APOE ε4 Increases Risk for Dementia in Pure Synucleinopathies

Debby Tsuang, MD, MSc; James B. Leverenz, MD; Oscar L. Lopez, MD; Ronald L. Hamilton, MD; David A. Bennett, MD; Julie A. Schneider, MD, MS; Aron S. Buchman, MD; Eric B. Larson, MD, MPH; Paul K. Crane, MD, MPH; Jeffrey A. Kaye, MD; Patricia Kramer, PhD; Randy Woltjer, PhD; John Q. Trojanowski, MD, PhD; Daniel Weintraub, MD; Alice S. Chen-Plotkin, MD; David J. Irwin, MD; Eliezer Masliah, MD; Joseph F. Quinn, MD; Kathryn A. Chung, MD; Dora Yearout, BS; Ignacio F. Mata, PhD; Jia Y. Wan, MS; Karen L. Edwards, PhD; Thomas J. Montine, MD, PhD; Cyrus P. Zabetian, MD, MS

Objective: To test for an association between the apolipoprotein E (APOE) ε4 allele and dementias with synucleinopathy.

Design: Genetic case-control association study.

Setting: Academic research.

Patients: Autopsied subjects were classified into 5 categories: dementia with high-level Alzheimer disease (AD) neuropathologic changes (NCs) but without Lewy body disease (LBD) NCs (AD group; n=244), dementia with LBDNCs and high-level ADNCs (LBD-AD group; n=224), dementia with LBDNCs and no or low levels of ADNCs (pure DLB [pDLB] group; n=91), Parkinson disease dementia (PDD) with no or low levels of ADNCs (n=81), and control group (n=269).

Main Outcome Measure: The APOE allele frequencies.

Results: The APOE ε4 allele frequency was significantly higher in the AD (38.1%), LBD-AD (40.6%), pDLB (31.9%), and PDD (19.1%) groups compared with the control group (7.2%; overall $\chi^2=185.25; P=5.56 \times 10^{-39}$), and it was higher in the pDLB group than the PDD group ($P=0.01$). In an age-adjusted and sex-adjusted dominant model, ε4 was strongly associated with AD (odds ratio, 9.9; 95% CI, 6.4-15.3), LBD-AD (odds ratio, 12.6; 95% CI, 8.1-19.8), pDLB (odds ratio, 6.1; 95% CI, 3.5-10.5), and PDD (odds ratio, 3.1; 95% CI, 1.7-5.6).

Conclusions: The APOE ε4 allele is a strong risk factor across the LBD spectrum and occurs at an increased frequency in pDLB relative to PDD. This suggests that ε4 increases the likelihood of presenting with dementia in the context of a pure synucleinopathy. The elevated ε4 frequency in the pDLB and PDD groups, in which the overall brain neuritic plaque burden was low, indicates that apoE might contribute to neurodegeneration through mechanisms unrelated to amyloid processing.


Lewy body disease (LBD) encompasses a spectrum of clinicopathologic entities that include Parkinson disease (PD), PD with dementia (PDD), and dementia with Lewy bodies (DLB). Dementia with Lewy bodies and PDD are differentiated from one another based on clinical criteria. Dementia with Lewy bodies is diagnosed when dementia occurs before or concurrently with parkinsonism, whereas in PDD, parkinsonism precedes dementia by at least 12 months.1 Lewy body disease neuropathologic changes (NCs) include classic histologic inclusions (Lewy bodies) and α-synuclein immunopositive neuronal inclusions and processes (Lewy neurites) in partially overlapping regions of the brain. However, the pathologic classification of DLB is complex because some cases show LBDNCs with no or low levels of Alzheimer disease (AD) NCs, which we refer to as pure DLB (pDLB), while many other cases show LBDNCs with coexistent high levels of ADNCs (LBD-AD). Importantly, the pathophysiologic relationship between LBD-AD, pDLB, and PDD has not been delineated, and whether these disorders share common risk factors remains unclear.

