the ADRC National Cell Repository in Indianapolis. The diagnostic status of the autopsy-confirmed unrelated AD cases, 42 of the spouse control subjects, and 66 of the 74 AD families were previously described.[4,15]

Data analysis. Kaplan-Meier plots were used to describe the patterns of onset and survival in subjects with different numbers of ε4 alleles.[33,34] Genotype-specific plots were compared with log rank tests. Duration of AD was calculated as age at death minus age at the onset of the clinical symptoms of AD. Cox proportional hazard models were used to test whether survival from onset was related to ε4 gene dose controlling for age at onset and gender.[35,36] Changes in allele frequencies with age at the time of evaluation were tested with the Mantel-Haenszel (M-H) statistic.[37] Between-group comparisons were made with *t* tests. Tests are two-sided and significance was declared at the $\alpha = 0.05$ level.

Table 1. Age at onset (yr)

Affected sporadic case subjects

	Men			Women			All		
Genotype	n	Mean	(SD)	n	Mean	(SD)	n	Mean	(SD)
ε3/ε3	10	70.6	(5.2)	19	71.8	(8.4)	29	71.4	(7.4)
ε3/ε4	15	71.5	(6.0)	37	71.6	(7.8)	52	71.6	(7.2)
ε4/ε4	7	71.1	(6.0)	9	68.2	(5.9)	16	69.5	(6.0)
Total	32	71.1	(5.6)	65	71.2	(7.7)	97	71.2	(7.1)

Affected members of AD families

	Men			Women			All		
Genotype	n	Mean	(SD)	n	Mean	(SD)	n	Mean	(SD)
ε3/ε3	7	71.3	(8.4)	20	75.7	(8.0)	27	74.5	(8.2)
ε3/ε4	28	68.9	(5.8)	62	70.5	(5.1)	90	70.0	(5.4)
ε4/ε4	20	68.8	(4.8)	17	69.2	(5.4)	37	69.0	(5.0)
Total	55	69.2	(5.8)	99	71.3	(6.9)	154	70.6	(6.1)

	Probands			Others			All		
Genotype	n	Mean	(SD)	n	Mean	(SD)	n	Mean	(SD)
ε3/ε3	7	70.3	(6.7)	20	76.0	(8.3)	27	74.5	(8.2)
ε3/ε4	27	69.3	(5.6)	63	70.4	(5.3)	90	70.0	(5.4)
ε4/ε4	11	67.2	(4.4)	26	69.7	(5.2)	37	69.0	(5.0)
Total	45	68.9	(5.5)	109	71.2	(6.3)	154	70.6	(6.1)

AD Alzheimer's disease.

Results. *Age at onset.* Table 1 describes age at the onset of AD for the unrelated AD cases and for the affected members of the AD families. In the unrelated cases, ascertained at autopsy, age at onset was similar in men and women, ie, 71 years. There was no evidence that age at onset was related to the number of ε4 alleles in the unrelated AD cases (logrank $\chi^2 = 2.7$, 2 *df*, $p = 0.34$), although there was a suggestion that onset tended to be earlier in those with the ε4/ε4 genotype (figure). In contrast to the unrelated AD case subjects, affected men in the AD families tended to have earlier age at onset compared with affected women in the AD families ($p = 0.03$), especially among members with the ε3/ε3 genotype. Combining men and women, age at onset in the AD families was inversely related to ε4 gene dose (logrank $\chi^2 = 15.3$, 2 *df*, $p = 0.005$). This inverse relationship was found both for probands and for subsequently ascertained affected members of the AD families. For each gene dose of ε4, probands tended to have earlier age at onset than subsequently ascertained affected members of the AD families ($p = 0.02$).

