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Resolving the Relationship between Apolipoprotein E and Depression

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Abstract

Several studies have reported an association between the ApolipoproteinE-ε4 (APOE4) allele and depression among elders. However others have failed to find an association. Since APOE4 is a well recognized risk factor for Alzheimer dementia, cognitive status may represent an important confounder between APOE4 and depression. In this investigation, we examined the relationship between the ApolipoproteinE-ε4 allele and depression among elders accounting for cognitive status.

Methods—Using a case-control design (n=1052), we investigated the association between ApolipoproteinE-ε4 and depression in Alzheimer disease patients (n=528) and in cognitively intact controls (n=524).

Results—We demonstrated an apparent association between the APOE4 allele and depression in the combined dataset (p=0.001) when not controlling for cognitive status. However, once stratified by the presence of Alzheimer disease, there was no association in either the Alzheimer group (p=0.290) or the cognitively intact controls (p=0.494).

Conclusions—In this dataset there is no association between the ApolipoproteinE-ε4 allele and depression among those with Alzheimer disease or among cognitively intact elders. However there is a significant association between female gender and depression in the cognitively intact (p=0.003) but not among those with Alzheimer disease. Additionally, individuals with Alzheimer disease and depression had a significantly younger age of onset for their Alzheimer disease than those without depression (p=0.017).

Introduction

Late-onset Alzheimer disease (LOAD) and late-onset depression (LOD) are common and devastating late-onset disorders affecting millions of Americans [40]. As the population ages, the prevalence is expected to climb exponentially [13]. Despite decades of research, identification of genetic risk factors for these disorders remains challenging [33]. The only consistently replicated genetic risk factor for LOAD is the ApolipoproteinE-ε4 allele (APOE4). In the search for genetic variants governing depression, few findings have been replicated and no variant of even moderate effect has been reported. However, in addition to LOAD, APOE4 has been implicated as a risk factor for several neuropsychiatric disorders including LOD. At least nine studies have reported an association between APOE4 and depressive phenomenology

(Table 1) [4,6,9,16,25,27,29,30,35]. While there are positive studies demonstrating association between APOE4 and depression in the elderly, there are also negative reports [7,8,11,12,17,18,20–23,37,39].

It is difficult to draw any consistent conclusion from the literature. Previous studies utilized widely varying criteria to determine depression status. Even within single studies that utilize a common diagnostic methodology, prevalence of depression in Alzheimer disease (AD) could vary between ascertainment sites by more than twofold [40]. Also, eliciting symptoms of depression in the elderly may require different approaches with different psychometric instruments than those used to assess depression in the young [15]. Therefore, It is not surprising that prior investigations found a concomitant variable prevalence of depression ranging from 2% – 69% [4,8] respectively. Additionally low power to detect genetic effects, differing ethnicities, disparate age ranges among the studies (mean ages range from 60 to 84 years; [11,16] respectively), all conspire to make direct comparisons among studies difficult.

The American Journal of Geriatric Psychiatry under the auspices of the National Institutes of Health and the American Association for Geriatric Psychiatry published provisional diagnostic criteria for the Depression of Alzheimer disease (DAD) in 2002, after all the previously published studies were initiated [28]. As a result, the aggregate of prior investigations was unable to take advantage of a consistent set of diagnostic criteria to account for AD in their analyses of depression. Notably, DAD and LOD appear to be clinically and perhaps etiologically distinct entities. DAD occurs in around half of those with AD and generally onset is proximate (often prodromally or early in the course of) the cognitive symptoms of AD, and prevalence of DAD may increase modestly over the clinical course of dementia [3,28]. In contrast, LOD is a new onset depressive disorder generally appearing after age 45 to 65 [1,16] and prevalence among elders is only around 1.8–13.5% and appears to decrease with age [2,31]. Symptomatically, patients with DAD report more indecisiveness with impairments in concentration whereas patients with LOD report more sleep disturbances, feelings of worthlessness and excessive guilt [40]. Furthermore, DAD (versus AD without DAD) may serve as a relevant landmark distinguishing neuropathological pathways to the development of Alzheimer disease [39]. Additionally, there is evidence that APOE genotype may be a predictor of response to pharmacological treatment of depression among the elderly [26]. Therefore, distinguishing DAD from LOD could have important clinical implications. The objective of this study is to assess, in a dataset independent from previous reports, whether the APOE4 allele is associated with late-onset depression in Alzheimer disease (i.e. DAD) and among cognitively intact elders (i.e. LOD) using psychometric instruments known to be valid across the entire cognitive range included in the dataset [14].

