The Utility of Apolipoprotein E Genotyping in the Diagnosis of Alzheimer Disease in a Community-Based Case Series

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Context: A recent collaborative study found that apolipoprotein E (APOE) genotype, in conjunction with the clinical diagnosis of Alzheimer disease (AD), was useful in improving diagnostic specificity (correctly not diagnosing AD) relative to the clinical diagnosis alone. Since these samples are particularly enriched with patients with AD and the APOE e4 allele, results may not be generalizable to patients seen in the general medical community.

Objective: To evaluate the diagnostic utility of the APOE genotype in diagnosing AD in a community-based case series from the largest health maintenance organization in an urban area.

Design: We examined the effect of including APOE genotype on the diagnosis of AD in a community-based case series of patients presenting with memory complaints.

Patients: Clinical and neuropathologic diagnoses and APOE genotype were obtained from 132 patients who underwent evaluation for dementia and subsequent autopsy.

Main Outcome Measures: Sensitivity, specificity, and positive and negative predictive values given various combinations of clinical diagnoses and the presence of an APOE e4 allele.

Results: Of the 132 patients, 94 had neuropathologically confirmed AD, yielding a prevalence of 71%. The clinical diagnosis alone yielded a sensitivity of 84%, an estimated specificity of 50%, and positive and negative predictive values of 81% and 56%, respectively. The presence of an e4 allele alone was associated with an estimated sensitivity of 59%, specificity of 71%, and positive and negative predictive values of 83% and 41%, respectively. Using the presence of clinical AD and an e4 allele decreased the sensitivity to 49% and increased the specificity to 84%. The positive and negative predictive values were 88% and 40%, respectively. Alternatively, the clinical diagnosis of AD or the presence of an e4 allele in individuals not meeting clinical criteria for AD increases the estimated sensitivity to 94% but decreases the specificity to 37%. The positive and negative predictive values were 79% and 70%, respectively. The changes in the sensitivity and specificity for the combined tests relative to clinical diagnosis alone offset each other. For lower prevalence communities, the positive predictive value will be much lower than those observed herein.

Conclusions: Our findings do not support the use of APOE genotyping alone in the diagnosis of AD in the general medical community. Although the presence of an e4 allele in older persons with clinical AD increased the probability of having AD and the absence of an e4 allele in this group decreased the probability of having AD, the association is not strong enough in the differential diagnosis of non-Alzheimer dementia and AD.

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PATIENTS AND METHODS

CLINICAL DIAGNOSIS

The University of Washington–Group Health Cooperative Alzheimer’s Disease Patient Registry (ADPR) is a population-based registry of incident dementia cases; it attempts to identify all new dementia cases within Group Health Cooperative, the largest health maintenance organization in the Puget Sound area, serving more than 350,000 members statewide. The ADPR is based on the Seattle area Group Health population that includes approximately 23,000 persons aged 60 years or older. Patients who were eligible received an ADPR diagnostic workup for dementia; patients with previously diagnosed (more than 1 year earlier) dementia were excluded. A total of 1028 patients were enrolled from April 1, 1987, to July 1, 1996.

The ADPR case-finding strategy has been described in detail elsewhere. In general, all Group Health Cooperative patients with clinical indications of possible dementia (eg, computed tomographic scan logs, neurology clinic notes, discharge diagnoses) but no previous diagnosis of dementia were asked to undergo a complete, standardized diagnostic workup, including medical history; physical, neurologic, and neuropsychological evaluations; laboratory tests; and computed tomographic imaging of the brain. When the workup was completed, a panel of physicians and neuropsychologists arrived at a consensus diagnosis for each patient based on NINCDS-ADRDA and Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised criteria. All patients in the ADPR received annual follow-up with interim history, neuropsychological testing, and additional physical and neurologic examinations if indicated by a change in clinical symptoms. All patients gave informed consent according to guidelines approved by the Human Subjects Review Divisions at the University of Washington and Group Health Cooperative.

