Apolipoprotein E and Dementia in Parkinson Disease

A Meta-analysis

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Objective: To understand the relationship of apolipoprotein E (APOE) polymorphism to dementia in Parkinson disease (PD) because the APOE ε4 allele is linked to Alzheimer disease.

Data Source: We reviewed MEDLINE, BIOSIS Previews, and ISI Web of Science from January 1, 1966, to May 7, 2004, supplemented by citation analysis from retrieved articles.

Study Selection: Case-control studies using clinical or pathologic criteria for PD and dementia, and with complete APOE genotype frequencies data.

Data Extraction: We compared estimated prevalence odds ratios for dementia in PD in relation to each allele. We also looked for evidence of heterogeneity and publication bias and performed a stratified analysis on several study characteristics.

Data Synthesis: Data analyses suggest publication bias and heterogeneity of source data for the ε4 allele (homogeneity P=.2; Begg and Mazumdar, P=.06; and Egger et al, P=.1). The estimated odds ratios for development of dementia in PD are 1.6 for ε4 (95% confidence interval, 1.0-2.5); 1.3 for ε2 (95% confidence interval, 0.73-2.4); and 0.54 for ε3 (95% confidence interval, 0.18-1.6). The odds ratio estimates for ε4 were higher for studies published in 1996 or later (2.3 vs 1.0) and for studies conducted outside North American sites (2.4 vs 1.2).

Conclusions: The APOE ε4 allele appears to be associated with a higher prevalence of dementia in PD. Publication bias and heterogeneous source data may, however, confound this conclusion. Confirmatory studies that use standardized and validated diagnostic criteria for dementia in PD are needed.

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The ε4 allele of apolipoprotein E (APOE) is a susceptibility gene for Alzheimer disease (AD) and is associated with increased risk and lower age at disease onset. In addition, β-amyloid plaques and tau protein–associated tangles are increased in the brains of individuals with the APOE ε4 allele. Parkinson disease (PD) shares some clinical, neurochemical, and pathologic features with AD. For example, patients with PD frequently develop dementia, and patients with AD often develop parkinsonism. Both diseases are characterized by neuronal death and protein deposition (eg, amyloid or α-synuclein).

Previous studies evaluating the role of APOE in dementia associated with PD have been inconclusive. Although some studies reported the ε4 allele to be overrepresented in dementia in PD (PDD), others did not. Given the overlapping clinical features of AD, PDD, and diffuse Lewy body disease, we suspected that these contradictory results may, in part, reflect differences in study sample characteristics and diagnostic criteria. To clarify the role of APOE in PDD, we conducted a meta-analysis of existing studies.

METHODS

SOURCE OF DATA

We searched the MEDLINE (PubMed), BIOSIS Previews, and ISI Web of Science databases for English-language publications from January 1, 1966, to May 7, 2004, with keywords Parkinson and APOE or apolipoprotein. The search revealed 77 publications. Additional information was obtained from reference citations within retrieved articles.

We established the following 2 a priori inclusion criteria: (1) case-control studies in which the cases were defined as clinically diagnosed or pathologically confirmed PD or PDD, and (2) availability of information on
genotype frequency in the report or from the investigators. The following information was extracted (Table 1) from each included study: sample size, APOE genotype, age and sex ratios of the subjects, criteria for dementia diagnosis, publication year, and country of study origin.

**STATISTICAL ANALYSIS**

We first conducted a χ² test of Hardy-Weinberg equilibrium (on 5 df) in the control group for each study. The test results indicated all control groups were within Hardy-Weinberg equilibrium (P>.1) (Table 1).

We calculated the odds ratios (ORs) for the 3 APOE allele types by contrasting persons with at least 1 copy of the specified allele to those without the allele. These analyses were conducted with and without adjustment for confounding among alleles. The adjusted analyses used the Mantel-Haenszel OR estimator to adjust, for instance, for ε3 and ε4 in estimating the association between PDD and the ε2 allele. Because some studies had very small sample size, the analyses were performed with sparse data smoothing (ie, the overall prevalence of each allele of genotypes among the control subjects was added to the number of exposed cases and controls, and the prevalence was added to the number of unexposed cases and controls). We computed the fixed-effects summary OR estimates and 95% confidence intervals (CIs). We used the 95% confidence limit ratio (ie, the ratio of the upper to lower 95% confidence limit) to gauge the precision of the summary estimates.19

The OR from the larger studies should show less variability than that from the smaller studies. In the absence of publication bias, all the estimates should be symmetrically distributed on either side of the summary estimate on a graph known as a funnel plot.20 An asymmetrical funnel plot can reflect publication bias, in which OR estimates suggesting strong associations in an expected direction (especially those that are statistically significant) are preferentially published. Begg and Mazumdar13 and Egger et al22 have developed statistical tests for funnel plot asymmetry that we used to test for publication bias. Overall homogeneity test P values were computed from the Cochran Q statistic. Low P values indicate heterogeneity or inconsistency of the OR estimates from the different studies, suggesting the presence of important differences among the study populations or research methods.

