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APOE ε2 is associated with intact cognition but increased Alzheimer pathology in the oldest old

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ABSTRACT

Background: Many studies have examined the role of APOE genotype in the development of dementia, specifically Alzheimer disease (AD). The APOE ε4 allele (APOE4) is a risk factor for both clinical and neuropathologic AD whereas the APOE ε2 allele (APOE2) seems to be protective. This would predict, even with advanced age, that APOE2 carriers would be less likely to have dementia and less likely to meet pathologic criteria for AD.

Methods: The first 85 genotyped participants from The 90+ Study to come to autopsy were included. All-cause dementia (using *DSM-IV* criteria) and AD (using National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria) diagnoses were made by consensus conference using all available information including neuropsychological testing, neurologic examination, and medical records. Neuropathologic examination included Braak and Braak staging for plaques and tangles and diagnosis of neuropathologic AD using National Institute on Aging–Reagan criteria.

Results: Across all genotypes, 58.5% of subjects were diagnosed with clinical dementia (81% of dementia was AD) and 50.0% met neuropathologic criteria for AD. Compared to those with an APOE ε3/ε3 genotype (APOE3/3), APOE4 carriers were more likely to be diagnosed with dementia (odds ratio [OR] = 12.2, 95% confidence interval [CI] = 1.5–102.0), whereas APOE2 carriers were not (OR = 0.3, 95% CI = 0.1–1.3). Surprisingly, both APOE4 (OR = 4.6, 95% CI = 1.3–16.5) and APOE2 (OR = 7.8, 95% CI = 1.5–40.2) carriers were more likely to meet neuropathologic criteria for AD than those with APOE3/3 genotype.

Conclusions: In the oldest old, the presence of the APOE ε2 allele (APOE2) was associated with a somewhat reduced risk of dementia, but paradoxically was associated with increased Alzheimer disease (AD) neuropathology. Therefore, oldest old APOE2 carriers may have some mechanism that contributes to the maintenance of cognition independently of the formation of AD pathology.

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GLOSSARY

AD = Alzheimer disease; **APOE2** = the APOE ε2 allele; **APOE4** = the APOE ε4 allele; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **CI** = confidence interval; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **MMSE** = Mini-Mental State Examination.

The role of APOE genotype has been studied extensively in the context of the risk of development of Alzheimer disease (AD). Of the three APOE alleles (ε2, ε3, ε4), the ε3 allele is the most common in humans, representing approximately 77% of all alleles in Caucasians, whereas the ε2 (8%) and ε4 (15%) alleles are much less frequent.[1]

Previous research suggests that the ε2 allele (APOE2) has a protective effect against the development of AD. In particular, APOE2 is associated with a delayed age at onset of AD[2] and is present with reduced frequency in sporadic cases of AD.[3] Moreover, APOE2 carriers have less cortical β-amyloid,[4] fewer senile plaques, and fewer neurofibrillary tangles[5-8] than people with the more com-

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mon ε3/ε3 genotype (APOE3/3). In cognition, APOE2 is associated with preserved memory[9-11] in normal elderly.

Whereas the majority of studies demonstrate that APOE2 is protective against clinical AD as well as AD neuropathology, it has been hypothesized that this protective influence may be different in older populations.[12] There has been no direct investigation of the prevalence of clinical AD and AD neuropathology in the oldest old (aged 90 and older) with respect to the distribution of APOE genotype in this population. Determining if the relationship among these three factors is consistent with findings from younger age groups will allow for a better understanding of the clinicopathologic relationship in human populations of more advanced ages. Therefore, we examined the relationship among APOE, cognition, and AD neuropathology in the oldest old participants of The 90+ Study, a population-based study of aging and dementia.

METHODS

Participants. Participants in the study were enrolled in The 90+ Study, a prospective longitudinal population-based study of aging and dementia in the oldest old. Of the first 89 individuals to come to autopsy, APOE genotype was determined in 85 cases. To maintain mutually exclusive groups, three participants who had the APOE genotype ε2/ε4 were excluded from all analyses. Thus, there were 82 participants (22 men and 60 women) included in the final analysis. The demographic information of the participant population is summarized in table 1.

