Published in final edited form as:

J Alzheimers Dis. 2018 ; 62(4): 1527–1530. doi:10.3233/JAD-171060.

Pathologically Confirmed Alzheimer's Disease in *APOE ε2* Homozygotes is Rare but Does Occur

Faissal Stipho, Robert Jackson, Marwan N. Sabbagh*

Department of Neurology, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

Abstract

Background: Homozygous *APOE ε4* status is a well-known risk factor in the development of Alzheimer's disease (AD). However, other genotypes of *APOE* have not yet been found to have equal clinical significance. There is a paucity of reports regarding clinically or pathologically described AD in *APOE ε2* homozygotes compared to the other alleles.

Objective: To notify clinicians that patients with homozygous *APOE ε2* are also at risk of developing AD based on results from the largest prospectively gathered registry of brain samples to date.

Methods: We queried the National Alzheimer's Coordinating Center (NACC) database for autopsy-confirmed AD cases. Of the Uniform Data Set (UDS) participants who are deceased, 5,779 were diagnosed with dementia at their last UDS visit prior to death, and autopsy data is available for 3,518.

Results: Of the brains in the NACC database with pathologically confirmed dementia, seven were found to be homozygous for *APOE ε2*, which represents only 0.2% of the autopsy-confirmed sample. Furthermore, pathology-confirmed AD represents 29% (2/7) of the *APOE ε2/ε2* patients diagnosed with dementia.

Conclusions: Although rare, autopsy-confirmed AD can be present in *APOE ε2/ε2* carriers.

Keywords

Alzheimer's disease; apolipoprotein; brain-derived neurotrophic factor; corticobasal degeneration; dementia; frontotemporal dementia

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia in the elderly population [1]. Scientific research into AD focuses on risk factors and on treatments to postpone the morbidity and mortality associated with AD. One of those risk factors is the apolipoprotein gene group, which codes for apolipoprotein E (ApoE), a protein that is crucial in the

*Correspondence to: Marwan N. Sabbagh, MD, c/o Neuro-science Publications; Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, 350 W. Thomas Rd., Phoenix, AZ 85013, USA. Tel.: +1 602 406 3593; Fax: +1 602 406 4104; Neuropub@barrowneuro.org.

Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/17-1060r1>).

catabolism of lipids. It has three primary isoforms: *APOE ε2*, *APOE ε3*, and *APOE ε4*. *APOE ε2/ε2* is the rarest form of this genotype, occurring only in 1.4% of the population [2]. Studies have shown that the *APOE ε4* allele increases the risk for developing AD pathology, while *APOE ε3* is seemingly neutral, and *APOE ε2* has typically been described as being protective against AD pathology [3, 4]. AD is associated with a high number of neurofibrillary tangles and plaques in the cortical areas of the brain [5–7]. It is also characterized by an extensive amount of amyloid deposition in the cortex and blood vessels of the brain [5, 6]. *APOE ε2* has been considered protective in that it seemingly limits neurofibrillary tangles to cortical areas of the brain and is associated with lower amounts of deposition of amyloid-β. In addition, recent studies have shown that astrocytes from persons with the *APOE ε2* allele secrete three times more brain-derived neurotrophic factor (BDNF) than those from persons with the *APOE ε3* allele, while those with *APOE ε4* secrete 3–4 times less BDNF [8]. BDNF is extremely important in the survival, differentiation, and functional maturation of synapses which play a crucial function in retaining long-term memory.

Even though *APOE ε2* does not promote AD pathology as significantly as the other isoforms, studies have shown that AD can still develop in individuals who are homozygous for *APOE ε2* [9–11]. In this study, we investigated the prevalence of autopsy-confirmed AD in individuals who were homozygous for *APOE ε2* in the prospectively characterized dataset of the National Alzheimer's Coordinating Center (NACC). Our hypothesis is that AD occurs in *APOE ε2/ε2* carriers.

MATERIALS AND METHODS

Study sample

All data were obtained from the Uniform Data Set (UDS), the Neuropathology Data Set, and the Researcher's Data Dictionary-Genetic Data from the NACC, which is funded by the National Institute on Aging (NIA); the data began to be collected in September 2005. The dataset includes subjects with a range of cognitive characteristics including normal cognition, mild cognitive impairment, and dementia. The demographic, clinical, and specimen data from 39 past and present Alzheimer's Disease Centers, which enroll and follow subjects with their own various protocols, were also analyzed. The UDS was collected via a standardized evaluation of subjects during either an office visit, a home visit, or by telephone by trained clinicians or clinic personnel, gathering the information needed from either the subjects themselves or their informants during an annual assessment. Written informed consent was obtained from all subjects and informants. Research using the NACC database was approved by the Institutional Review Board at the University of Washington.