Of 1028 potential cases, 38 died or withdrew before evaluation; 970 patients underwent evaluation. Of those evaluated, 471 (48.6%) met NINCDS-ADRDA diagnostic criteria for probable AD; 91 (9.4%), possible AD; and 184 (19.0%), other dementia. Two hundred twenty-four (23.1%) did not meet any specific dementia criteria, and were therefore classified as having no dementia. From this overall group, 425 deaths occurred; results of autopsy and neuropathologic studies were obtained from 132 patients within the study period. Demographic characteristics of subjects who consented to autopsy and of those who did not were not significantly different. This group consisted of 58 men (43.9%) and 74 women (56.1%), most of whom were white (126 [95.4%]) and had completed at least a high school education (96 [72.7%]). Mean ± SD age at enrollment was 80 ± 7 years, and mean age at death was 83 ± 7 years. The mean ± SD Mini-Mental State Examination score on intake was 19 ± 6, and the mean ± SD duration of follow-up in the ADPR was 3.0 ± 1.8 years.

APOE GENOTYPING

Sixty-one patients had DNA available from blood samples. Apolipoprotein E genotyping in these samples was performed using the dot-blot method and replicated using a restriction enzyme digest method. Both methods yielded the same APOE genotype in all cases. In the remaining 71 patients, APOE genotyping was performed on DNA extracted from paraffin-embedded tissue. To ensure reliability of the paraffin-fixed genotyping method, 10 randomly selected tissue samples from patients previously genotyped using DNA derived from blood samples were sent for a second analysis. We obtained the same APOE genotypes in all 10. Apolipoprotein E genotype was available for all 132 patients.

NEUROPATHOLOGIC EXAMINATION

All autopsies were performed at the University of Washington Medical Center by neuropathologists from the Department of Pathology and Alzheimer’s Disease Research Center (D.N. and Mark Sumi, MD). The pathologists were aware of the clinical history and diagnosis before making the neuropathologic diagnosis. Semiquantitative analysis of neuritic plaques and neurofibrillary tangles was performed according to the guidelines established by the Neuropathology Task Force of the CERAD using a standardized set of photomicrographs for comparison. Tissue preparation consisted of staining with hematoxylin-eosin, modified Bielschowsky silver method, and thioflavine S. Neuropathologic examinations focused on the following brain regions: cingulate gyrus; superior and middle frontal gyri; medial orbital cortex; superior, middle, and inferior temporal gyri; inferior parietal lobule; medial occipital cortex; hippocampus; amygdala; parahippocampal gyrus; hypothalamus; mammillary bodies; thalamus; midbrain; pons; medulla; and cerebellum. The neuropathologic diagnosis of AD required a semiquantitative assessment of neuritic plaques in selected regions as described and, in addition, determination of an age-related neocortical plaque score on the basis of patient age at death. Finally, age-related plaque score was correlated with clinical information regarding the presence or absence of dementia to determine the level of certainty of the neuropathologic diagnosis.

DATA ANALYSIS

The clinical diagnosis of AD included NINCDS-ADRDA probable and possible AD. Neuropathologic diagnoses were categorized as CERAD definite and probable AD, compared with absence of those diagnoses. Apolipoprotein E genotypes were categorized as those with and without an e4 allele. The sensitivity and specificity (against neuropathologic determination of AD) were estimated for clinical diagnosis of AD (combined probable and possible AD) and the presence of an APOE e4 allele, first separately and then in combination. When used sequentially, both diagnostic methods were defined by a positive clinical diagnosis and an e4 allele (the AND criterion) and by a positive clinical diagnosis of AD or an e4 allele (genotyping only in those who did not meet clinical criteria for AD but had an e4 allele [the OR criterion]). Furthermore, conditional (posttest) probabilities of AD were calculated for the various diagnostic definitions using the Bayes theorem. Comparisons of estimated test accuracies were performed using the normal approximation to the binomial distribution.
APOE genotyping decreased the sensitivity to 61% and increased the specificity to 84%. These investigators concluded that APOE genotyping does not provide sufficient sensitivity or specificity to be used alone. However, when genotyping is combined with clinical evaluation, specificity (ie, correctly not diagnosing AD) is improved. These results were confirmed in another study using data generated from a cooperative multicenter AD centers—Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) site. In well-defined research AD cases, results suggest that APOE genotyping has a high predictive value in the neuropathologic diagnosis of AD.

