SHORT REPORT

No effect of the α1-antichymotrypsin A allele in Alzheimer’s disease

O Didierjean, M Martínez, D Campion, D Hannequin, B Dubois, C Martín, M Puel, C Thomas Anterion, F Pasquier, O Moreau, M C Babron, C Penet, Y Agid, F Clerget-Darpoux, T Frebourg, A Brice

Abstract

The apolipoprotein E (ApoE)-ε4 allele is associated in a dose dependent manner to an increased risk for Alzheimer’s disease. However, the ApoE-ε4 allele effect does not account for all patients with Alzheimer’s disease, and the existence of other genetic risk factors has been postulated. Kamboh et al. reported an association between Alzheimer’s disease and the A allele of α1-antichymotrypsin (Aact) gene, which was not confirmed in a larger series more recently analysed. The ApoE and Aact genotypes were analysed in 314 patients with Alzheimer’s disease and 173 healthy controls, confirming the dose dependent effect of the ApoE-ε4 allele. Nevertheless, even using odds ratios adjusted for age and sex, there was no significant effect of the Aact genotype on Alzheimer’s disease or on the ApoE-ε4 allele associated risk for Alzheimer’s disease.

(shape) STATISTICAL ANALYSIS

The apolipoprotein E (ApoE) and Aact alleles were analysed in 314 series of patients with Alzheimer’s disease and 173 healthy controls. The mean age at examination of the controls was 61.7 (SD 10.1) years. The mean age at onset was 66.7 (SD 11.8) years; 173 healthy white subjects (91 women and 82 men) matched for age and sex were used as controls. The mean age at examination of the controls was 61.7 (SD 10.1) years.

Materials and methods

The patients and control subjects were all white people living in France. A total of 314 unrelated patients (221 women and 93 men), fulfilling the clinical criteria for probable Alzheimer’s disease,12 were included after exclusion of those belonging to families with autosomal dominant inheritance and with age at onset under 60 in all patients. The mean age at onset was 66.7 (SD 11.8) years; 173 healthy white subjects (91 women and 82 men) matched for age and sex were used as controls. The mean age at examination of the controls was 61.7 (SD 10.1) years.

Genotyping

Blood samples were obtained, after informed consent, from all subjects, and genomic DNA was extracted directly from blood using standard techniques. The ApoE and Aact genotypes were determined by the polymerase chain reaction restriction technique as described.11 13 Statistical analysis

Allele frequencies were estimated by allele counting. Allele and genotype frequencies were
Table 1  Distribution of ApoE and Aact genotypes

<table>
<thead>
<tr>
<th>ApoE genotypes</th>
<th>AA</th>
<th>AT</th>
<th>TT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AD</td>
<td>Control</td>
<td>AD</td>
<td>Control</td>
</tr>
<tr>
<td>2/2</td>
<td>0</td>
<td>0.00</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>2/3</td>
<td>1</td>
<td>0.10</td>
<td>8</td>
<td>0.32</td>
</tr>
<tr>
<td>2/4</td>
<td>2</td>
<td>0.40</td>
<td>2</td>
<td>0.40</td>
</tr>
<tr>
<td>3/3</td>
<td>38</td>
<td>0.38</td>
<td>20</td>
<td>0.20</td>
</tr>
<tr>
<td>3/4</td>
<td>35</td>
<td>0.35</td>
<td>9</td>
<td>0.22</td>
</tr>
<tr>
<td>4/4</td>
<td>13</td>
<td>0.24</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>0.39</td>
<td>156</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Table 2  Odds ratio (OR) for developing Alzheimer’s disease for both the ApoE and the Aact genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoE:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/3</td>
<td>1.0</td>
<td>Referent group</td>
</tr>
<tr>
<td>3/4</td>
<td>2.3</td>
<td>1.4–3.8</td>
</tr>
<tr>
<td>4/4</td>
<td>20.9</td>
<td>4.8–90.4</td>
</tr>
<tr>
<td>2/4</td>
<td>0.45</td>
<td>0.1–2.3</td>
</tr>
<tr>
<td>2/3</td>
<td>0.30</td>
<td>0.1–0.7</td>
</tr>
<tr>
<td>Aact:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td>1.0</td>
<td>Referent group</td>
</tr>
<tr>
<td>A/T</td>
<td>0.88</td>
<td>0.5–1.5</td>
</tr>
<tr>
<td>A/A</td>
<td>1.29</td>
<td>0.7–2.5</td>
</tr>
</tbody>
</table>

Odds ratios are adjusted for age and sex.