To explore associations between characteristics of studies and their results, we performed stratified and metaregression analyses. The dependent variable was the log OR, and the independent variables were the study characteristics. The metaregression data were fit using fixed- and random-effect, inverse variance–weighted linear regression, with the among-studies variance estimated by restricted maximum likelihood. The log OR was transformed back to the original ratio scale, and the metaregression coefficient was calculated to estimate the ratio of the average OR in studies with one characteristic to the average OR with another characteristic. The following study characteristics were examined with cut points for binary variable specifications selected to achieve as close as possible balanced distributions: year
of publication (≤1995 or ≥1996), geographic locale (North America or outside North America), average age of study participants (≤72 or >72 years), and clinical vs pathologic diagnosis. All analyses were conducted using Stata software versions 7 and 8 (Stata Corp, College Station, Tex).

**RESULTS**

We identified 9 reports that met our selection criteria and had accessible genotype information to study the association of APOE with PDD (Table 1). The pooled subjects included a total of 295 PD and 163 PDD cases.

Visual inspection of the funnel plot (Figure 1) indicates asymmetrical distribution of OR estimations, suggesting publication bias, especially for the ε4 allele. Relatively low Beggs and Mazumdar21 and Egger et al.22 P values (.06 and .1, respectively) for the ε4 allele support this impression. There was also evidence of overall heterogeneity for the ε4 allele (homogeneity P = .2).

The relationship among the 3 main APOE alleles and PDD is shown in Figure 2. The ε4 allele was associated with dementia in PD subjects, whereas the ε2 allele was not. There is a suggestion of an inverse association between the ε3 allele and PDD. This association, however,
was not very precise (ie, a high confidence limit ratio\(^1\), probably owing to the extremely high frequency of the \(\varepsilon^3\) allele. We also estimated the association of specific genotypes with PDD, but the OR estimations are very imprecise and not reported herein (data available on request).

All of the \(\varepsilon^2\) and \(\varepsilon^3\) meta-regressions lacked precision (Table 2). Although the \(\varepsilon^4\) meta-regressions are imprecise, they are relatively more precise than those for the other alleles. Consequently, we only performed a stratified analysis on this allele. Studies published in 1996 or later and those conducted outside North America yielded higher estimates of ORs for development of PDD (Table 3). Additional evidence suggested that studies that used pathologic diagnostic criteria for dementia and/or included subjects 72 years or younger yielded higher estimates of OR for development of PDD (Tables 2 and 3), especially if a random-effect model was used to estimate these ORs (2.7 [95% CI, 0.7-11] vs 1.5 [95% CI, 0.8-3.0] for pathologic vs clinical diagnosis, and 2.5 [95% CI, 0.9-6.8] vs 1.3 [95% CI, 0.6-2.9] for subjects 72 years or younger vs those older than 72 years). The relatively large discrepancy on the estimation between fixed and random effects models for pathologic diagnosis and studies including subjects 72 years or younger suggests that such studies suffered greater heterogeneity and possible publication bias.

### Table 2. Meta-Regression Results

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>No. of Studies</th>
<th>(\varepsilon^2) Allele</th>
<th>(\varepsilon^3) Allele</th>
<th>(\varepsilon^4) Allele</th>
</tr>
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<tbody>
<tr>
<td>Diagnostic criteria</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>5</td>
<td>0.8 (0.2-3.7)</td>
<td>1.8 (0.2-16)</td>
<td>0.7 (0.2-2.4)</td>
</tr>
<tr>
<td>Pathologic</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geographic locale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>4</td>
<td>0.6 (0.2-2.1)</td>
<td>1.0 (0.1-9.5)</td>
<td>0.5 (0.2-1.2)</td>
</tr>
<tr>
<td>Others</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of study population, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age &gt; 72</td>
<td>4</td>
<td>1.4 (0.6-6.4)</td>
<td>1.2 (0.1-11)</td>
<td>0.6 (0.2-1.9)</td>
</tr>
<tr>
<td>Mean age = 72</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Publication year</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≥1996</td>
<td>5</td>
<td>1.0 (0.4-2.2)</td>
<td>1.2 (0.1-11)</td>
<td>2.2 (0.9-5.4)</td>
</tr>
<tr>
<td>≤1995</td>
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</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

### Table 3. Stratified Analysis of \(\text{APOE} \varepsilon^4\) Allele

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>No. of Subjects</th>
<th>Fixed-Effects Summary, OR (95% CI)</th>
<th>Homogeneity P Value</th>
</tr>
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<tr>
<td>Diagnostic criteria</td>
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<tr>
<td>Clinical</td>
<td>5</td>
<td>1.5 (0.9-2.7)</td>
<td>.2</td>
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<tr>
<td>Pathologic</td>
<td>4</td>
<td>1.7 (0.8-3.4)</td>
<td>.1</td>
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<td>Geographic locale</td>
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<td></td>
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<tr>
<td>North America</td>
<td>4</td>
<td>1.2 (0.6-2.1)</td>
<td>.2</td>
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<tr>
<td>Others</td>
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<td>2.4 (1.4-6.6)</td>
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<td>Age of study population, y</td>
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<td>Mean age &gt; 72</td>
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<td>.2</td>
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<tr>
<td>Mean age = 72</td>
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<td>1.8 (0.9-3.4)</td>
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<td>≥1996</td>
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<td>.6</td>
</tr>
<tr>
<td>≤1995</td>
<td>4</td>
<td>1.0 (0.5-2.0)</td>
<td>.1</td>
</tr>
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</table>

Abbreviations: APOE, apolipoprotein E; CI, confidence interval; OR, odds ratio.