Our study examined the diagnostic parameters of the APOE ε4 allele in the clinical diagnosis of AD in a sample of patients more typical of those seen in the general community medical setting. Previous reports have shown that patients with AD from an AD research center differ from those sampled from the general medical community. Patients with AD from research registries are likely to be younger, have less medical comorbidity, and have higher APOE ε4 allele frequencies compared with community-based samples of patients with AD. Demographic characteristics from our current sample (from an Alzheimer’s Disease Patient Registry) are more similar to those observed in the Greater Seattle, Wash, area. Therefore, findings from our sample are thus more likely generalizable to patients encountered in the general community medical setting.

A second purpose of our study was to quantify the probability of having AD neuropathologically in individuals with symptoms suggestive of dementia. Sensitivity and specificity are independent of pretest probability; however, the usefulness of diagnostic methods needs to be assessed in the context of the likelihood of disease in the population under consideration. The probability that any target disorder is present, given a positive test result, is known formally as positive predictive value (PPV). Given a positive test result, the probability of disease also depends on the likelihood of disease before testing (pretest probability). Bayes theorem is used to incorporate the pretest probability in the calculation of predictive values (or posttest probabilities). A positive test result in a patient with a low previous probability of disease is of limited diagnostic value, even if the test is highly sensitive and specific. Consider a test with 80% sensitivity and 70% specificity. In a patient with the low pretest probability of disease of 5%, the posttest probability of disease is 12% for an individual with positive test result and 1% for an individual with negative result. In a patient with the intermediate pretest probability of disease of 50%, the posttest probability of disease is 73% for an individual with positive test result and 22% for an individual with negative result. In a patient with the high pretest probability of disease of 90%, the posttest probability of disease is 96% for an individual with positive test result and 72% for an individual with negative result. In general, diagnostic tests are most useful in patients with an intermediate pretest probability of disease.

### RESULTS

Of the 132 patients with symptoms suggestive of dementia, 94 had a neuropathologic diagnosis of AD, yielding a pretest probability of 71%. The NINCDS-ADRDA clinical diagnosis and the CERAD neuropathologic diagnosis of AD or no AD as well as APOE genotypes of patients are presented in Table 1. Forty-six individuals with the clinical diagnosis of AD and an ε4 allele had a neuropathologic diagnosis of AD, whereas 33 individuals with a clinical diagnosis of AD who did not have an ε4 allele also had a neuropathologic diagnosis of AD. There were 6 individuals with clinical AD and an ε4 allele who did not have AD on results of neuropathologic examination. There was 1 individual homozygous for the ε4 allele who had neither a clinical diagnosis of AD nor neuropathologic evidence of AD.

Previously, Lim et al. reported the sensitivity and specificity of the NINCDS-ADRDA criteria for the clinical diagnosis of AD in correctly diagnosing AD (confirmed by neuropathologic evaluation) to be 84% and 50%, respectively (Table 2). Using the presence of the APOE ε4 allele alone generated a sensitivity of 59% and specificity of 71% (Table 3). We used 2 sequential criteria to calculate diagnostic features (Table 3). For positive di-
agnosis defined by the OR criterion, we found an estimated sensitivity and specificity of 94% and 37%, respectively, as well as PPV and negative predictive value (NPV) of 79% and 70%, respectively. The changes in sensitivity and specificity between the 2 sequential criteria relative to clinical diagnosis alone offset each other.

The accuracy (or diagnostic efficiency) of a diagnostic test measures the overall rate of correct diagnoses (true positive and true negative results). A diagnostic test based on APOE ε4 determination alone has lower accuracy than a clinical diagnosis alone (62% vs 74%; \( P = .04 \)), and the sequential test AND criterion (individuals with both a positive clinical diagnosis and an ε4 allele) has lower accuracy than a clinical diagnosis alone (59% vs 74%; \( P = .003 \)). The highest estimated accuracy was defined using the OR criterion (individuals with a positive clinical diagnosis or any genotyping only in those without a clinical diagnosis of AD who have an ε4 allele), although this accuracy is not significantly different from that of clinical diagnosis alone (77% vs 74%; \( P = .28 \)). This latter combination, the OR criterion, requires genotyping only in subjects who clinically do not have AD (only 34/132 subjects [25.8%]; Table 1). However, although this OR combination testing yields a higher sensitivity (94%) than clinical diagnosis alone (84%), it also yields a lower specificity (37% vs 50%, respectively). The higher sensitivity means that more of the patients with true AD receive a correct diagnosis, but the lower specificity means that fewer of the patients without AD receive a correct diagnosis. The lower specificity in this combined test is due to the presence of individuals who are positive for the ε4 allele but do not have AD.