For this study, our sample included seven subjects that were *APOE ε2* homozygotes. We investigated whether any subjects had pathologically confirmed AD and whether other neurodegenerative conditions were discovered.

APOE $\epsilon 2/\epsilon 2$ and concurrent pathologic AD diagnosis

We used the NACC database to catalog *APOE* $\epsilon 2/\epsilon 2$ individuals. We then looked at the preautopsy clinical diagnoses of those specific individuals to see if they were previously diagnosed with AD. We were then able to compare these diagnoses with their post-mortem pathology. In addition, the NACC database provided the specific Braak stage for neurofibrillary degeneration (stages 1–6) for each individual. Braak staging is used to measure the degree of neurofibrillary tangles. Stages 1 and 2 signify the involvement of tangles in the entorhinal cortex, stages 3 and 4 signify the involvement of neurofibrillary tangles in the limbic system, and stages 5 and 6 signify extensive tangles in the neocortex of the brain.

Other factors

We also reviewed the gender, level of education, age of first signs of impairment, and age of death of each of the individuals obtained from the NACC database.

RESULTS

Of the UDS participants who are deceased, 5,779 were diagnosed with dementia at their last UDS visit prior to death, of which 3,518 had autopsy data. Seven of the 3,518 were found to be homozygous for *APOE* $\epsilon 2$, as shown in Table 1. These 7 individuals included 4 women (57%) and 3 men (43%). Mean age at first sign of impairment was 66.7 years (range 56–89 years). Mean age at time of death was 72.7 years (range 60 to 96 years). Three of the 7 *APOE* $\epsilon 2/\epsilon 2$ subjects were clinically diagnosed with AD (1 man and 2 women). However, only two of the three were confirmed on autopsy to have AD (Table 1). The third patient was instead assessed to have had frontotemporal dementia (FTD).

The man who was clinically diagnosed with AD was classified as Braak stage 4, and had no plaques. His impairment started at age 89; he completed 16 years of education. In contrast, the 2 women who were clinically diagnosed with AD were both classified as Braak Stage 6 and both had frequent plaques. The age of impairment started fairly early for these two women, at 57 and 61 years, and they died at ages 65 and 68 years. One completed 12 years of education, and the other completed 20 years of education.

One of the subjects that neither had a clinical diagnosis of nor pathologically confirmed AD was assessed as having progressive supranuclear palsy. Her impairment began at age 65; the subject completed 13 years of education and died at age 72. This subject had no neuritic plaques and was classified as Braak stage 1. One male subject was diagnosed with FTD with start of impairment at age 64; he completed 20 years of education, and died at age 67. This subject had no plaques and was classified as Braak stage 1. The other 2 subjects were both clinically diagnosed with corticobasal degeneration (CBD), with impairment beginning at ages 56 and 67 years; they completed 16 and 12 years of education, respectively, and they died at age 60 and 81, respectively. Of these, the subject who died at age 60 had no plaques and was classified as Braak stage 1. The subject who died at age 81 was classified as Braak stage 2 and had sparse plaques.

DISCUSSION

In this case series derived from prospectively characterized, autopsy-confirmed dementia, we found that subjects who are homozygous for *APOE ε2* can indeed develop Alzheimer-type dementia. *APOE ε2/ε2* is reported to be found in 0.5–1.4% of the population. It was discovered in only 0.2% of the NACC autopsy confirmed sample and, of those, 29% had pathologically confirmed AD. In general, AD is expected to be found in 2/3 of dementia autopsies. It looks like the *ε2/ε2* genotype is found at a lower frequency in the autopsy sample than the expected population rate with lower rates of AD pathology than would be expected. Thus, *APOE ε2/ε2* status should not immediately eliminate the consideration of AD as a diagnosis. This point is especially true because we show that AD represents 29% of cases of progressive dementia in patients that are found to be *APOE ε2/ε2* carriers.

An *APOE ε2* homozygous genotype, while extremely rare, is NOT neuro-protective. Furthermore, our study raises the question if such presentation increases the risk of non-AD progressive dementias. It appears that dementia in *APOE ε2/ε2* carriers is more likely to occur from other neurodegenerative conditions. It is not clear if there is a predilection for more tauopathy-related conditions given that the non-AD *APOE ε2/ε2* subjects had FTD, CBD, and progressive supranuclear palsy. Non-AD dementia cases had generally low Braak staging suggesting limited tauopathy. AD must be kept on the list of conditions in the differential diagnosis while considering other types of progressive dementias such as FTD, CBD, and progressive supranuclear palsy. Further study is warranted to investigate the features of tau in *APOE ε2/ε2* carriers. It may be of interest in the future to identify databases similar to the NACC in Europe or Asia to see if this pattern is consistent worldwide or is a unique finding to the North American population.