Humans are unlike other mammals in that we possess 3 common alleles of the apolipoprotein E (APOE) gene that are determined by 2 single nucleotide polymorphisms located in exon 4 at positions 3937 (T/C; rs429358) and 4075 (C/T; rs7412). The corresponding apoE isoforms (299

Author Affiliations are listed at the end of this article.
Subjects and Clinical Evaluation

The study population comprised 640 patients with dementia and 269 control subjects who all reported their race as white. Subjects with dementia but without a clinical diagnosis of PD were enrolled in 1 of 7 AD centers (ADCs) (Oregon Health and Science University; Rush University; University of California, San Diego; University of Kentucky; University of Pennsylvania; University of Pittsburgh; and University of Washington), in the Rush Memory and Aging Project, or in the Group Health/University of Washington Alzheimer Disease Patient Registry (ADPR)/Adult Changes in Thought (ACT) study. The ADPR-ACT study is a community-based longitudinal study that enrolled individuals aged 65 years or older with dementia (ADPR/ACT) or without dementia (ACT) from a health-maintenance organization as part of the ADPR/ACT and Rush Memory and Aging Project, or 6 ADCs (Oregon Health and Science University; Rush University; University of California, San Diego; University of Kentucky; University of Pittsburgh; and University of Washington). All control subjects were aged 65 years or older with dementia (ADPR/ACT) or 269 control subjects who all reported their race as white. The study population comprised 640 patients with dementia and 269 control subjects who all reported their race as white. Subjects with dementia but without a clinical diagnosis of PD were enrolled in 1 of 7 AD centers (ADCs) (Oregon Health and Science University; Rush University; University of California, San Diego; University of Kentucky; University of Pennsylvania; University of Pittsburgh; and University of Washington), in the Rush Memory and Aging Project, or in the Group Health/University of Washington Alzheimer Disease Patient Registry (ADPR)/Adult Changes in Thought (ACT) study. The ADPR-ACT study is a community-based longitudinal study that enrolled individuals aged 65 years or older with dementia (ADPR/ACT) or without dementia (ACT) from a health-maintenance organization as part of the ADPR/ACT and Rush Memory and Aging Project, or 6 ADCs (Oregon Health and Science University; Rush University; University of California, San Diego; University of Kentucky; University of Pittsburgh; and University of Washington). All control subjects were aged 65 years or older with dementia (ADPR/ACT) or 269 control subjects who all reported their race as white. The study population comprised 640 patients with dementia and 269 control subjects who all reported their race as white. Subjects with dementia but without a clinical diagnosis of PD were enrolled in 1 of 7 AD centers (ADCs) (Oregon Health and Science University; Rush University; University of California, San Diego; University of Kentucky; University of Pennsylvania; University of Pittsburgh; and University of Washington), in the Rush Memory and Aging Project, or in the Group Health/University of Washington Alzheimer Disease Patient Registry (ADPR)/Adult Changes in Thought (ACT) study. The ADPR-ACT study is a community-based longitudinal study that enrolled individuals aged 65 years or older with dementia (ADPR/ACT) or without dementia (ACT) from a health-maintenance organization as part of the ADPR/ACT and Rush Memory and Aging Project, or 6 ADCs (Oregon Health and Science University; Rush University; University of California, San Diego; University of Kentucky; University of Pittsburgh; and University of Washington). All control subjects were aged 65 years or older with dementia (ADPR/ACT) or 269 control subjects who all reported their race as white. The study population comprised 640 patients with dementia and 269 control subjects who all reported their race as white. Subjects with dementia but without a clinical diagnosis of PD were enrolled in 1 of 7 AD centers (ADCs) (Oregon Health and Science University; Rush University; University of California, San Diego; University of Kentucky; University of Pennsylvania; University of Pittsburgh; and University of Washington), in the Rush Memory and Aging Project, or in the Group Health/University of Washington Alzheimer Disease Patient Registry (ADPR)/Adult Changes in Thought (ACT) study. The ADPR-ACT study is a community-based longitudinal study that enrolled individuals aged 65 years or older with dementia (ADPR/ACT) or without dementia (ACT) from a health-maintenance organization as part of the ADPR/ACT and Rush Memory and Aging Project, or 6 ADCs (Oregon Health and Science University; Rush University; University of California, San Diego; University of Kentucky; University of Pittsburgh; and University of Washington). All control
RESULTS

The demographic and clinical characteristics of the study population are shown in Table 1. Control subjects were slightly older at death than those in all 4 dementia groups, and a substantially greater proportion of subjects with PDD and pDLB were male (P<1×10^{-4} for all). There was no significant difference in age at onset of dementia among the case groups.

The APOE genotype and allele frequencies observed in the sample are presented in Table 2. There was a highly significant overrepresentation of the ε4 allele in all case groups, including PDD (χ^2 = 18.25; P = 1.94×10^{-5}) and pDLB (χ^2 = 68.61; P = 1.2×10^{-16}). In a dominant genetic model adjusting for sex and age at death with control subjects as the reference, the ORs were 9.9 (95% CI, 6.4-15.3) for AD, 12.6 (95% CI, 8.1-19.8) for LBD-AD, 6.1 (95% CI, 3.5-10.5) for pDLB, and 3.1 (95% CI, 1.7-5.6) for PDD (Table 3).

