

# Interactions between Apolipoprotein E and Apolipoprotein(a) in Patients with Late-Onset Alzheimer Disease

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**Background:** Apolipoprotein(a) [apo(a)], the distinctive, highly polymorphic glycoprotein of lipoprotein(a), shares a series of common features with apolipoprotein E (apoE), which is implicated in the development of Alzheimer disease.

**Objective:** To determine whether apo(a) is associated with Alzheimer disease.

**Design:** Case-control study.

**Setting:** University hospitals in Europe.

**Participants:** 285 patients with Alzheimer disease and 296 controls.

**Measurements:** Plasma lipoprotein(a) levels, size of the apo(a) isoforms, and apoE and apo(a) genotyping.

**Results:** Among carriers of the apoE  $\epsilon$ 4 allele, lipoprotein(a) was associated with a progressive, age-dependent increased risk for late-onset Alzheimer disease (odds ratio for patients >80 years of age, 6.0 [95% CI, 1.2 to 30.8];  $P < 0.01$ ). Among noncarriers older than 80 years of age, lipoprotein(a) was associated with a reduced risk for Alzheimer disease (odds ratio, 0.4 [CI, 0.2 to 0.9];  $P < 0.05$ ).

**Conclusions:** In this convenience sample, lipoprotein(a) was an additional risk factor for late-onset Alzheimer disease in carriers of the apoE  $\epsilon$ 4 allele. However, lipoprotein(a) may protect against late-onset Alzheimer disease in noncarriers.

The apolipoprotein E (apoE) E4 isoform has been implicated in the pathogenesis of Alzheimer disease (1). Not all carriers of the apoE  $\epsilon$ 4 allele develop Alzheimer disease; therefore, additional risk factors probably exist (2). The very-low-density lipoprotein receptor (3) and the low-density lipoprotein receptor-related protein (4) (a receptor that is expressed by human neurons and internalizes apoE [5]) have been associated with Alzheimer disease and with defects in neuronal migration (6).

Apolipoprotein E shares a series of features with another polymorphic apolipoprotein, apolipoprotein(a) [apo(a)]. Apolipoprotein(a) is a glycoprotein of unknown function that is present only in humans, great apes, and hedgehogs (7, 8). Apolipoprotein(a) is partly homologous to plasminogen, which contains five copies of a motif called kringles (kringle I to kringle V). Apolipoprotein(a) does not contain kringle I through kringle III but does contain a variable number of kringle IV copies that are repeated in tandem. The liver is the major site of synthesis of apo(a). In plasma, apo(a) circulates, bound to apolipoprotein B-100 on low-density lipoproteins, to form the atherogenic lipoprotein(a) particle. In addition, apo(a) is expressed in monkeys' brains (9), where its role remains unknown. Apolipoprotein(a) binds to the same receptors as apoE (10, 11). Because of the similarities between apoE and apo(a), we hypothesized that apo(a) is also associated with Alzheimer disease.

## Methods

### Clinical Study

We examined plasma levels of lipoprotein(a) in patients with Alzheimer disease and in controls. All participants underwent genotyping for apoE, all participants were white and were recruited in Europe, and all women were postmenopausal. We identified 285 patients with Alzheimer disease (according to *Diagnostic and Statistical Manual of Mental Disorders IIR* criteria and National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria) who were initially part of a French clinical trial on a new anti-Alzheimer disease drug. We randomly recruited controls in northern France who

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**Table 1. Clinical Characteristics of Participants**

Variable	Persons without the Apolipoprotein E $\epsilon$ 4 Allele		Persons with the Apolipoprotein E $\epsilon$ 4 Allele	
	Controls	Patients with Alzheimer Disease	Controls	Patients with Alzheimer Disease
Participants, <i>n</i>	222	115	74	170
Men/women, <i>n/n</i>	80/142	51/64	18/56	66/104
Men, %	36	44	24	39
Mean age $\pm$ SD (range), <i>y</i>	77.6 $\pm$ 7.4 (60–88)	71.4 $\pm$ 7.1 (57–88)	77.1 $\pm$ 7.3 (61–88)	71.2 $\pm$ 6.0 (59–87)
Mean age at onset of Alzheimer disease $\pm$ SD, <i>y</i>	–	68.3 $\pm$ 7.5	–	67.8 $\pm$ 6.5
Professional status at retirement age, <i>n</i> (%)				
Self-employed	29 (13)	9 (8)	12 (16)	21 (12)
Executives	18 (8)	27 (23)	6 (8)	28 (16)
Employees	146 (66)	38 (33)	48 (65)	75 (44)
Unemployed	20 (9)	23 (20)	7 (9)	20 (12)
Unknown	9 (4)	18 (16)	1 (1)	26 (15)
Plasma lipoprotein(a) level, <i>mg/L</i> *				
0 percentile	10	4	2	1
25th percentile	32	31	29	37
50th percentile	85	86	69	98
75th percentile	290	178	155	201
100th percentile	1750	1260	700	1170
Mean size of apolipoprotein(a) isoforms (kringle IV (TTTTA) <sub>6</sub> repeats, %	23.1 $\pm$ 4.7	24.2 $\pm$ 4.6	24.0 $\pm$ 4.5	24.1 $\pm$ 4.6
	69	72	68	70