Since predictive values are dependent on the prevalence of a disease, we calculated PPVs and NPVs using the OR criterion in several hypothetical pretest probability estimates. Table 4 demonstrates the utility of the ε4 allele as a diagnostic test among persons with memory complaints, with pretest probability of AD hypothesized from 10% to 90%. It demonstrates that in a patient with a pretest probability of disease of 10%, the PPV is low (14%). In other words, in this population, only 14% of those with positive test results according to this criterion are truly affected. Meanwhile, the NPV is very high (98%), indicating that 98% of those with negative test results are truly not affected. On the other hand, in a patient with pretest probability of disease of 90%, 93% of those with positive test results are truly affected, whereas 41% of those with negative test results are truly not affected. Table 4 shows that a higher pretest probability inevitably is associated with an increase in the meaningfulness of a positive test (PPV) accompanied by a decrease in the meaningfulness of a negative test (NPV).

We also summarized the PPVs of the individual tests and the possible combinations of their positive and negative outcomes, ie, we used Bayes theorem to calculate the conditional probability of having AD using various combinations of tests (Table 5). In our sample, which yielded a prevalence of AD of 71%, individuals with a clinical diagnosis of AD and an ε4 allele demonstrate a 17% increase in the probability of having AD (up to 88%). However, in individuals who meet clinical criteria for AD but who do not have an ε4 allele, the probability of having AD does not change much from baseline (72%). Since the ε2 allele may have a protective effect, in a separate analysis the individuals with the ε2/ε4 genotype were removed from the ε4-positive group. Results from this analysis did not change significantly (data not shown).

### Table 2: Sensitivity and Specificity of Clinical Diagnosis of AD Compared With Neuropathologic AD

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Neuropathologic AD</th>
<th>Neuropathologic non-AD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical AD(\dagger)</td>
<td>79</td>
<td>19</td>
<td>98</td>
</tr>
<tr>
<td>Clinical non-AD(\dagger)</td>
<td>15</td>
<td>19</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>38</td>
<td>132</td>
</tr>
</tbody>
</table>

\(\dagger\)Indicates neuropathologic definite and probable AD by Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) criteria. 
\(\dagger\)Indicates other CERAD diagnoses. 
\(\dagger\)Indicates probable and possible AD by National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria. 
\(\dagger\)Indicates “no dementia” and “other types of dementia” by NINCDS-ADRDA criteria.

### Table 3: Diagnostic Characteristics of Clinical Diagnosis and Presence of ε4 Allele

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical diagnosis of AD only(\dagger)</td>
<td>84</td>
<td>50</td>
<td>74</td>
<td>81</td>
</tr>
<tr>
<td>ε4 Only</td>
<td>59</td>
<td>71</td>
<td>62</td>
<td>83</td>
</tr>
<tr>
<td>Clinical diagnosis of AD and ε4 (AND criterion)(\dagger)</td>
<td>49</td>
<td>84</td>
<td>59</td>
<td>88</td>
</tr>
<tr>
<td>Clinical diagnosis or ε4 (OR criterion)(\dagger)</td>
<td>94</td>
<td>37</td>
<td>77</td>
<td>79</td>
</tr>
</tbody>
</table>

\(\dagger\)Calculation of sensitivity, specificity, accuracy, PPV, and NPV are provided in the first footnote to Table 2.

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Table 5 also shows that for patients who do not meet neuropathologic criteria for AD (even those with an ε4 allele), there is a decrease in the probability of having AD compared with baseline.

Of the 38 patients who did not meet neuropathologic criteria for AD, 11 had an ε4 allele. Table 6 lists APOE genotypes and neuropathologic diagnoses for these patients. Of these, 6 had a clinical diagnosis of probable AD but did not have AD confirmed neuropathologically.