Within the groups with synucleinopathy, the ε4 allele frequency was significantly lower in subjects with PDD (19.1%) than those with pDLB (31.9%; χ^2 = 5.6; P = 0.02) or LBD-AD (40.6%; χ^2 = 2.24; P = 1.43×10^{-6}).

Inspection of the ORs suggested that for individuals with PDD and pDLB, the ε4 allele might convey risks intermediate between the control group and the LBD-AD and AD groups. We assessed this hypothesis using a trend test, coding control subjects as 0, PDD as 1, pDLB as 2, and AD and LBD-AD as 3. The results indicated an increased likelihood of carrying the ε4 allele across groups (control<PDD<pDLB<LBD-AD/AD [χ^2 = 166.47; P = 4.37×10^{-30}]).

COMMENT

We observed a strong overall association between the APOE ε4 allele and AD, LBD-AD, pDLB, and PDD. While the ε4 allele is a well-established risk factor for AD13 and

Table 1. Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients, No.</th>
<th>Male, No. (%)</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>269</td>
<td>121 (45.0)</td>
<td>84.5 (7.5)</td>
<td>54-106</td>
<td>72.7 (9.0)</td>
<td>47-88</td>
</tr>
<tr>
<td>PDD</td>
<td>81</td>
<td>59 (72.8)</td>
<td>77.5 (7.9)</td>
<td>58-96</td>
<td>72.9 (11.4)</td>
<td>48-96</td>
</tr>
<tr>
<td>pDLB</td>
<td>91</td>
<td>68 (74.7)</td>
<td>80.2 (9.1)</td>
<td>57-99</td>
<td>73.3 (10.8)</td>
<td>46-99</td>
</tr>
<tr>
<td>LBD-AD</td>
<td>224</td>
<td>100 (44.6)</td>
<td>81.4 (8.6)</td>
<td>60-103</td>
<td>73.1 (9.4)</td>
<td>47-100</td>
</tr>
<tr>
<td>AD</td>
<td>244</td>
<td>89 (36.5)</td>
<td>81.7 (8.4)</td>
<td>53-101</td>
<td>73.1 (9.4)</td>
<td>47-100</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease (group with dementia with high-level AD neuropathologic changes without Lewy body disease neuropathologic changes); LBD-AD, Lewy body disease–AD (group with dementia with LBD neuropathologic changes and high-level AD neuropathologic changes); PDD, Parkinson disease with dementia; pDLB, pure dementia with Lewy bodies (group with dementia with LBD neuropathologic changes and no or low-level AD neuropathologic changes).

Table 2. APOE Allele and Genotype Frequencies by Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients, No.</th>
<th>Genotype Frequency</th>
<th>Allele Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2/2</td>
<td>2/3</td>
</tr>
<tr>
<td>Control</td>
<td>269</td>
<td>3 (1.1)</td>
<td>37 (13.8)</td>
</tr>
<tr>
<td>PDD</td>
<td>81</td>
<td>0 (0.0)</td>
<td>6 (7.4)</td>
</tr>
<tr>
<td>pDLB</td>
<td>91</td>
<td>1 (1.1)</td>
<td>6 (6.6)</td>
</tr>
<tr>
<td>LBD-AD</td>
<td>224</td>
<td>0 (0.0)</td>
<td>5 (2.2)</td>
</tr>
<tr>
<td>AD</td>
<td>244</td>
<td>0 (0.0)</td>
<td>6 (2.5)</td>
</tr>
</tbody>
</table>