Age at death. Age at death information was available for the unrelated case subjects and the 56 affected members of AD families no longer alive. Age at death in the unrelated AD cases was similar in men and in women ($p = 0.38$) and for subjects with different numbers of APOE ε4 alleles (logrank $\chi^2 = 2.6$, 2 *df*, $p = 0.27$). However, the figure does suggest earlier age at death in unrelated case sub-

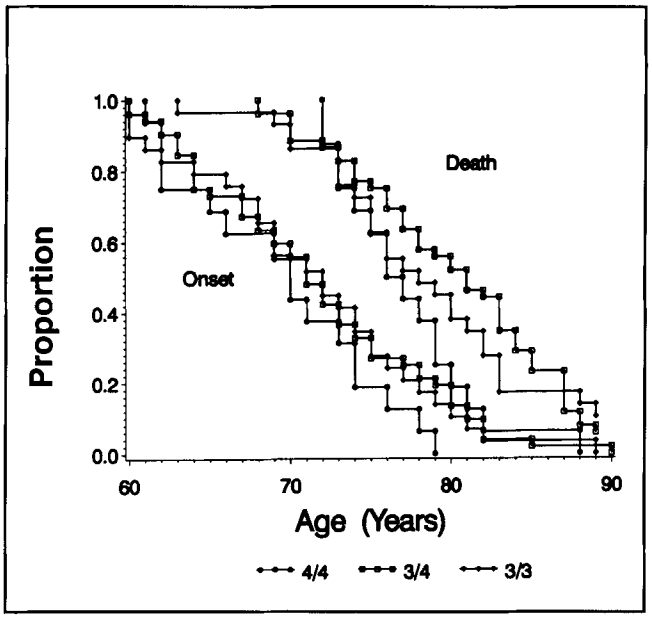

Figure. APOE ε4 gene dose and the empiric distributions of age at onset and age at death in unrelated AD patients.

jects with the ε4/ε4 genotype. Age at death in the AD families was clearly earlier in affected men than in affected women ($p = 0.001$) and was also earlier in probands than for subsequently obtained affected family members ($p = 0.02$). There was no relationship between age at death and ε4 gene dose in the affected men in the AD families; in women, age at death tended to be inversely related to ε4 gene dose.

Duration of AD. There was no evidence that survival from the onset of AD depended on APOE ε4 gene dose in either the unrelated subjects or the affected members of the AD families (table 2). Instead, survival from onset decreased with increasing age at onset, was longer in women than in men, and was unrelated to ε4 gene dose. In the unrelated cases, risk of death in each succeeding year following onset was increased by a factor of 1.05 (95% CI, 1.02 to 1.08) for each additional year of age at onset. Risk of death tended to be lower in women than in men (hazard ratio [HR] = 0.75; 95% CI, 0.49 to 1.16) and did not depend on ε4 gene dose (HR = 0.92; 95% CI, 0.66 to 1.30).

A similar picture emerged in the affected members of the AD families who had been followed from onset until death. However, the duration of AD in affected members of the AD families was longer than was found among the unrelated AD patients. Proportional hazard model estimates indicated that risk of death after onset of AD in members of AD families increased with increasing age at onset by a factor of 1.08 (95% CI, 1.02 to 1.14) for each additional year of age at the onset of AD, was lower in women than in men (HR = 0.47; 95% CI, 0.26 to 0.85), and did not depend on ε4 gene dose (HR = 0.93; 95% CI, 0.61 to 1.41). Duration of AD was similar in probands and in other affected AD family members ($p = 0.85$) despite earlier average onset in probands.