Since the initial report of the association between the APOE ε4 allele and AD, APOE genotyping has been suggested as a diagnostic adjunct in the workup of dementia. Using a community-based sample of subjects with symptoms suggestive of dementia who came to medical attention, we found that 71% had neuropathologically confirmed AD. When positive diagnosis was defined by clinical diagnosis and the presence of an ε4 allele, the sensitivity decreased but the specificity increased relative to the use of the clinical diagnosis alone. Our findings confirm and extend those of Mayeux et al, who reported that along with the increase in specificity (55% to 84%), there was a decrease in sensitivity (93% to 61%) when comparing clinical diagnosis alone with the AND criterion. Although we found the highest accuracy using an additional criterion—the OR criterion—it is not significantly greater than that of using clinical diagnosis alone. In a community sample of older adults with symptoms suggestive of dementia, the presence of the ε4 allele increases the probability of having AD, but absence of the ε4 allele is not helpful in ruling out AD. The association is not strong enough to warrant the routine use of APOE genotyping alone in the differential diagnosis of dementia. There were 11 individuals in our sample of 38 subjects without neuropathologically confirmed AD who had an ε4 allele. Although ε4 homozygosity is highly predictive of AD, it is not completely accurate, even in individuals with substantial cognitive disturbance. Regardless of how one views the controversy surrounding the use of APOE genotyping, even individuals with AD can have additional treatable components that contribute to dementia (eg, AD plus thyroid deficiency). Apolipoprotein E genotyping should not replace a careful history and evaluation for comorbid causes of dementia.

**Table 4. Impact of Pretest Probability on Positive and Negative Predictive Values of Clinical Diagnosis of AD or Presence of an ε4 Allele**

<table>
<thead>
<tr>
<th>Pretest Probability</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>14</td>
<td>98</td>
</tr>
<tr>
<td>30</td>
<td>39</td>
<td>94</td>
</tr>
<tr>
<td>50</td>
<td>60</td>
<td>86</td>
</tr>
<tr>
<td>70</td>
<td>78</td>
<td>73</td>
</tr>
<tr>
<td>90</td>
<td>95</td>
<td>41</td>
</tr>
</tbody>
</table>

* Data are given as percentages. AD indicates Alzheimer disease.

**Table 5. Conditional Probability of Having Neuropathologic AD Given Various Clinical and APOE ε4 Test Results**

<table>
<thead>
<tr>
<th>APOE ε4 Allele</th>
<th>NINCDS-ADRDA not applied</th>
<th>NINCDS-ADRDA criteria not applied</th>
<th>NINCDS-ADRDA probable or possible AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>88</td>
<td>83</td>
<td>67</td>
</tr>
<tr>
<td>Not Determined</td>
<td>80</td>
<td>71</td>
<td>44</td>
</tr>
<tr>
<td>Absent</td>
<td>72</td>
<td>59</td>
<td>26</td>
</tr>
</tbody>
</table>

*Pretest probability of sample was 71%. AD indicates Alzheimer disease; APOE, apolipoprotein E; and NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association. Data are given as percentages.

**Table 6. Clinical and Neuropathologic Diagnoses for 11 Patients With an ε4 Allele but No Neuropathologic Diagnosis of Definite or Probable AD**