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COMMENT

We observed a strong overall association between the APOE ε4 allele and AD, LBD-AD, pDLB, and PDD. While the ε4 allele is a well-established risk factor for AD13 and...
several studies have reported an association between APOE and LBD-AD.5-7 the finding that ε4 was overrepresented in pDLB and PDD was unexpected. By far, the most widely held view for the mechanism by which APOE ε4 influences AD risk is that apoE isoforms have direct or indirect effects on amyloid-β (Aβ) peptide metabolism. There is a large body of evidence to support this hypothesis, including experiments in mice overexpressing human apoE isoforms in which the ε4 allele results in lower Aβ clearance and increased deposition of insoluble Aβ in the brain than the ε2 and ε3 alleles.7-24 Thus, in humans, ε4 is predicted to accelerate the accumulation of neurotoxic Aβ, which ultimately leads to neuritic plaque formation and neurodegeneration. However, our observation of an elevated ε4 frequency in the pDLB and PDD groups in which the overall brain neuritic plaque burden is low suggests the possibility that apoE isoforms also might modulate neurodegeneration by nonamyloidogenic mechanisms. A caveat is that we were not able to account for the potential influence of ε4 on soluble oligomeric Aβ levels because soluble oligomeric Aβ might not be well represented by measures of histologically detectable Aβ plaques, and soluble oligomeric Aβ could adversely affect cognition. Nonetheless, evidence that Aβ-independent pathways might exist is beginning to emerge from work in model systems. For example, C-terminal-truncated fragments of apoE4 are neurotoxic in vivo and in vitro, possibly through impairment of mitochondrial function or disruption of the cytoskeleton.25-26 In the presence of lipids, apoE4 impairs neuronal plasticity in vitro.25 Also, greater microglia-mediated neurotoxicity has been observed in mice expressing human apoE4 than other apoE isoforms.27 Interpreting previous studies of APOE in D LB has been challenging given the wide difference in methods and diagnostic criteria used between studies. Few neuropathologically verified studies have reported separate APOE frequencies in LBD-AD and pDLB,26,28 and some did not collect sufficient information to exclude subjects with PDD.28 Furthermore, the sample size of the pDLB group in these previous studies ranged from 6 to 18 subjects, and the ε4 allele frequency varied from 6% to 22%, precluding firm conclusions about the association of APOE with pDLB. On the other hand, a number of studies have reported a significant overrepresentation of APOE ε4 in subjects with LBD-AD, with ε4 allele frequencies ranging from 29% to 47%.5-7,28,29 Finally, several studies have examined APOE in D LB without making a distinction between LBD-AD and pDLB, often because the diagnosis was solely based on clinical criteria.5-10 Data from genomewide association studies indicate that APOE is not a susceptibility gene for PD.30-32 While PD is clinically defined by motor symptoms, more than 50% of patients develop dementia within 10 years of diagnosis.33-34 Whether APOE acts as a modifier gene by influencing the manifestation of cognitive dysfunction in PD is still a matter of debate. There are several possible approaches to address this question, including assessing whether APOE genotypes (1) differ in frequency between patients with PDD and control subjects or cognitively intact patients with PD, (2) influence the rate of progression to dementia in PD cohorts, or (3) associate with performance on cognitive testing in cross-sectional or longitudinal studies of patients with PD. In a meta-analysis of 17 studies, Williams-Gray and colleagues35 reported a significantly higher APOE ε4 frequency in patients with PDD (n = 501) compared with nondemented patients with PD (n = 1145; OR, 1.74; 95% CI, 1.36-2.23). However, interpretation of the results was made difficult because there was evidence of significant heterogeneity of ORs and publication bias, and the criteria used to define PDD varied substantially across individual studies. Williams-Gray and colleagues35 also longitudinally assessed an incident cohort of 107 patients with PD for 5 years and found no effect of APOE ε4 on the risk for dementia or rate of cognitive decline. In contrast, a recent longitudinal study of 212 patients with PD reported that ε4 carriers displayed a more rapid decline in total score on the Mattis Dementia Rating Scale than noncarriers.36 In a cross-sectional study of 937 patients with PD, we observed that the ε4 allele is associated with lower psychometric test scores across multiple cognitive domains after adjusting for disease duration.37 Together with findings from the present study, we believe that the preponderance of the evidence indicates that APOE is a risk factor for cognitive dysfunction in PD. However, in our data set, the magnitude of the APOE ε4 effect was smaller for PDD than for LBD-AD and pDLB, as evidenced by the 2-fold (or more) larger ORs observed in the LBD-AD and pDLB groups (Table 3) and the r esults of the trend test. One explanation for these findings is that in the presence of synucleinopathy, APOE ε4