Determination of clinical diagnosis. As members of The 90+ Study, all participants received a neurologic examination and neuropsychological testing every 6 months, which included the Mini-Mental State Examination (MMSE) and other tests previously described.[13] Medical history information was obtained including comorbidities such as depression, stroke, congestive heart failure, atrial fibrillation, and Parkinson disease. Additionally, most participants had available medical records and neuroimaging (CT/MRI) that were used in the clinical diagnosis. Clinical diagnoses were determined by a consensus diagnostic conference, using all available information. Dementia diagnosis was established using *DSM-IV* criteria. Clinical Alzheimer's Disease diagnoses were established using National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria[14] for possible or probable AD. Investigators were blinded to the participants' APOE genotypes when clinical diagnoses were made. The Institutional Review Board of the University of California, Irvine, approved all procedures.

Neuropathologic measures and diagnosis. Before dissection, the whole brain was weighed. One hemisphere of each individual was selected based on a neurologist's impression of any asymmetry in clinical features for use in the final neuropathology diagnosis. Braak & Braak neurofibrillary tangle and beta-amyloid plaque staging was based upon previously published criteria.[15] Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria were used to determine the frequency of both diffuse and neuritic plaques.[16] National Institute on Aging (NIA)-Reagan criteria[17] were used to determine neuropathologic AD diagnosis. For the purposes of this study, the participants were considered to have a pathologic diagnosis of AD if they met criteria for intermediate or high likelihood of AD. Intermediate or high likelihood of AD was defined as CERAD stages B or C combined with Braak tangle stage III–VI. All procedures were performed at the University of California, Irvine, Alzheimer's Disease Research Center using previously published methods.[18]

Statistical analysis. The majority of subjects included in the autopsy study had multiple visits to the clinic as subjects were evaluated every 6 months. We used clinical data from the visit closest to the time of death (mean = 4.6 months) for statistical analyses. We examined the relationship between APOE genotype, age at death, postmortem interval, gender, and education to determine if these variables should be included as covariates in subsequent analyses. Although none of the variables were associated with the outcome variables, age at death and gender were retained in the model as covariates, in order to maintain statistical continuity with APOE studies in younger groups. A logistic regression was performed to examine the relationship of APOE genotype to both clinical dementia diagnosis and neuropathologic AD diagnosis. A linear regression was performed to examine the effect of APOE genotype on MMSE scores while controlling for age at last visit and gender. Plaque and tangle measures were compared using ordinal logistic regression controlling for age at death and gender. All statistical analyses were performed using SAS (version 9.1) and SPSS (version 15).

RESULTS

The baseline characteristics for the participants are summarized in table 1. Participants were 26.8% men with a mean age at death of 97.3 years. Most participants (68.3%) had APOE3/3, 13.4% had APOE2, and 18.3% had APOE4. Of all participants, 58.5% were clinically diagnosed with all-cause dementia (indicated in table 1 as clinical dementia), 47.6% were diagnosed with clinical AD, and 50.0% met NIA-Reagan criteria for intermediate or high likelihood of AD at autopsy. There were no significant differences between genotypes in age, sex, education, Braak tangle staging, brain weight, other neuropathologic features (table 1), or any of the comorbidities (data not shown). However, there were significant differences between genotypes in dementia status, clinical AD status, NIA-Reagan criteria, Braak plaque staging, and MMSE scores.

Of the 9 participants (10.9%) who had a non-AD dementia diagnosis, 5 had vascular dementia, 1 had dementia with Lewy bodies, 1 had frontotemporal dementia, and 3 had dementia of unknown etiology. Similarly, of the participants who were demented but did not meet criteria for pathologic AD, the most common neuropathological feature was simply mild Braak changes, although a few participants had Lewy bodies, hippocampal sclerosis and infarctions (table 1).