The main purpose of our study was to review the published literature and attempt to clarify the role of \(\text{APOE} \varepsilon^4\) polymorphisms in PDD. Given the robust association between the \(\text{APOE} \varepsilon^4\) allele and risk of AD, we examined whether cognitive dysfunction or dementia would be similarly associated with the \(\text{APOE} \varepsilon^4\) allele in patients with PD. Our finding of an increased OR (1.6) for the \(\text{APOE} \varepsilon^4\) allele in PDD provisionally supports this hypothesis.

There are, however, methodological and neurobiological issues that bear addressing.

Publication bias likely influences the present findings supporting the role of \(\text{APOE} \varepsilon^4\) in PDD. Asymmetrical “missing” data on the left side of the \(\varepsilon^4\) funnel plot (Figure 1) suggest that studies failing to demonstrate an association between \(\text{APOE} \varepsilon^4\) and PDD may not have been reported or published. The OR differences between later and earlier publications also imply publication bias. The differences between geographic locales may reflect greater publication bias in studies performed in countries outside North America. In addition, the marked heterogeneity of subjects across studies in terms of age, geographic locale, and diagnostic criteria also influences our final OR estimation of dementia prevalence in the PD population.

Age may have a complex influence on the association between \(\text{APOE} \varepsilon^4\) and PDD. The finding of age-related differences in PDD with \(\text{APOE} \varepsilon^4\) is not surprising given the known age dependence of \(\text{APOE} \varepsilon^4\) on risk of AD.\(^1\) In AD, \(\text{APOE} \varepsilon^4\) is associated with higher risk and younger age at onset. Our finding of the greater association of PDD with \(\text{APOE} \varepsilon^4\) in younger compared with older subjects is consistent, as noted earlier for AD. Although advancing age is a well-known risk factor for development of PDD, the fact that most of the studies included in this meta-analysis matched subjects by age would be expected to offset potential bias associated with greater dementia prevalence in older subjects with PD.

Dementia in PD is clinically and pathologically heterogeneous. The different OR estimations between clinical and pathologic diagnoses highlight the broader issue of how \(\text{APOE} \varepsilon^4\) is pathophysiologically linked to PDD, specifically suggesting an influence mediated by concomitant AD pathologic features (amyloid plaques, in particular). Specific pathologic diagnostic criteria for PDD do not yet exist, and those proposed for dementia with Lewy bodies do not account for multiple pathologic substrates. Although dementia with Lewy bodies is defined in terms of core neurobehavioral features (including visual hallucinations and fluctuating consciousness), these features may not be generally associated with PDD.\(^1\) In general, using pathology-based diagnostic criteria allows for the pathologic features of AD and PD to be separated,
whereas clinically defined criteria are likely to be relatively blind to the presence or absence of concomitant AD pathology. Eight of the 9 studies included in this meta-analysis used either clinical or pathologic diagnostic criteria for PDD. Even within study groups of clinically or pathologically defined subjects, however, no 2 studies used exactly the same diagnostic criteria to define subjects, further contributing to subject heterogeneity.

Only 1 study\(^5\) carefully restricted the diagnosis of PDD to those in whom the onset of parkinsonian signs had clearly preceded the cognitive changes, consistent with the prevailing, if generic, definition of PDD.\(^6\) In that study, pathologic diagnosis categories included AD plus PD (reflecting an AD-predominant clinical presentation with multiple pathologic features), and PD plus AD (representing a PD-like clinical presentation with combined pathologic features). Among all studies, this classification points out the heterogeneity in clinicopathologic associations and strongly argues for the need to characterize samples on both clinical and pathologic grounds. Extrapolating these groupings back to other studies suggests that clinically defined PDD samples included a subset of subjects with Lewy body pathology who did not manifest motor signs may have been excluded. To address the issue of whether the association of APOE with PDD merely reflects coexisting AD will require more comprehensive and standardized diagnostic criteria that account for clinical and pathologic heterogeneity. A recent multicenter placebo-controlled therapeutic trial showing benefits of the cholinesterase inhibitor rivastigmine tartrate in PDD\(^7\)\(^8\) may bring greater attention to defining more specific and rigorous criteria for PDD.

Our analyses of these data suggest that the APOE \(\epsilon 4\) allele seems to be associated with higher prevalence of dementia in the population with PD. It is also clear that further study is warranted using standard diagnostic criteria, clear recording of subject ethnicity, and age at onset of PDD.

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REFERENCES

20. Stuck AE, Rubenstein LZ, Wieland D. Bias in meta-analysis detected by a simple, graphical test: asymmetry detected in funnel plot was probably due to true heterogeneity. BMJ. 1998;316:469-471.