<table>
<thead>
<tr>
<th>Group</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>Value</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDD</td>
<td>3.7 (2.1-6.5)</td>
<td>6.9 × 10⁻⁶</td>
<td></td>
<td>3.1 (1.7-5.6)</td>
<td>1.5 × 10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>pDLB</td>
<td>6.7 (3.9-11.5)</td>
<td>4.3 × 10⁻¹²</td>
<td></td>
<td>6.1 (3.5-10.5)</td>
<td>1.3 × 10⁻¹⁰</td>
<td></td>
</tr>
<tr>
<td>LBD-AD</td>
<td>13.5 (8.6-21.1)</td>
<td>3.2 × 10⁻⁳</td>
<td></td>
<td>12.6 (8.1-19.8)</td>
<td>2.1 × 10⁻²⁸</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>10.5 (6.8-16.3)</td>
<td>1.6 × 10⁻²⁶</td>
<td></td>
<td>9.9 (6.4-15.3)</td>
<td>1.2 × 10⁻²⁴</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease (group with dementia with high-level AD neuropathologic changes without Lewy body disease neuropathologic changes); LBD-AD, Lewy body disease–AD (group with dementia with LBD neuropathologic changes and high-level AD neuropathologic changes); OR, odds ratio; PDD, Parkinson disease with dementia; pDLB, pure dementia with Lewy bodies (group with dementia with LBD neuropathologic changes and no or low-level AD neuropathologic changes).

*Under a dominant model for the ε4 allele.

*Adjusted for age at death and sex.
might increase the likelihood that dementia precedes parkinsonism, hence a clinical diagnosis of DLB rather than PDD is rendered.

This study had some limitations. Because most of the subjects died prior to the publication of the consensus clinical criteria for DLB, we were unable to fully apply these criteria retrospectively, in particular the fluctuating cognition and rapid eye movement sleep behavior disorder features. Although we limited the sample to white subjects, we did not have data available for ancestry informative genetic markers, thus we cannot entirely exclude the possibility of unrecognized population structure in our data set.

We have shown that APOE ε4 increases the risk for dementia in subjects with LBDNCs but with no or low levels of ADNCs, which provides further rationale for exploring how apoE isoforms might modulate neurodegeneration through mechanisms unrelated to Aβ metabolism. Longitudinal studies comparing cerebrospinal fluid profiles in subjects clinically diagnosed as having DLB or PDD and stratified by APOE genotype and amyloid burden by in vivo imaging might complement work in model systems to address this question in the future.

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Author Affiliations: Veterans Affairs Puget Sound Health Care System (Drs Tsuang, Leverenz, Watson, Mata, and Zabetian, and Ms Yearout); Departments of Psychiatry and Behavioral Sciences (Drs Tsuang, Leverenz, and Watson), Neurology (Drs Leverenz, Mata, and Zabetian, and Ms Yearout), Medicine (Drs Larson and Crane), Epidemiology (Drs Kukull and Edwards, and Ms Wan), and Pathology (Dr Montine), University of Washington; Group Health Cooperative (Dr Larson), Seattle, Washington; Departments of Neurology (Dr Lopez) and Pathology (Dr Hamilton), University of Pittsburgh, Pittsburgh; Departments of Pathology and Laboratory Medicine (Drs Trojanowski, Irwin, and Schellenberg), Neurology (Drs Weintraub, Chen-Plotkin, Irwin, and Rick), and Psychiatry (Dr Weintraub), and Institute on Aging (Dr Trojanowski), University of Pennsylvania, Philadelphia; Philadelphia Veterans Affairs Medical Center (Dr Weintraub), Pennsylvania; Departments of Neurological Sciences (Drs Bennett and Buchman) and Pathology (Dr Schneider), Rush University, Chicago, Illinois; Departments of Neurology (Drs Kaye, Kramer, Quinn, and Chung) and Pathology (Dr Woltjer), Oregon Health and Science University; Portland Veterans Affairs Medical Center (Drs Quinn and Chung), Portland, Oregon; Departments of Pathology (Drs Nelson and NelTner) and Neurology (Dr Jicha), University of Kentucky, Lexington; and Departments of Neurology (Dr Galasko) and Pathology (Dr Masliah), University of California, San Diego.

Correspondence: Cyrus P. Zabetian, MD, MS, VA Puget Sound Health Care System, GRECC S-182, 1600 S Columbian Way, Seattle, WA 98108 (zabetian@u.washington.edu).

Author Contributions: Drs Tsuang and Leverenz contributed equally to this study. Study concept and design: Tsuang, Leverenz, Lopez, Trojanowski, Galasko, and Zabetian. Acquisition of data: Tsuang, Leverenz, Hamilton, Bennett, Schneider, Larson, Crane, Kaye, Kramer, Woltjer, Trojanowski, Chen-Plotkin, Irwin, Rick, Schellenberg, Kukull, Nelson, Jicha, Neltner, Galasko, Masliah, Quinn, Chung, Yearout, Montine, and Zabetian.


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