Table 2. Duration of Alzheimer's disease (AD) (yr)

Affected sporadic case subjects

	Men			Women			All		
Genotype	n	Mean	(SD)	n	Mean	(SD)	n	Mean	(SD)
ε3/ε3	10	6.3	(2.7)	19	7.8	(3.2)	29	7.3	(3.0)
ε3/ε4	15	8.1	(3.8)	37	9.1	(4.2)	52	8.8	(4.1)
ε4/ε4	7	7.6	(3.9)	9	7.7	(3.9)	16	7.6	(3.7)
Total	32	7.4	(3.5)	65	8.5	(3.9)	97	8.2	(3.8)

Affected members of AD families

	Men			Women			All		
Genotype	n	Mean	(SD)	n	Mean	(SD)	n	Mean	(SD)
ε3/ε3	2	9.0	(2.8)	8	9.3	(4.5)	10	9.2	(4.0)
ε3/ε4	10	6.7	(3.0)	21	10.1	(3.9)	31	9.0	(2.9)
ε4/ε4	6	9.0	(4.8)	9	10.7	(4.6)	15	10.0	(4.6)
Total	18	7.7	(3.7)	38	10.1	(4.1)	56	9.3	(4.1)

	Probands			Others			All		
Genotype	n	Mean	(SD)	n	Mean	(SD)	n	Mean	(SD)
ε3/ε3	3	12.7	(2.9)	7	7.7	(3.6)	10	9.2	(4.0)
ε3/ε4	10	8.4	(2.6)	21	9.3	(4.4)	31	9.0	(3.9)
ε4/ε4	7	9.6	(3.9)	8	10.4	(5.4)	15	10.0	(4.6)
Total	20	9.5	(3.3)	36	9.3	(4.5)	56	9.3	(4.1)

Allele and genotype frequencies. There was evidence that the ε2/ε3 genotype becomes more frequent with age. The frequency of the ε2 allele (found in the ε2/ε3 and ε2/ε4 genotypes) increased with age in each subject group. However, this trend was not statistically significant when both the ε2/ε3 and ε2/ε4 genotypes were evaluated together (M-H controlling for subject group, $p = 0.06$). Looking specifically at the ε2/ε3 genotype, table 3 shows genotypic frequencies for each group. The frequency of ε2/ε3 increased with age in each subgroup and this increase was statistically significant (M-H controlling for subgroup, $p = 0.004$). The increase in ε2/ε3 with age was most evident in the control subjects (who were cognitively intact), from 7% to 23% ($p = 0.02$).

The ε4 allele was less frequently found with increasing age in each group except in the control subjects, who experienced essentially no change in ε4 frequency with age. Substantial decreases in ε4 were seen with increasing age of onset in the affected subjects, especially the affected members of AD families ($p = 0.004$). Substantial decreases in ε4 were also seen with increasing age at examination in members of the AD families who had normal cognitive function at the time of examination: from 30% to 21% ($p = 0.06$). These decreases are consistent with the prior diagnosis of AD in subjects with the ε4/ε4 and ε3/ε4 genotypes. They imply that a large proportion of persons in AD families who have the ε4/ε4 genotype are diagnosed as having AD by age 75. As unaffected ε4/ε4 subjects were lost to attrition, the increased risk for AD shifted to the ε3/ε4 and other lower-risk genotypes.

The ε4 frequency decreased, but not significantly, with age in the unrelated AD case subjects

Table 3. Genotypic frequencies*

	Apolipoprotein E genotype									
	ε2/ε3†		ε2/ε4		ε3/ε3		ε3/ε4		ε4/ε4	
Group	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)
Controls										
60-66	6.7	(4)	6.7	(4)	68.3	(41)	16.7	(10)	1.7	(1)
67-74	16.9	(22)	2.4	(3)	53.2	(66)	23.4	(29)	3.2	(4)
75+	23.1	(12)	0.0	(0)	48.1	(25)	28.9	(15)	0.0	(0)
AD cases										
60-66	0.0	(0)	3.6	(1)	25.0	(7)	50.0	(14)	21.4	(6)
67-74	0.0	(0)	4.8	(2)	28.6	(12)	50.0	(21)	16.7	(7)
75+	3.0	(1)	6.1	(2)	30.3	(10)	51.5	(17)	9.1	(3)
Unaffected‡										
60-66	4.2	(3)	2.8	(3)	36.6	(26)	54.9	(39)	1.4	(1)
67-74	5.7	(4)	4.3	(3)	44.3	(31)	42.9	(30)	2.9	(2)
75+	8.9	(7)	1.3	(1)	53.2	(42)	32.9	(26)	3.8	(3)
Affected‡										
60-66	0.0	(0)	0.0	(0)	10.0	(4)	52.5	(21)	37.5	(15)
67-74	2.5	(2)	0.0	(0)	13.8	(11)	63.8	(51)	20.0	(16)
75+	2.6	(1)	2.6	(1)	31.6	(12)	47.4	(18)	15.8	(6)
Expected§	14.4		2.6		58.7		22.2		2.1	