\* Nine extreme values were not included in the analysis.

were residents of nursing homes and were at least 60 years of age. Only patients without signs of dementia whose Mini-Mental State Examination scores were within normal limits for age, sex, and education level were included in the analysis ( $n = 296$ ). Because precise information on education was available for only a subset of participants and because of the association between occupation, education, and Alzheimer disease (12), participants were divided into five groups according to their professional status when they had reached retirement age: self-employed, executives, employees, unemployed, and unknown.

### Laboratory Methods

Levels of lipoprotein(a) and the size of the apo(a) isoforms were determined on plasma samples, which had been stored for 3 to 5 years at  $-80^{\circ}\text{C}$  and had not previously been thawed (13, 14). We used the sandwich enzyme-linked immunosorbent assay to measure the plasma concentrations of lipoprotein(a); the assay used mouse monoclonal antibodies of well-defined specificity and was independent of the size of the apo(a) isoforms (13). In addition, we characterized the (TTTTA)<sub>*n*</sub> pentanucleotide repeat polymorphism in the apo(a) gene using polymerase chain reaction amplification of genomic DNA and size fractionation of amplified fragments by polyacrylamide gel electrophoresis (15). We performed apoE genotyping using polymerase chain reaction amplification and cleavage with *Hha*I (16).

### Statistical Analysis

Statistical analysis was performed by using SAS software, version 6.12 (SAS Institute, Inc., Cary,

North Carolina). Means and SDs were calculated for quantitative variables. Categorical data were tested by using the Pearson chi-square statistic or the Fisher exact test, when necessary. A multivariate logistic regression model was used to estimate adjusted odds ratios and 95% CIs. Covariates were age, sex, professional status, apo(a) genotype, and size of the smaller apo(a) isoform.

## Results

A total of 285 patients with Alzheimer disease (117 men and 168 women; mean age  $\pm$  SD, 71  $\pm$  7 years) and 296 controls (98 men and 198 women; mean age  $\pm$  SD, 77  $\pm$  7 years) were included in the study. Of the 285 patients with Alzheimer disease, 200 (70.2%) had received a diagnosis of dementia at or after 65 years of age (late-onset Alzheimer disease). All participants were categorized according to apoE genotype (apoE  $\epsilon$ 4 carriers or noncarriers) (Table 1). As expected (1), the percentage of carriers was higher among patients with Alzheimer disease (170 of 285 [60%]) than among controls (74 of 296 [25%]; odds ratio, 4.4 [95% CI, 3.1 to 6.4];  $P < 0.001$ ). At retirement age, patients with Alzheimer disease were more likely than controls to have held executive positions and were less likely to have been employees.

Plasma lipoprotein(a) levels ranged from less than 1 mg/L to 1750 mg/L. As was observed in other samples of white persons (7, 17), the overall distribution of plasma lipoprotein(a) levels was markedly skewed toward lower values (median, 86 mg/L [ $n = 581$ ]). Among carriers of the apoE  $\epsilon$ 4 allele, plasma lipoprotein(a) levels were higher in

patients with Alzheimer disease than in controls (median, 98 mg/L [ $n = 170$ ] compared with 69 mg/L [ $n = 74$ ];  $P = 0.049$ ); in addition, patients with Alzheimer disease were less likely than controls to have plasma lipoprotein(a) levels less than 100 mg/L (51% compared with 66%;  $P = 0.03$ ). The difference in the distribution of plasma lipoprotein(a) levels among apoE  $\epsilon 4$  carriers with or without Alzheimer disease was similar to that reported by Sandholzer and colleagues (17) for patients with or without coronary artery disease. Among noncarriers, median plasma lipoprotein(a) levels were similar in patients with Alzheimer disease and in controls (86 mg/L [ $n = 115$ ] compared with 85 mg/L [ $n = 222$ ];  $P > 0.2$ ). However, values for the 75th and 100th percentiles were lower in patients with Alzheimer disease than in controls (178 mg/L compared with 290 mg/L and 1260 mg/L compared with 1750 mg/L, respectively).