Table 1 Participant demographic information

	APOE 2/-	APOE 3/3	APOE 4/-	All participants*
All participants	11 (13.4)	56 (68.3)	15 (18.3)	82 (100)
Men	3 (27.3)	15 (26.2)	4 (26.7)	22 (26.8)
Education				
Less than college	6 (54.5)	15 (27.3)	5 (33.3)	26 (32.1)
Any college	4 (36.4)	26 (47.3)	6 (40.0)	36 (44.4)
Any graduate school	1 (9.1)	14 (25.5)	4 (26.7)	19 (23.5)
Clinical dementia†	3 (27.3)	31 (55.4)	14 (93.3)	48 (58.5)
Clinical Alzheimer disease†	3 (27.3)	25 (44.6)	11 (73.3)	39 (47.6)
NIA-Reagan criteria†				
No AD	1 (9.1)	19 (33.9)	0 (0)	20 (24.4)
Low likelihood	1 (9.1)	16 (28.6)	4 (26.7)	21 (25.6)
Intermediate likelihood	7 (63.6)	16 (28.6)	4 (26.7)	27 (32.9)
High likelihood	2 (18.2)	5 (8.9)	7 (46.7)	14 (17.1)
Braak plaque staging†				
Stage 0	0 (0)	21 (37.5)	0 (0)	21 (25.6)
Stage A	1 (9.1)	16 (28.6)	3 (20.0)	20 (24.4)
Stage B	8 (72.7)	16 (28.6)	4 (26.7)	28 (34.1)
Stage C	2 (18.2)	3 (5.4)	8 (53.3)	13 (15.9)
Braak tangle staging				
Stages I–II	1 (9.1)	13 (23.2)	1 (6.7)	15 (18.3)
Stages III–IV	6 (54.5)	26 (46.4)	4 (26.7)	36 (43.9)
Stages V–VI	4 (36.4)	17 (30.4)	10 (66.7)	31 (37.8)
Other neuropathologic features				
Hippocampal sclerosis	1 (9.1)	4 (7.1)	4 (26.7)	9 (11.0)
Infarctions	5 (45.5)	13 (23.2)	2 (13.3)	20 (24.4)
Lewy bodies	1 (9.1)	4 (7.1)	1 (6.7)	6 (7.3)
Age at final visit (y), mean (SD)	97.4 (3.4)	96.8 (3.7)	96.7 (3.2)	96.9 (3.6)
Age at death (y), mean (SD)	97.8 (3.4)	97.2 (3.7)	97.1 (3.3)	97.3 (3.6)
Visit–death interval (mo), mean (SD)	4.4 (3.4)	4.8 (4.0)	4.2 (3.0)	4.6 (3.7)
MMSE, mean (SD) ‡	23.6 (9.3)	17.3 (9.7)	12.2 (10.3)	17.2 (10.0)
Brain weight (g), mean (SD)	1,198 (83)	1,133 (118)	1,143 (142)	1,142 (118)

Values are n (% of genotype) unless otherwise noted.
*Three participants with the genotype APOE 2/4 were excluded from all analyses.
†χ^2 is significant at $p < 0.05$.
‡Analysis of variance is significant at $p < 0.05$.

Table 2 summarizes the associations between APOE genotype, AD neuropathology, and dementia status. Participants with APOE4 were more likely to be diagnosed with dementia (OR = 12.2, 95% confidence interval [CI] = 1.5–102.0) and clinical AD (OR = 11.5, 95% CI = 1.3–99.3) and were more likely to meet neuropathologic criteria for intermediate or high likelihood of AD at autopsy (OR = 4.6, 95% CI = 1.3–16.5) compared to those with APOE3/3 while controlling for age and gender. Participants with APOE2, like participants with APOE4, were also more likely to meet neuropathologic criteria for intermediate or high likelihood of AD compared to participants with APOE3/3 (OR = 7.8, 95% CI = 1.5–40.2); however, they were not more likely to be diagnosed with dementia (OR = 0.3, 95% CI = 0.1–1.3).

When examining specific neuropathologic markers, the oldest-old subjects with APOE2 had a higher Braak plaque stage (OR = 8.2, 95% CI = 2.2–30.4), more frequent neuritic plaques (OR = 4.4, 95% CI = 1.3–15.2), and trended toward more frequent diffuse plaques (OR = 3.0, 95% CI = 0.9–10.1) than those with APOE3/3. APOE2 carriers did not, however, have a higher Braak tangle stage (OR = 1.9, 95% CI = 0.6–6.2) than those with APOE3/3. APOE4 carriers, on the other hand, had greater levels of neuropathology than APOE3/3 carriers on all measures, including Braak plaque stage (OR = 19.6, 95% CI = 5.4–70.7), neuritic plaques (OR = 10.5, 95% CI = 3.2–34.3), diffuse plaques (OR = 9.9, 95% CI = 2.8–35.3), and Braak tangle stage (OR = 4.9, 95% CI = 1.7–14.2). The APOE4 neuropathologic findings are consistent with what would be expected with a diagnosis of dementia and intermediate or high likelihood of AD at autopsy in younger aged populations. There were no significant differences between APOE2 and APOE4 carriers on any plaque or tangle measures. The dissociation of neuropathologic and clinical determinants of AD diagnosis in APOE2 carriers, however, is striking.