ACKNOWLEDGMENTS

The authors thank the staff of Neuroscience Publications at Barrow Neurological Institute for assistance with manuscript preparation.

Supported by the National Institute on Aging (NIA) (P30 AG19610) and the Barrow Neurological Foundation. The The National Alzheimer's Coordinating Center (NACC) database is funded by NIA/National Institutes of Health Grant U01 AG016976. NACC data are contributed by the NIA-funded Alzheimer Disease Centers: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Thomas Wisniewski, MD), P30 AG013854 (PI M. Marsel Mesulam, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG005131 (PI James Brewer, MD, PhD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), P50 AG047270 (PI Stephen Strittmatter, MD, PhD).

REFERENCES

- [1]. Lane CA, Hardy J, Schott JM (2018) Alzheimer's disease. *Eur J Neurol* 25, 59–70. [PubMed: 28872215]

- [2]. Iacono D, Zandi P, Gross M, Markesbery WR, Pletnikova O, Rudow G, Troncoso JC (2015) APOepsilon2 and education in cognitively normal older subjects with high levels of AD pathology at autopsy: Findings from the Nun Study. *Oncotarget* 6, 14082–14091. [PubMed: 26101858]
- [3]. Ignatov I, Belden C, Jacobson S, Connor D, Sabbagh M (2009) Possible Alzheimer's disease in an apolipoprotein E2 homozygote. *J Alzheimers Dis* 16, 35–38. [PubMed: 19158419]
- [4]. Roses AD (2006) On the discovery of the genetic association of Apolipoprotein E genotypes and common late-onset Alzheimer disease. *J Alzheimers Dis* 9, 361–366.
- [5]. McCarron MO, Nicoll JA (1998) High frequency of apolipoprotein E epsilon 2 allele is specific for patients with cerebral amyloid angiopathy-related haemorrhage. *Neurosci Lett* 247, 45–48. [PubMed: 9637406]
- [6]. Nagy Z, Smith M, Esiri MM, Jobst KA, Barneston L, Smith A (1995) Influence of the apolipoprotein E genotype on amyloid deposition and neurofibrillary tangle formation in Alzheimer's disease. *Neuroscience* 69, 757–761. [PubMed: 8596645]
- [7]. Hoglund K, Kern S, Zettergren A, Borjesson-Hansson A, Zetterberg H, Skoog I, Blennow K (2017) Preclinical amyloid pathology biomarker positivity: Effects on tau pathology and neurodegeneration. *Transl Psychiatry* 7, 995.
- [8]. Sen A, Nelson TJ, Alkon DL (2017) ApoE isoforms differentially regulates cleavage and secretion of BDNF. *Mol Brain* 10, 19. [PubMed: 28569173]
- [9]. Cole L, Belden C, Jacobson S, Liebsack C, Myers K, Reninger C, Berk C, Sabbagh MN (2010) Probable early-onset Alzheimer's disease in an apolipoprotein E2 homozygote. *Dement Geriatr Cogn Disord* 30, 387–391. [PubMed: 20975270]
- [10]. Attems J, Yamaguchi H, Saido TC, Thal DR (2010) Capillary CAA and perivascular Abeta-deposition: Two distinct features of Alzheimer's disease pathology. *J Neurol Sci* 299, 155–162. [PubMed: 20850138]
- [11]. Ohm TG, Scharnagl H, Marz W, Bohl J (1999) Apolipoprotein E isoforms and the development of low and high Braak stages of Alzheimer's disease-related lesions. *Acta Neuropathol* 98, 273–280. [PubMed: 10483785]

Table 1

Characteristics of patients with *APOE* $\epsilon 2/\epsilon 2$ genotypes

Subject No.	Sex	Years of Education	Age that Impairment Started	Primary Diagnosis	Braak Stage for Neurofibrillary Degeneration	Density of Neocortical Neuritic Plaques (CERAD Score)	Age at Death
289	F	13	65	PSP	Stage 1	No plaques	72
490	M	20	64	FTD	Stage 1	No plaques	67
2289	M	16	89	AD	Stage 4	No plaques	96
2578	F	20	61	AD	Stage 6	Frequent plaques	68
4347	M	16	56	CBD	Not present	No plaques	60
8354	F	12	75	CBD	Stage 2	Sparse plaques	81
8361	F	12	57	AD	Stage 6	Frequent plaques	65

AD, Alzheimer’s disease; CBD, corticobasal degeneration; CERAD, Consortium to Establish a Registry for Alzheimer’s Disease; FTD, frontotemporal dementia; PSP, progressive supranuclear palsy.