Multivariate logistic analysis was performed to estimate the lipoprotein(a)-associated risk for late-onset Alzheimer disease. Covariates were age, sex, and professional status; plasma lipoprotein(a) level was included in the model as a continuous variable. Among carriers of the apoE  $\epsilon 4$  allele, lipoprotein(a) was associated with an age-dependent, progressive risk for Alzheimer disease, as expressed by the odds ratio, which increased from 0.1 (CI, 0.0 to 0.6) for patients 65 to 69 years of age to 6.0 (CI, 1.2 to 30.8) ( $P \leq 0.01$ ) for patients older than 80 years of age (Table 2). Strikingly, the association between lipoprotein(a) levels and Alzheimer disease among noncarriers was conversely related to that observed among carriers: The odds ratio decreased from 3.4 (CI, 0.8 to 13.7) for patients 65 to 69 years of age to 0.4 (CI, 0.2 to 0.9) for patients older than 80 years of age. These associations persisted when patients with early-onset Alzheimer disease were included in the analyses, when various thresholds for plasma lipoprotein(a) levels were selected, and when log-transformed values rather than raw plasma lipoprotein(a) levels were used in the analyses.

Binding of lipoprotein(a) to the very-low-density lipoprotein receptor (11) and the low-density lipoprotein receptor-related protein (10) may depend

on the size of the apo(a) glycoprotein. We examined the size of the apo(a) isoforms in our cohort. Overall, 10% of participants (57 of 581) had no apo(a) isoform detectable by immunoblot analysis. The frequency distribution of the size of the apolipoprotein(a) isoforms was similar for all participants (Table 1). We also characterized the (TTTTA)<sub>n</sub> polymorphism in the 5' flanking region of the apo(a) gene, which is in strong linkage disequilibrium with the size of the apo(a) gene. As was observed in other samples of white persons (15), the most frequent allele contained 8 copies of the TTTTA repeat (69.3%) (Table 1). No significant difference was seen in the distribution of the TTTTA alleles among all participants. In addition, the associations between plasma lipoprotein(a) levels and the risk for Alzheimer disease persisted in multivariate logistic analysis when the apo(a) genotype or the size of the smaller apo(a) isoform was added to the model (data not shown). Taken together, these analyses indicate that the association between Alzheimer disease and lipoprotein(a) level was independent of the size of the apo(a) isoforms.

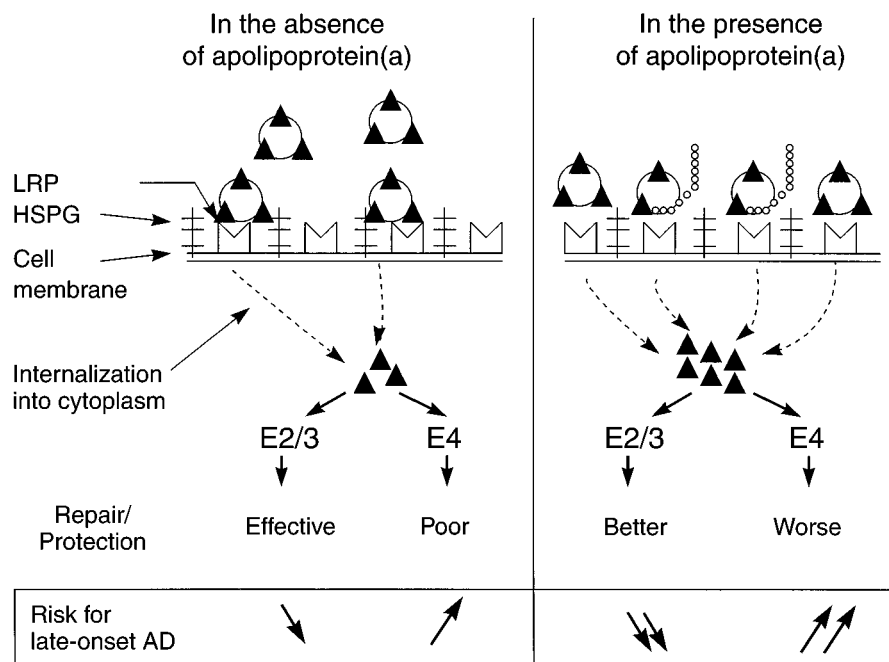
## Discussion

The major finding of our study is the age-dependent and apoE genotype-dependent association between lipoprotein(a) and the risk for late-onset Alzheimer disease. Lipoprotein(a) was associated with an increased risk for late-onset Alzheimer disease in carriers of the apoE  $\epsilon 4$  allele and with a reduced risk in noncarriers.