Materials and Methods

Subjects

Our analysis uses a case-control design. The sample is clinic bases and derived from the Collaborative Alzheimer Project (CAP: The Center for Human Genetics at Duke University Medical Center and The Center for Human Genetics Research at Vanderbilt University Medical Center). The CAP dataset is independent from those previously published in the examination of depression. After complete description of the study to the subjects, written informed consent was obtained from all participants in agreement with protocols approved by the institutional review board at each contributing center. For inclusion, each individual must be greater than 60 years old and have adequate data to determine AD affection status and screening for the possible presence of depression. All AD affected individuals meet the NINCDS/ADRDA criteria for probable or definite AD[24]. Cognitive controls were spouses, friends, and other biologically unrelated individuals who were age and sex matched to the cases, and all were from within the Duke or Vanderbilt clinical catchment areas. All cognitive controls were

examined and showed no signs of dementia by history or upon interview. Additionally, cognitive controls each have a documented Mini-Mental State Exam (MMSE) ≥ 27 [10] or Modified Mini-Mental State Exam (3MS) ≥ 87 [36]. Individuals of ambiguous cognitive status (e.g. cognitive impairment not dementia (CIND) or mild cognitive impairment (MCI)) were dropped from the primary analyses because it remains unclear whether they have incipient dementia and are vulnerable to the DAD or are cognitively stable.

Depression status was determined by score on the Geriatric Depression Scale greater than or equal to 10 (mild depression) [38] at ascertainment or well documented history of depression with a known age at onset and treatment in the medical record. All subjects who screened positive for depression were asked about the historical course and first onset of depression symptoms. Since the GDS is a reliable measure of depression in individuals with MMSE score above 15 [14,28] all those with MMSE ≤ 15 (i.e. severe dementia) at assessment were dropped from the primary analyses. Since previous reports have not demonstrated an association between APOE alleles and “typical” early-in-life depression [16], individuals who had depression with an onset prior to age 50 were dropped from the primary analyses. We determined the possible presence of prior depressive episodes based on historical review with the participant, informant and medical record. Empirically, no individuals in the dataset had a recognized new-onset depression between the ages of 30 and 54. All individuals who were dropped because of an early-in-life onset of depression had their first identified depressive episode prior to age 30 ($n = 29$). DAD was defined operationally as an LOD in the presence of Alzheimer disease.

The final data set contains 1052 Caucasian individuals (528 with AD and 524 cognitively intact elders). The average age-at-onset in LOAD affected individuals is 72.2 ± 6.2 with an age range of 60–89 years. The average age-at-exam (AAE) for the cognitively intact controls is 73.7 ± 7.2 with an age range of 60–94 years. 64% of AD cases and 62% of cognitive controls are female. The gender ratio was not significantly different between these groups ($p=0.503$) (Table 2).

Genotyping

We extracted DNA for individuals ascertained by CAP with the Puregene system (Gentra Systems, Minneapolis, MN, USA). The ABI 7900 Taqman[®] system was used to generate APOE genotypes corresponding to allele combinations at SNP +3937/rs429358 and SNP +4075/rs7412. Genotyping efficiency was greater than 99% and quality control (QC) was achieved by including 2 sets of 12 control samples and 4 sets of 2 standard samples on each 384 well plate. The lab was blinded to affection status and quality control samples.

Statistical Analysis

Tests for deviation from Hardy-Weinberg equilibrium were conducted using the exact test from the Genetic Data Analysis software [19]. Chi square tests and logistic regression were conducted using SAS (SAS/Genetics 9.1; SAS Institute Inc., Cary NC, USQ. 2004). Chi square tests were performed to detect differences in the frequency of APOE alleles in the overall data set and the dataset stratified by LOAD affection status. Logistic regression was used to model depression susceptibility using LOAD affection status, APOE4 presence, gender and age-at-onset (for LOAD cases) and age-at exam (for cognitive controls) as covariates. Power calculations for the chi-square tests were based on the methods published by Schlesselman [32].

Results

We found no evidence of deviation from Hardy-Weinberg equilibrium among those with LOAD or cognitive controls (data not shown). In the combined data set of LOAD cases and cognitively intact controls (n=1052) the estimated APOE4 allele frequency is 0.276. Among those with LOAD, the estimated APOE4 allele frequency is 0.423 (versus 0.128 among the cognitive controls) and is strongly associated with LOAD ($p<0.001$) as has been replicated many times in previous studies (Table 3). To be consistent with other studies [5,6,9,17,21, 23,27,30,35] we also tested genotypes based on presence or absence of the APOE4 allele and found strong association between carriers and LOAD (OR=6.5; $p<0.001$; Table 3).