Additionally, we compared the level of AD neuropathology in the 8 APOE2 carriers without dementia with the 25 APOE3/3 participants without dementia (data not shown). The APOE2 carriers without dementia were more likely to meet criteria for neuropathologic AD than were the participants with APOE3/3 without dementia ($p < 0.01$). The APOE2 carriers without dementia also had a greater Braak plaque stage ($p < 0.01$) than the APOE3/3 participants without dementia, but not a greater Braak tangle stage ($p > 0.05$).

Because a compensatory mechanism might benefit the APOE2 carriers, we tested the hypothesis that total brain weight, as an indirect measure of tissue atrophy and neuronal loss, may differentiate APOE2 carriers from noncarriers. APOE2 carriers did not have a lower brain weight compared to those with APOE3/3 ($p > 0.05$), despite their significantly higher levels of AD neuropathology (table 1). There was no difference in brain weight between APOE3/3 and APOE4 carriers ($p > 0.05$).

DISCUSSION The present findings from The 90+ Study demonstrate that the presence of APOE2 was associated with reduced risk of clinical dementia in the oldest-old, despite being associated with ad-

Table 2 Associations between APOE genotype and clinical and neuropathologic outcomes

Genotype*	APOE2/-	APOE3/3	APOE4/-
Clinical outcomes†			
Clinical dementia	0.3 (0.1–1.3)	1 (Reference)	12.2 (1.5–102.0)
AD	0.4 (0.1–1.5)	1 (Reference)	11.5 (1.3–99.3)
Neuropathologic outcomes†			
AD neuropathology‡	7.8 (1.5–40.2)	1 (Reference)	4.6 (1.3–16.5)
Braak plaque stage	8.2 (2.2–30.4)	1 (Reference)	19.6 (5.4–70.7)
Neuritic plaques	4.4 (1.3–15.2)	1 (Reference)	10.5 (3.2–34.3)
Diffuse plaques	3.0 (0.9–10.1)	1 (Reference)	9.9 (2.8–35.3)
Braak tangle stage	1.9 (0.6–6.2)	1 (Reference)	4.86 (1.7–14.2)

Values represent odds ratio (95% confidence interval) unless otherwise noted.
*Three participants with the genotype APOE 2/4 were excluded from all analyses.
†Adjusted for age and gender.
‡Defined as intermediate or high likelihood of Alzheimer disease (AD) using National Institute on Aging–Reagan criteria.

vanced AD neuropathology. This dissociation parallels our previous case report of a 92-year-old woman with an APOE 2/2 genotype, who was also a participant in the current study.[19] The current study suggests that APOE2 carriers have a compensatory/protective mechanism that permits the maintenance of cognition independently of, or despite, the formation of advanced AD neuropathology. APOE2 could exert its protective effects through several different mechanisms, which are discussed in the following paragraphs.

The APOE2 allele could protect cognition through the maintenance of synaptic integrity. Using preexisting data from a previously published study in a subset of the current participants,[18] we tested for differences in the levels of the presynaptic protein synaptophysin in the frontal cortex. Synaptophysin, a marker of synaptic integrity in the brain, is significantly reduced in AD.[20] APOE2 carriers (n = 3) trended ($p = 0.07$) toward higher levels of synaptophysin in the frontal cortex compared to those with APOE3/3 (n = 27), despite the small sample of APOE2 carriers. Because synaptophysin is very sensitive to postmortem delay, all tissue included in this study had a very short postmortem delay (mean = 4.4 hours) and there was no difference in delay across genotypes. It is possible that, despite greater levels of beta-amyloid pathology, APOE2 carriers have preserved synaptic function and thus intact cognition.

The present study found that the APOE2 carriers did not have a decreased brain weight compared to noncarriers. Furthermore, if only participants without dementia were included in the analysis, APOE2 carriers had larger brains ($p < 0.05$) than those with APOE3/3 (data not shown). These results may suggest that a larger brain may be associated with preservation of cognition despite high levels of neuritic plaques. Although a crude measure of neuronal loss, patients with AD have lower brain weights when measured immediately postmortem.[21] However, a larger brain size may not only reflect higher neuron numbers but also increased vascularization, glial cell numbers, and dendritic branching.

In addition, recent research suggests a link between various isoforms of apoE and degradation of β-amyloid.[22] ApoE2 is more effective at clearing soluble β-amyloid relative to apoE4. Despite the observation of similar neuritic plaque numbers (associated with fibrillar β-amyloid), differences in β-amyloid clearance mediated by apoE2 may lead to lower levels of oligomers or other toxic assembly states of β-amyloid, which have been linked to impaired behavior in transgenic mice.[23] We are currently investigating this relationship.