Plasma levels of lipoprotein(a) are principally determined by the apo(a) gene (7, 18, 19). In our study, it is unlikely that age, environmental factors (such as hormone replacement therapy in women), or Alzheimer disease itself can explain the finding of higher plasma lipoprotein(a) levels in patients with Alzheimer disease who were carriers of the apoE  $\epsilon 4$  allele. If such factors had affected the association, a similar elevation in plasma lipoprotein(a) levels would have been observed among patients with Alzheimer disease who were not carriers.

**Table 2. Association between Plasma Lipoprotein(a) Levels and Late-Onset Alzheimer Disease, according to Age at Disease Onset and Presence or Absence of an Apolipoprotein E  $\epsilon 4$  Allele**

Age	Persons without the Apolipoprotein E $\epsilon 4$ Allele			Persons with the Apolipoprotein E $\epsilon 4$ Allele		
	Patients with Alzheimer Disease	Controls	Odds Ratio (95% CI)	Patients with Alzheimer Disease	Controls	Odds Ratio (95% CI)
<i>y</i>	<i>n</i>			<i>n</i>		
65-69	11	24	3.4 (0.8-13.7)	22	9	0.1 (0.0-0.6)
70-74	31	30	0.8 (0.4-1.6)	53	11	0.8 (0.2-2.7)
75-80	19	45	1.2 (0.4-3.4)	31	13	4.6 (1.2-17.7)
>80	18	104	0.4 (0.2-0.9)	15	35	6.0 (1.2-30.8)



**Figure.** Proposed model for the dual, apolipoprotein E (apoE) genotype-dependent association between lipoprotein(a) and Alzheimer disease (AD). **Left.** Absorption of apoE in the absence of apolipoprotein(a) [apo(a)]. ApoE-containing lipoproteins bind heparan sulfate proteoglycans (HSPG) and low-density lipoprotein receptor-related protein (LRP) to be internalized in the neuron. Once internalized, apoE E2/3 isoforms have a protective effect; the apoE E4 isoform has the opposite effect. **Right.** Absorption of apoE in the presence of apo(a). Lipoproteins that contain both apoE and apo(a) bind to the cell surface with a higher affinity than those that contain only apoE, and a larger fraction of apoE is internalized in the cell. In persons without the apoE  $\epsilon 4$  allele, the increased amount of apoE in the cell contributes to better protection; in carriers of this allele, neurons have a higher risk for degeneration. Small circles represent kringles of apo(a); triangles represent apoE; large circles represent apoE-containing lipoproteins.

Accordingly, our data strongly support the concept of gene-gene interactions in the pathogenesis of Alzheimer disease.

The mechanism by which lipoprotein(a) is associated with Alzheimer disease and the reasons why this association depends on age and apoE genotype remain speculative. We propose the following hypothesis (**Figure**). In vitro studies have demonstrated that lipoproteins containing apoE bind heparan sulfate proteoglycans and low-density-lipoprotein receptor-related protein at the surface of neuronal cells to be internalized (20). Once internalized, the apoE E2/E3 isoforms protect against neuronal degeneration and promote neurite outgrowth, whereas the apoE E4 isoform has the opposite effect. A fraction of lipoprotein(a) particles carry apoE (21); these particles have a greater affinity for heparan sulfate proteoglycans than lipoprotein(a) particles without apoE (22). We believe that apo(a) or lipoprotein(a) particles—transported by the blood, diffused through the blood-brain barrier, or synthesized locally—promote the binding of apoE-containing lipoproteins to the cell surface and the internalization of apoE. In persons without the apoE  $\epsilon 4$  allele, an increased intracellular amount of apoE2/E3 mediated by lipoprotein(a) may, in the long term, have a beneficial effect on neuronal function and survival. In carriers of apoE  $\epsilon 4$ , however, an elevation in the intracellular

content of apoE E4 may promote neuronal degeneration in aging, even if it is potentially beneficial earlier in life (as suggested by the decreased odds ratio observed in persons 65 to 69 years of age). Our hypothesis is supported by the co-localization of apo(a) and apoE in the human brain (data not shown) and in vessel walls, where a preferential deposition of apo(a) and apoE was detected in relation to vessel wall proteoglycans (23). Furthermore, the protective effect of lipoprotein(a) may account for the unexpectedly high plasma concentrations of lipoprotein(a) in centenarians (24). Finally, our hypothesis may provide some clue for the unusual species distribution of apo(a) (7).

Our study was performed on a limited convenience sample of white persons. Additional studies are warranted to examine whether the dual, apoE-dependent association between lipoprotein(a) and Alzheimer disease is valid in other populations. If confirmed, our observations may have a major effect on the prognosis, treatment, and understanding of Alzheimer disease.

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