There is also significant association between APOE4 and depression (OR=1.6 for APOE4 carriers; $p=0.001$) in the dataset when combining LOAD cases and cognitive controls (Table 3). However once stratified by dementia status, APOE4 is not associated with depression in either the AD group (n= 528; $p=0.290$) or in the cognitively intact controls (n=525; $p=0.494$) (Table 3). In fact, the weak non-significant associations are both in the direction opposite of that expected for depression risk (OR = 0.82 and 0.80 respectively) (Table 3).

Subsequent analyses, examined the effect of the exclusion criteria (early-onset depressive episodes or severe cognitive impairment at ascertainment) by repeating the analyses including these individuals. However, these criteria did not appreciably affect the results. Additionally, we found no significant differences in depression or APOE4 prevalence within the overall dataset or stratified dataset between the ascertainment sites (data not shown).

Discussion

In these data, APOE4 is not associated with depression of Alzheimer disease or late-onset depression among the cognitively intact. Because a spurious association could be created between APOE4 and depression ($p=0.001$; table 3) by combining the Alzheimer disease affected participants with the cognitively intact controls, these results support the hypothesis that the confounding of Alzheimer disease with APOE4 explains the apparent depression effect in the full dataset. The same phenomena could be responsible for apparent associations in other datasets as well. In our dataset, this association is driven by the much higher prevalence of DAD (39%) among those with AD compared to the lower prevalence of LOD (13%) among the cognitively intact controls combined with the much higher frequency of the APOE4 allele among those with Alzheimer disease (0.423 vs. 0.128). There is no known method to reliably distinguish DAD from the coincidence of a pre-existing but unrecognized depression with Alzheimer disease in a given individual. Operationally, we used the presence of LOD with AD to define DAD. Empirically, onset of DAD within this dataset occurred from between two years prior to diagnosis of Alzheimer disease to five years after diagnosis of Alzheimer disease. All of those with a DAD onset prior to their Alzheimer disease diagnosis had a known intercurrent history of cognitive impairment not yet sufficiently severe to meet criteria for probable or definite Alzheimer disease.

32 individuals were dropped from the analyses due to unclear cognitive status. 24 of these meet criteria for cognitive impairment not dementia (CIND) and the remainder were diagnosed with mild cognitive impairment (MCI). Because the ascertainment protocol focuses on ascertainment of clinically diagnosed cases of dementia and cognitively intact elderly, those of unclear cognitive status (e.g. CIND or MCI) are not likely to be referred for research participation and therefore compared to a community cohort are under-represented in this sample. Furthermore, because the number of participants with an unclear cognitive status is only 32, we do not have adequate power to determine genetic or depression effects within this group.

The present analysis represents the largest study of APOE4 and depression among elders with and without documented dementia. Furthermore, this study is the first to use psychometric instruments known to be valid across the entire range of cognitive function within the dataset of LOAD cases and cognitive controls dataset [14]. We estimate that our analyses have 98% power to detect an association between depression and APOE4 at the identified odds ratio in the overall dataset (OR = 1.6) at a significance level of $p < 0.05$. At the upper limit of the confidence interval for risk of depression (OR = 2.1) we estimate a 100% power to detect an association between APOE4 and depression while at the lower limit (OR = 1.2) we estimated a 43% power to detect an association. Therefore, we expect to have adequate power to detect a significant effect at an odds ratio of 1.5, even in the stratified samples.

Secondary analyses utilizing logistic regression demonstrated no APOE4 effect on depression based on site of ascertainment, or method of determining depression status (GDS score vs. medical record history of depression and treatment). Additionally, we found no significant difference in effect size when using a higher GDS cut off scores of 15 and 20 to declare depression. There is one previous report of an effect of APOE in advanced age, strongest in those older than 80 years [34]. We did not detect this effect in our sample, when testing age under a linear model or when stratifying by age at several cut offs (ages 75, 80, or 85). However, the onset of LOAD was significantly younger in those with DAD compared to those without DAD by 1.3 years ($p = 0.017$) (Table 2). Additionally, the cognitive controls with LOD were disproportionately female ($P = 0.003$) compared with cognitive controls without LOD, while LOAD cases with DAD were not significantly more female ($p = 0.09$) than LOAD cases without DAD. The lack of a significant gender effect in DAD is interesting, because this study has more power to detect a gender difference in DAD than in LOD because of the much higher number of individuals with DAD ($n = 207$) than LOD ($n = 67$) in the sample. Adding in excluded individuals with early onset depressions or severe cognitive impairment at ascertainment did not significantly change our conclusions. Secondary analyses also found no effect for APOE4 homozygosity among the AD cases. The rate of depression is essentially the same among APOE4 homozygotes ($n = 91$; 38% depressed) as it is among APOE4 heterozygotes ($n = 265$; 37% depressed; $p = 0.801$). Additionally, while there are few ApolipoproteinE- $\epsilon 2$ alleles in this dataset ($n = 43$), there is no trend favoring a main effect for ApolipoproteinE- $\epsilon 2$ on depression (data not shown).