Results

Table 1 shows the distribution of the ApoE and Aact genotypes in controls and patients. Controls were in Hardy-Weinberg equilibrium for ApoE and ACT genotypes. The ApoE allele distributions were significantly different in patients and controls (P<0.001); ApoE-ε4 frequency was significantly higher in patients (0.37 v 0.14, P<0.001), and corresponded to a decrease in the frequency of the ApoE-ε2, more than the ε3 allele. Thus the ApoE-ε2 allele frequency was significantly lower in patients than in controls (0.02 v 0.09, P=0.001). No significant differences in Aact genotype (P=0.38) or allele (P=0.23) distributions were found between patients and controls. Stratification of the data according to the presence or absence of the ApoE-ε4 allele disclosed no difference in the Aact-A frequency between controls and patients with Alzheimer’s disease. Among those with ε4/ε4 and ε3/ε4 genotypes, the frequency of the Aact-A allele was 0.53 in patients and 0.52 in controls, (P=0.89). Among those with ε3/ε3 genotype, the values were 0.53 and 0.48 respectively (P=0.26).

The logistic regression analysis (table 2) showed that age (P=0.01), sex (P=0.02), and ApoE-ε4/ε4 (P=0.001), ε3/ε4 (P=0.001), and ε2/ε3 genotypes (P=0.0045) were significant predictors of Alzheimer’s disease. The following genotypes had no significant effect: ApoE-ε2/ε4 (P=0.34), Aact-A/A (P=0.44), and A/T (P=0.64). The dose dependent effect of the ApoE-ε4 allele was confirmed: ε4/ε4 homozygotes had a higher risk (OR=20.9, 95% confidence interval 95% CI 4.8–90.4) than ε4/ε3 heterozygotes (OR=2.3, 95% CI 1.4–3.8). Those with ApoE-ε2/ε3 had a lower risk (OR=0.30, 95% CI 0.1–0.7), whereas the adjusted OR for ApoE-ε2/ε4 genotype was not significantly different from 1 (OR=0.45, 95 CI 0.09–2.3). None of the 12 two way interactions between ApoE and ACT genotypes were significant (P>0.10).

Discussion

Our data, using patients with Alzheimer's disease and controls from the same population, confirmed the dose dependent effect of the ApoE-ε4 allele with ORs similar to those calculated in previous studies. In the initial association study of Aact polymorphism in Alzheimer’s disease, the Aact-A allele increased the risk associated with the ApoE-ε4 allele in a dose dependent manner. In our series, including a larger number of patients with Alzheimer’s disease, we found no significant difference between the Aact allele and genotype distributions in patients compared with controls, and no modification of the risk associated with the ApoE-ε4 allele by Aact genotypes. These results are very similar to those recently reported by Haines et al., but do not confirm the findings of Kamboh et al. This difference is not likely to be due to sample size, as the number of patients was larger in the study of Haines et al (n=576) and in ours (n=314) than in that of Kamboh et al (n=222). In addition, age and sex were taken into account as covariables in two studies, but not in the study of Kamboh et al. The results of Kamboh et al might be explained by random fluctuations in the control group between ApoE-ε4 allele and non ApoE-ε4 allele carriers.

In conclusion, our study shows that the risk conferred by the ApoE-ε4 allele is not modified by the A/T polymorphism in the signal sequence of the Aact gene. Additional analyses in more varied populations will permit more definite conclusions to be drawn as to the influence of the Aact-A allele on Alzheimer’s disease.
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