Past studies have previously described similarly nondemented subjects with pathologically confirmed AD.[24] However, these subjects could have eventually developed clinical AD, but were in a preclinical state at the time of testing. Similarly, one cannot rule out the possibility that the APOE2 carriers in this study were in a preclinical state of disease. With the high mortality rates of the oldest old, these preclinical APOE2 carriers may have simply come to autopsy before cognitive impairment was evident.

The APOE2 participants in the study had significantly increased plaque pathology compared with APOE3/3, but not an increased tangle level. Furthermore, 36.4% of the APOE2 carriers had neocortical tangles as measured by Braak stages V and VI, which is comparable to the 30.4% of the APOE3/3 carriers with neocortical tangles. Thus, it seems that the APOE2 carriers have increased plaque pathology, but no increased tangle pathology. This is in contrast to the APOE4 carriers who had increased plaque and tangle pathology. These results suggest that the mechanisms by which APOE2 and APOE4 are affecting neuropathology may be different. APOE2 may exert its protective effect by modifying the formation of tangles in the neocortex, despite high levels of β-amyloid neuropathology.

The study excluded three participants who had the rare APOE2/4 genotype. Based on the current findings, one might expect them to have high levels of AD neuropathology, with moderate cognition. However, surprisingly, all three participants with APOE2/4 met criteria for dementia, but did not meet criteria for AD neuropathology. These results suggest a more complex relationship exists between APOE polymorphisms, such that APOE2/4 participants do not have a blended effect of both genes. It is of note that, at autopsy, multiple infarctions were found in the brain of one of these APOE2/4 partici-

pants. The interaction between APOE polymorphisms and dementia phenotype is a target of future research.

Our results suggest that the association between APOE genotype, AD neuropathology, and cognition is variable with age. While APOE2 is found to be protective against both clinical AD and AD neuropathology in younger populations, an examination of AD characteristics in APOE2 carriers in the oldest old suggests otherwise: people aged 90 and older with the APOE2 allele do not have clinical dementia, but in fact do develop advanced AD pathology (specifically neuritic plaques). This putative change with advancing age may be partially due to a shift in the link between AD neuropathology and clinical AD in the oldest old. For example, there is evidence for a relationship between the stage of plaque and tangle accumulation and the severity of clinical dementia in younger individuals.[25-28] In contrast, complementary research in older populations suggests that this association may change or even become weaker in the oldest old.[29-31] Several studies demonstrate that the oldest old often meet pathologic criteria for AD without being clinically demented[24,32,33] despite the fact that the prevalence of AD is as high as 48–74% in nonagenarians.[34-37] Many of the studies that have found APOE2 carriers with reduced AD pathology[4,5,7,38] include little data from participants over age 85; however, with a mean age of over 97, the present study is uniquely focused on the oldest old. This focus may allow The 90+ Study to identify relationships between APOE, cognition, and neuropathology that may be different from those in younger age groups.

Even ignoring age differences between studies, a closer examination of the literature indicates that the relationship between APOE2 and neuropathology has always been somewhat ambiguous. There is evidence that APOE2 carriers have reduced β-amyloid plaques and neurofibrillary tangles in the neocortex[8]; however, other studies have found a reduction of β-amyloid plaques, but no reduction in neurofibrillary tangles in APOE2 carriers.[4,7,39] In contrast, a study in elderly Norwegians found that the APOE2 allele was associated with decreased levels of neurofibrillary tangles, but not β-amyloid plaques.[38] There have also been several studies that failed to find a reduction in either β-amyloid plaques or neurofibrillary tangles in APOE2 carriers.[12,40] In fact, with increasing age (85 or older), APOE2 carriers were more likely to be at a higher neuropathologic stage of tangle formation than APOE3/3 carriers.[12] Therefore, whereas the prevailing view is that APOE2 is associated with decreased levels of β-amyloid plaques and tangles, many studies find that APOE2 carriers have no reduction in tangles, no reduction in plaques, or no reduction in either. These results suggest that the relationship between APOE2 and AD neuropathology may be more complex than previously described and advanced age may further modify this relationship.

The current study shows that whereas APOE2 is protective against a clinical diagnosis of AD, it is associated with increased AD neuropathology in subjects aged 90 and older. Whether this finding can be generalized to APOE2 carriers of all ages requires further investigation of subjects in younger age groups. Thus far, we may conclude that carriers of APOE2 aged 90 and older appear protected from the cognitive impairment normally associated with AD neuropathology.

AUTHOR CONTRIBUTIONS

D.J.B. conducted the statistical analysis.

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