Importantly, this study is the first large study of APOE and depression that uses psychometric instruments known to be valid across the entire range of cognitive function included in the primary analyses. This allows direct comparison between the cognitively intact group and AD affected group. In our sample, depression was three times more prevalent in the AD group than in the cognitively intact group. While no depression effect for APOE4 was found in either group, this study helps explain how a positive association might be found if cognitive impairment is not accounted for in the evaluation of depression. Additionally, we demonstrate a significant effect for female gender in LOD ($p = 0.003$) that differentiates LOD from DAD in our sample. Furthermore, we found a significantly younger age-at-onset for AD in individuals affected by depression. These data contribute to the growing body of evidence distinguishing DAD and support a significant clinical role for DAD.

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Table 1

Positive Studies: Association of ApoE4 with Depression

Study Name:	n	Results: ApoE4 associated with
Krishnan 1996	41	Late-onset depression ($p<0.05$)
Ramachandran 1996	181	Depressive symptoms in Alzheimer disease ($p=0.002$)
Cacabelos 1997	207	Depression in Alzheimer disease (significance level not reported)
Nebes 2001	92	An interaction with white matter hyperintensities and depression among elderly ($p=0.005$)
Rigaud 2001	189	Late-onset depression (OR 6.1; 95% CI=1.9–19.0)
Stewart 2001	243	Depression and subjective memory complaints among non-demented ($p<0.05$)
Mueller-Thomsen 2002	137	Depression among women with Alz. disease ($p=0.006$)
Caselli 2004	212	Worsening depressive Symptoms among non-demented ($p=0.001$)
Flicker 2004	299	Depressive symptoms in elderly men; (OR 2.59; 95% CI=1.25–4.29)

Table 2

Dataset Description

subset	n	Age* +/- (SD)	% female	p-value (gender ratio)	OR (95% CI)
LOAD	528	72.2 (6.2)	63.8	0.503	1.1 (0.85–1.4)
CC	524	73.7 (7.2)	61.8		
Dep+	274	na	71.1	0.002	1.6 (1.2–2.3)
Dep –	778	na	59.9		
DAD	207	71.2 (6.1)**	68.4	0.090	1.4 (0.95–2.1)
LOAD (no DAD)	321	72.5 (6.1)	60.6		
LOD	67	na	78.5	0.003	2.5 (1.3–4.6)
CC (no LOD)	457	na	59.4		
Total	1052	na	62.8	na	na

LOAD = Late-Onset Alzheimer Disease

CC = Cognitive Controls

Dep+ = Any Depression with a late in life onset (i.e. DAD + LLD)

Dep– = No History of Depression

DAD = Depression of Alzheimer Disease

LOD = Late-Onset Depression

Age* = Age-at-onset for those with LOAD, and age-at-exam for cognitive controls

*** DAD cases are significantly younger than LOAD (not DAD) cases p=0.017.

ApoE4 Results

Table 3

subset	ApoE4 frequency	p-value ¹	n ApoE4+	% ApoE4+	p-value ²	OR (95% CI)
LOAD	0.423	<0.001	356	67.4	<0.001	6.5 (4.9–8.5)
CC	0.128		127	24.2		
Dep+	0.342	<0.001	149	54.4	0.001	1.6 (1.2–2.1)
Dep –	0.254		334	42.9		
DAD	0.412	0.374	134	64.7	0.290	0.82 (0.56–1.8)
LOAD (no DAD)	0.441		222	69.2		
LLD	0.123	0.754	14	20.9	0.494	0.80 (0.43–1.5)
CC (no LLD)	0.129		113	24.7		
Total	0.276	na	483	45.9	na	na

LOAD = Late-Onset Alzheimer Disease

CC = Cognitive Controls

Dep+ = Depression

Dep– = No Depression

DAD = Depression of Alzheimer Disease

LLD = Late-Life Depression

p-value¹ = nominal significance level for difference in ApoE4 allele frequency

p-value² = nominal significance level for presence of ApoE4 allele (ApoE4/4 and ApoE4/X genotypes)