* Age indicates age at onset in affected persons and age at normal examination in unaffected persons. APOE allele frequencies were essentially equivalent in the black and white subjects in the Duke Established Population for Epidemiologic Studies in the Elderly: 0.12 and 0.12 for ε2, 0.71 and 0.74 for ε3, and 0.17 and 0.13 for ε4, respectively.
† The one control with the ε2/ε2 genotype was combined with those having the ε2/ε3 genotype.
‡ Members of AD families.
§ Utermann et al (1980) and Hardy-Weinberg equilibrium.
AD Alzheimer's disease.

($p = 0.25$). APOE ε4 frequency remained essentially constant in control subjects ($p = 0.57$). Nonetheless, the decrease from 21% to 9% with age in the AD case subjects who had the ε4/ε4 genotype and the absence of ε4/ε4 in controls older than age 75 suggests that unaffected persons with the ε4/ε4 genotype are uncommon by age 80.

Closer examination of the control group showed that the apparently constant ε4 allele frequency may have resulted from a decrease in ε4/ε4 counterbalanced by an increase in ε3/ε4. The increase in ε3/ε4 with age was unexpected given prior reports that associated the ε3/ε4 genotype with heart disease. Evaluation of the men in the data set, who in general have higher risk of cardiovascular disease, separately from the women in the data set indicated that the overall increase in ε3/ε4 was attributable solely to women. The frequency of ε3/ε4 was essentially constant in men over the various age groups (20.0%, n = 5, ages 60 to 66; 22.6%, n = 12, ages 67 to 74; and 20.0%, n = 5, ages 75+) and increased with age in women (14.3%, n = 5, ages 60 to 66; 23.9%, n = 17, ages 67 to 74; and 37.0%, n = 10, ages 75+).

Discussion. This study demonstrates that APOE gene dose does not have a significant effect on the duration of AD, defined as onset of clinical symptoms until death. The absence of a statistically significant association between ε4 gene dose and duration of AD in AD families and among unrelated AD cases contrasts sharply with the strong association found between ε4 gene dose and the risk of AD, both familial and sporadic.[3-16] These data suggest that the processes leading to the onset of the clinical symptoms of AD differ from those that determine its clinical course. Thus, factors other than APOE genotype may exist that contribute to the determination of the progression of symptomatic AD.

The longer duration of AD in multiplex AD families may involve the more stringent evaluation of age at onset and other clinical findings in members of the AD families where multiple family members are affected. It could also reflect sampling practices, such that probands with earlier onset ages are more likely to be identified and ascertained than cases with later onset. Hence, the earlier age at onset for probands in the AD families compared with the unrelated AD cases and with subsequently ascertained affected members of the AD families may indicate that AD families are identified through relatively young probands who have surviving siblings. However, we cannot exclude the possibility that this is a real phenomenon unique to familial AD cases.

The longer survival of affected women compared with affected men found in this study indicates that the higher age-specific prevalence of AD in women found in other studies[38] might arise, at least partially, from higher age-specific survival in affected women rather than from intrinsic differences in risk for AD in men and women. The higher prevalence of AD in women may also result from the longer survival of women (especially those with the ε3/ε4 genotype) compared with men that is also suggested by this study. The inverse relationship between ε4 gene dose and the ages at onset and at death in the AD families (seen primarily in women) may also reflect the longevity of women. Compared with men, a larger proportion of women, especially those with the ε3/ε4 and ε3/ε3 genotypes, survive into late age to have AD diagnosed. The absence of inverse relationships between ages at onset and at death in the unrelated cases may have resulted from the low autopsy rate, especially for women, at advanced ages.

