The butyrylcholinesterase K variant and susceptibility to Alzheimer’s disease

Patrick G Kehoe, Hywel Williams, Peter Holmans, Gordon Wilcock, Nigel J Cairns, Jim Neal, Michael J Owen

Abstract
Previous work has shown an association between the K variant of the butyrylcholinesterase (BCHE) gene and Alzheimer’s disease (AD) in patients carrying the ε4 allele of ApoE. We attempted to replicate this finding in 181 UK white AD cases and 71 controls. No difference was found in BCHE-K genotypes (p=0.75) or alleles (p=0.70) between patients and controls. Moreover, despite a significant excess of ApoE ε4 in patients versus controls (p<0.0001), we found no evidence to support previous reports of an interaction between ApoE and BCHE-K (χ²=1.49, df=4, p=0.83).

Keywords: Alzheimer’s disease, butyrylcholinesterase K variant; genetics

Four genes have been implicated in the aetiology of Alzheimer’s disease (AD). Mutations in three of these, APP, PS1, and PS2, account for most cases of familial autosomal dominant AD.1, 2 The great majority of cases of AD do not show clear autosomal dominant patterns of inheritance and these probably reflect the co-action or interaction of several or many genes together with environmental factors. One gene that is clearly implicated in this form of the disorder is ApoE. The ε4 allele of ApoE, although neither necessary nor sufficient to cause AD, is associated with increased risk of early and late onset disease.3

Recently Lehmann et al4 reported an association between the so-called K variant (BCHE-K) of the butyrylcholinesterase (BCHE) gene and late onset AD in carriers of ApoE ε4 with an odds ratio of 6.9 (95% CI 1.65-29) in people over 65 years of age and of 12.8 (1.9-86) in those over 75 years. We attempted to replicate this finding in 94 AD cases confirmed at necropsy (PMAD), 87 clinically confirmed probable AD patients (CLAD), and 71 age matched controls (AMC). The PMAD group (n=94), comprising 32 males and 62 females, diagnosed clinically for probable AD under NINCDS-ADRDA criteria5 and later confirmed at necropsy,6 had an average age of death at 81.8 years (SD 7.5). Using available age of onset and age at death information (n=78) the overall mean onset of PMAD was 73.7 years (SD 8.9). This included 11 early (<65 years) onset cases (mean onset 58.0 years, SD 4.4) and 67 late (≥65 years) onset cases (onset 76.3 years, SD 6.5). Samples were collected from brain banks in Bristol (n=39), the Institute of Psychiatry, London (n=30), and Cardiff (n=25). No data on family history were available.

The CLAD group (n=87), comprising probable AD cases (NINCDS-ADRDA),7 had an average age of onset of 67.4 years (SD 9.2); 27 were early onset cases (onset 56.7 years, SD 6.4) and the remainder (n=60) late onset (onset 72.2 years, SD 5.6). The group (41 males, 46 females) were UK white subjects and 43 had a family history of AD (defined by having at least one first degree relative with the disease). The AMC group (34 males, 37 females) were collected locally having scored 28 or higher on the Mini Mental State Examination8 and had an average age of 73.46 years (SD 6.2) at collection. An additional group (PC) of unrelated white subjects (n=262) obtained locally were genotyped

Table 1  Genotype and allele distributions of the K variant of the BCHE gene

<table>
<thead>
<tr>
<th>Sample</th>
<th>Genotype</th>
<th>Allele</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>wt/wt</td>
<td>wt/k</td>
</tr>
<tr>
<td>CLAD (all cases) (n=87)</td>
<td>56 (0.65)</td>
<td>29 (0.33)</td>
</tr>
<tr>
<td>LOAD (onset ≥65 y) (n=60)</td>
<td>38 (0.63)</td>
<td>21 (0.35)</td>
</tr>
<tr>
<td>PMAD (all cases) (n=94)</td>
<td>57 (0.61)</td>
<td>30 (0.32)</td>
</tr>
<tr>
<td>LOADt (onset ≥65 y) (n=42)</td>
<td>27 (0.64)</td>
<td>12 (0.29)</td>
</tr>
<tr>
<td>CAD (n=181)</td>
<td>113 (0.62)</td>
<td>59 (0.33)</td>
</tr>
<tr>
<td>LOAD (onset ≥65 y) (n=102)</td>
<td>65 (0.64)</td>
<td>33 (0.32)</td>
</tr>
<tr>
<td>AMCl (n=71)</td>
<td>45 (0.64)</td>
<td>24 (0.33)</td>
</tr>
<tr>
<td>PC (n=262)</td>
<td>163 (0.64)</td>
<td>83 (0.32)</td>
</tr>
</tbody>
</table>

Numbers in parentheses represent corresponding percentages.
wt = wild type (normal) BCHE alleles.
K = the K variant of BCHE with diminished enzymatic activity.
No evidence of any departure from Hardy-Weinberg equilibrium for any of the groups.
CLAD = clinical AD; PMAD = post mortem AD; CAD = combined AD; AMC = aged matched controls; PC = population controls.
EOAD* and LOADt = data only shown for PMAD cases where actual age of onset information was available.

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Table 2 APOE ε4 and BCHE-K distributions in unaffected and affected groups

<table>
<thead>
<tr>
<th>B4</th>
<th>BCHE-K</th>
<th>Controls (AMC)</th>
<th>Cases (CAD)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>−</td>
<td>−</td>
<td>33</td>
<td>56</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>18</td>
<td>24</td>
<td>0.79</td>
<td>(0.37, 1.68)</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>12</td>
<td>58</td>
<td>2.85</td>
<td>(1.32, 6.16)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>8</td>
<td>46</td>
<td>3.39</td>
<td>(1.40, 8.19)</td>
</tr>
</tbody>
</table>

We have also failed to replicate the findings of Lehmann et al.14 Moreover, we were careful to match both groups of cases and the controls for ethnicity and this lessens the likelihood that differences between them were obscured by population stratification, a point which is reinforced by the fact that frequencies of BCHE-K in patients were similar in both studies. However, there was a marked difference in K allele frequency between control groups in the two studies (Oxford 0.09, mean age 78.1 years; Cardiff 0.20, mean age 73.5 years) though this is hard to explain since both contained elderly, non-demented, UK white subjects. Previous frequency estimates for the K polymorphism of 0.12 in UK white subjects were based on enzymatic assays in relatively small groups.4,14 We therefore genotyped a large sample and obtained a frequency of 0.22 which closely matches that observed in all our other sample groups and in the patient group of Lehmann et al.4 This suggests that the original findings may be in fact the result of a type I error, to which genetic association studies are known to be prone.15 Further studies are required to resolve this issue.

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