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Does the Apolipoprotein E ϵ 4 genotype influence the expression of depression with cognitive impairment?

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Dear Editor

Although Pritchard *et al.* (2007) argued against any association between the apolipoprotein E (APOE) ϵ 4 allele-type and depression with Alzheimer's disease (AD), others have suggested that this association might be confined only to women (Muller-Thomsen *et al.*, 2002). One explanation for such disparate results is that methods to identify depression in AD patients have varied in different studies. We recently found the proportions of cognitively impaired patients identified with depression depended on the source of information and/or assessment method (Chopra *et al.*, 2008). Hence, we examined our Alzheimer's Disease Center (ADC) data to learn whether associations of depression and APOE ϵ 4 allele-frequency groups depended upon the depression assessment method.

This well-characterized independent cohort of 172 consenting participants with a research consensus diagnosis of mild cognitive impairment (MCI, $n = 80$) or AD ($n = 92$), and a Mini Mental State Examination score ≥ 15 , was assessed for depression using participants' self-reports on the 15-item Geriatric Depression Scale (GDS-15) and a reliable collateral-sources' evaluation on the Neuropsychiatric Inventory Questionnaire (NPI-Q), obtained separately and independent from the participants. GDS-15 scores ≥ 4 and NPI-Q Depression (D)-item scores ≥ 1 have been considered as positive screens for depression by self- and collateral-source reports, respectively. Thereafter, ADC physicians interviewed all participants and their collateral-sources together and established a clinical diagnosis of major depression (MD) according to the DSM-IV criteria.

The GDS-15 questions were grouped so as to identify five different symptoms of depression: sad mood, loss of interest, low energy, death wishes and any negative depressive cognitions (the triad of hopelessness, helplessness or worthlessness). Methods have been described in details in Chopra *et al.* (2008). Consenting participants provided blood for ϵ 4-allele DNA analysis using the one-stage PCR and restriction endonuclease analysis. We compared the proportion of participants with depression identified by each of the assessment methods, and the frequency of the individual symptoms of depression among the different

CONFLICT OF INTEREST

None known.

APOE $\epsilon 4$ allele-frequency groups. Given the small number of participants with the $\epsilon 4/\epsilon 4$ genotype, all significance values involve the Fisher's exact tests, unless otherwise stated.

Mean ages (76.4 ± 5.4 years) and MMSE scores (22.8 ± 3.9) of the 11 participants with APOE $\epsilon 4/\epsilon 4$ were not significantly lower than the mean ages (78.0 ± 8.7 years) and MMSE scores (24.3 ± 4.0) of the other 161 participants. The different ϵ/ϵ allele groups in our cohort were found to be in Hardy-Weinberg equilibrium [$\chi^2(2) = 0.413$, $p = 0.813$]. The number of participants identified with depression, and those reporting the individual symptoms of depression, in the three APOE $\epsilon 4$ allele frequency groups are presented in Table 1.

The difference in the proportion of participant reporting 'low energy' between the three $\epsilon 4$ allele-frequency groups approached statistical significance ($p = 0.059$). Additional analyses revealed that only 28.3% (26/92) of those with one or more $\epsilon 4$ alleles reported low energy compared to 45% (36/80) of those with no $\epsilon 4$ alleles ($p = 0.026$). None of the 11 participants with $\epsilon 4/\epsilon 4$ reported experiencing any negative depressive cognitions whatsoever, compared to 23.6% (38/161) participants in the other APOE groups who endorsed at least one cognitive symptom ($p = 0.058$). For those with a GDS-15 score ≥ 1 , the mean GDS-15 score of the $\epsilon 4/\epsilon 4$ group (1.78 ± 1.2) was more than one point lower than the mean score for the others (3.06 ± 2.3), although this difference was not significant [$t(1, 134) = 1.6$, $p = 0.109$]. However, as many as 39% (36/92) of those with one or more $\epsilon 4$ alleles were described as depressed by collateral-sources compared to only 25% (20/80) of participants with no $\epsilon 4$ alleles ($p = 0.052$).

An important limitation is our small cohort size, and that the small proportions reporting individual symptoms could be an artifact of only 11 participants in the $\epsilon 4/\epsilon 4$ group. This study also found no association between the $\epsilon 4$ genotype and the frequency of depression with cognitive impairment, which is different from the consistent evidence of an association between APOE $\epsilon 4$ and psychosis with AD (Zdanys *et al.*, 2007). Nonetheless, these findings suggest that those with APOE $\epsilon 4/\epsilon 4$ and cognitive impairment might experience depression with a relative paucity of depressive symptoms compared to those without this genotype. Hence, it is possible that the APOE $\epsilon 4$ allele influences the phenotype of depression with AD, somewhat similar to its reported influence on the pattern of cognitive impairment (Smith *et al.*, 1998).

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Table 1

Participants with cognitive impairment and depression in the different APOE $\epsilon 4$ allele groups identified through different assessment methods

	APOE Genotype Groups		
	No $\epsilon 4$ allele	One $\epsilon 4$ (ϵ/ϵ 2/4 and 3/4)	Two $\epsilon 4$ s (ϵ/ϵ 4/4)
<i>N</i>	80	81	11
Self-report of Depression (GDS-15 ≥ 4) (%)	18 (23)	16 (20)	1 (9)
Collateral-source report of Depression (NPIQ-D ≥ 1) (%)	20 (25)	31 (38)	5 (46)
Clinicians' diagnosis of Major Depression (DSM-IV) (%)	11 (14)	11 (14)	2 (18)
Individual Symptoms of Depression reported			
Sad mood (%)	5 (6)	5 (6)	1 (9)
Loss of interest (%)	33 (41)	37 (46)	2 (18)
Low energy (%)	36 (45)	24 (30)	2 (18)
Death wishes (%)	6 (8)	13 (16)	2 (18)
Negative cognitions (%)	18 (23)	20 (25)	0 (0)
Mean GDS-15 Score ($\pm$ SD):	2.95 (0.28)	3.17 (0.29)	1.78 (0.77)

DSM-IV =Diagnostic and Statistical Manual, 4th edn; GDS-15 =Geriatric Depression Scale—15 item; NPIQ-D =Neuropsychiatric Inventory Questionnaire—Depression item.