AD patients with the ε4/ε4 genotype have greater amyloid β-peptide deposition at the onset of clinical symptoms than ε3/ε3 patients and continue to have a higher rate of deposition after diagnosis.[39] The lack of association between ε4 dose and the progress of AD implies that amyloid load, higher in ε4/ε4 than ε3/ε3 patients, also may not be a major determinant of the clinical course of AD.

The mean "age at onset" used in this study indicates the average age at the onset of AD in affected persons. It does not directly indicate the risk of AD. This usage contrasts with the use of "mean age at onset" in Corder et al[12] to describe the age at which half of surviving subjects in a cohort of AD families had become affected with AD, a measure of risk for developing AD. The "mean ages at onset," as used by Corder et al,[12] for each APOE ε4 gene dose illus-

trated the influence of APOE genotype on the risk of becoming affected with AD. For subjects with each APOE ε4 gene dose, they constructed "mean age at onset" from the proportion of living subjects still unaffected by AD after each successive occurrence of AD and from age information.[34] Thus, indirectly, survivorship affects the "mean age at onset." The differing patterns of risk for men and women in relation to APOE ε4 found by ourselves[40] (a gene dose effect for both men and women) and by Payami et al[41] (a more complex pattern of risk) underscore the need for prospective population-based studies to define the competing risks of AD and death for men and women in relation to APOE genotype.

This work extends previous work[15] identifying genotype-specific risks of AD that change with age. Both risk related to the ε4 allele and protection related to the ε2 allele appear to be strongest between ages 60 and 66 and then to diminish with age. This analysis is consistent with other reports[22-26] that indicate increases in ε2/ε3 with age in general populations and demonstrates that selective survival related to ε2/ε3 may operate as early as age 60 and continue into late age. The unexpectedly large increase in the frequency of the ε2/ε3 genotype with age in the control subjects, who were cognitively intact, is consistent with the belief that the ε2 allele is protective for both AD and death. The smaller increases in ε2/ε3 found for the AD-affected members in both the families and unrelated cases likely reflect a combination of the waning of protection for AD and the greater frequency of the ε2/ε3 genotype with age. There was evidence against strong selective mortality related to the ε3/ε4 genotype before age 80, especially among women.

Collectively, the changes in APOE allele frequencies with age imply that AD and death are dependent competing risks involving APOE genotype that change, individually and with respect to each other, with age. These competing risks have not been defined in the population-based studies that are needed to counsel patients appropriately, who despite the lack of preventive interventions for AD want to know their APOE genotype.

By age 75, the genotypic frequencies in affected members of the AD families approximate those found in the unrelated case subjects of the same age. Genotypic frequencies in unaffected members of the AD families examined after age 75 also appear to be converging with those in the control subjects, although they continue to have lower ε2/ε3 frequency and higher ε4/ε4 frequency than the control subjects. This later observation is not unexpected given that these individuals are related to AD patients.

In summary, APOE ε4 gene dose determines the risk of AD but other factors, including age at onset and gender, are more important determinants of survival in affected subjects. This implies that the processes that initiate AD are likely to differ from those that determine its clinical course. The higher prevalence of AD in women may be a result of longer survival in affected women and the longer survival of women with the ε3/ε4 genotype, at high risk of AD, compared with men. The ε2/ε3 genotype became more common with age, implying a decreased risk for common causes of death in persons with the ε2/ε3 genotype. The competing risks of AD and death depend on APOE genotype and change with age, individually and with respect to each other. These risks need to be defined in population-based studies to generate the appropriate risk data to counsel patients and their families accurately.

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