<table>
<thead>
<tr>
<th>Age of Death, y/Sex</th>
<th>NINCDS-ADRDA Diagnosis</th>
<th>APOE Genotype</th>
<th>Neuropathologic Diagnosis 1</th>
<th>Neuropathologic Diagnosis 2</th>
<th>Neuropathologic Diagnosis 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>84/M</td>
<td>Dementia, type unknown</td>
<td>ε4/4</td>
<td>Parkinson disease†</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>79/F</td>
<td>Dementia, type unknown</td>
<td>ε4/4</td>
<td>Parkinson disease†</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>77/F</td>
<td>Dementia, type unknown</td>
<td>ε4/4</td>
<td>Parkinson disease†</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>84/M</td>
<td>Dementia, type unknown</td>
<td>ε4/4</td>
<td>Possible AD‡</td>
<td>Parkinson disease–related changes</td>
<td>.</td>
</tr>
<tr>
<td>86/F</td>
<td>Possible AD</td>
<td>ε3/4</td>
<td>Frontal lobe degeneration</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>78/F</td>
<td>Probable AD</td>
<td>ε3/4</td>
<td>Possible AD‡</td>
<td>Motor neuron disease</td>
<td>.</td>
</tr>
<tr>
<td>86/M</td>
<td>Probable AD</td>
<td>ε3/4</td>
<td>Parkinson disease–related changes</td>
<td>Hemosiderosis, substantia nigra</td>
<td>Possible AD‡</td>
</tr>
<tr>
<td>73/F</td>
<td>Probable AD</td>
<td>ε3/4</td>
<td>Progressive supranuclear palsy</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>87/M</td>
<td>Probable AD</td>
<td>ε3/4</td>
<td>Possible AD‡</td>
<td>Hippocampal sclerosis</td>
<td>Possible dementia pugilistica</td>
</tr>
<tr>
<td>92/F</td>
<td>Probable AD</td>
<td>ε3/4</td>
<td>Parkinson disease–related changes§</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>88/M</td>
<td>No dementia</td>
<td>ε4/4</td>
<td>Hippocampal sclerosis</td>
<td>.</td>
<td>.</td>
</tr>
</tbody>
</table>

* AD indicates Alzheimer disease; APOE, apolipoprotein E; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association; and ellipses, not applicable.
† Indicates the presence of nidal degeneration with or without Lewy bodies and clinical diagnosis of Parkinson disease.
‡ Indicates insufficient age-related plaque score and clinical history of dementia. Other neuropathologic lesions that could cause dementia may coexist.
§ Indicates the presence of nidal degeneration and/or Lewy bodies at any site without clinical diagnosis of Parkinson disease.
Although the ε4 allele frequency in AD samples ranges from 35% to 56% and ε4 homozygotes make up 7% to 18% of subjects with AD, a substantial proportion of patients with AD do not have an ε4 allele. Apolipoprotein E genotyping does not help in the diagnosis of AD in these patients. The utility of APOE genotyping in the differential diagnosis of AD also depends on the prevalence of the ε4 allele in other dementing disorders. Significant elevation in ε4 allele frequency in these conditions would decrease the value of APOE genotyping in the diagnosis of AD. Conditions important in the differential diagnosis of dementia include multi-infarct dementia, diffuse Lewy body disease, frontotemporal dementia, dementia associated with Parkinson disease, Creutzfeldt-Jakob disease, and progressive supranuclear palsy. Frequencies of the ε4 allele in the first 3 conditions have been estimated to be 25%, 35%, and 29%, respectively. The ε4 association with frontotemporal dementia was reported before identification of the disease-causing tau mutations, although others have reported that other tau-positive disorders have an increased ε4 allele frequency. The relationship between APOE and cytoskeletal abnormalities needs to be investigated further. The 3 other disorders are less likely to be associated with the ε4 allele; preliminary studies have shown ε4 allele frequencies to be approximately 19% in dementia associated with Parkinson disease, 9% in Creutzfeldt-Jakob disease, and 13% in progressive supranuclear palsy.

The strength of our study is the inclusion of incident cases of dementia representative of patients seen in more typical community clinical settings. Although others have used autopsy series to examine the predictive value of APOE genotyping, to our knowledge ours is the only study that enrolled all patients with incident cases of dementia of any kind from a community setting. Our results can only be generalized to symptomatically affected individuals who consented to autopsy compared with those of kin who consented to autopsy or died before they could be asked. It is likely that family members of individuals with a clinical diagnosis of AD and those more severely affected are more likely to give consent. This type of bias likely exists in any autopsy study and is difficult to overcome.

In summary, although the presence of an ε4 allele increases the likelihood that a cognitively impaired elderly individual has AD, the association is not strong enough in most cases to alter the diagnosis substantially. The strongest association with AD occurs in the few individuals who are homozygous for the ε4 allele. However, even the presence of the ε4/ε4 genotype does not necessarily predict the presence of AD on neuropathologic examination. If APOE genotyping becomes a standard in the diagnosis of AD, the implications of a positive test result will need to be more clearly established.

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