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Lack of association of the apoE4 allele with hippocampal sclerosis dementia

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Abstract

We determined the apolipoprotein E4 (apoE) genotype in 12 cases of autopsy-confirmed hippocampal sclerosis dementia (HSD), a disorder characterized pathologically by neuronal degeneration, predominantly of temporal lobe structures, without senile plaques or neurofibrillary tangles. The frequency of the apoE4 allele in HSD was 12.5%, similar to that of a control population and significantly different from the ~40% found in Alzheimer's disease (AD) ($P < 0.001$). These observations suggest that apoE4 is not a risk factor for HSD.

Keywords: Aging; Alzheimer's disease; Frontal lobe dementia; Neurodegeneration

The association of apolipoprotein E4 (apoE4) with cases of late-onset familial and sporadic Alzheimer's disease (AD) [21] has been reported and confirmed by many investigators [16,19]. Based on this genetic association, it has also been proposed that apoE4 may have a role in the pathogenesis of AD [22,23]. Furthermore, increased apoE4 frequencies have also been reported in non-AD dementias, including Lewy body [1,9] and vascular [7,18] dementias. However, the correlation of apoE4 and vascular dementia has not been corroborated by other studies [2,14], and the subject remains controversial [8,15].

In the present study, we ask whether apoE4 is associated with hippocampal sclerosis dementia (HSD), an adult-onset progressive dementia with variable clinical expression. In most HSD cases, memory impairment is prominent compared to other cognitive domains and occasionally can present as a nearly pure amnestic syndrome [6]. In our experience, patients with HSD may also exhibit marked behavioral abnormalities such as disinhibition. However, half of our HSD cases could not be differentiated clinically from AD. Pathologically, HSD is characterized by severe loss of neurons, predominantly in the hippocampal formation, but also involving the neocortex of the temporal and frontal lobes and the substantia nigra [4,6,10,13]. The pattern of neuronal loss in HSD overlaps with that of frontal lobe and mesolimbocortical dementia and lobar atrophy without Pick bodies [3,12,24] and is not associated with significant amyloid deposits/senile plaques or neurofibrillary tangles [10].

Using the method of Hixson and Vernier [11], we determined apoE4 genotypes from frozen or paraffin-embedded brain tissues from 12 Caucasian individuals with autopsy-confirmed HSD (six males, six females, mean...
Table 1

<table>
<thead>
<tr>
<th>No. of alleles</th>
<th>E2</th>
<th>E3</th>
<th>E4</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSD</td>
<td>24</td>
<td>4.16</td>
<td>83.33</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>(1/24)</td>
<td>(20/24)</td>
<td>(2/24)</td>
<td>Present study</td>
</tr>
<tr>
<td>AD</td>
<td>202</td>
<td>3.5</td>
<td>54.9</td>
<td>41.6</td>
</tr>
<tr>
<td></td>
<td>Johns Hopkins ADRC a [5]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>352</td>
<td>7.8</td>
<td>78.3</td>
<td>13.9</td>
</tr>
<tr>
<td>Population controls</td>
<td>2000</td>
<td>7.8</td>
<td>78.3</td>
<td>13.9</td>
</tr>
</tbody>
</table>

aDifference for frequency of apoE4 between HSD and AD (Johns Hopkins ADRC cohort) was significantly different as determined by Fisher’s exact test, P < 0.001.

The age of onset 68.7 years) and compared their apoE4 allele frequency with published data for controls [17] and autopsy-confirmed sporadic AD [21] including our own series from the Alzheimer’s Disease Research Center [5] (see Table 1). The frequency of apoE4 in HSD was 12.5%, almost identical to that of a Caucasian control population [17], and significantly different (P < 0.001) from apoE4 frequency in AD [5,21].

Our observations indicate no association of apoE4 allele with HSD, suggesting that apoE4 is neither a risk nor a pathogenic factor for HSD. Although HSD and AD share a common pattern of neuronal degeneration, their differences in amyloid deposits/ senile plaques, neurofibrillary tangles, and association with apoE4 lead us to believe that HSD and AD are biologically different disorders. Finally, from a nosological perspective, it appears attractive to group HSD with the lobar atrophy/frontal lobe type of dementia, which also is characterized by lack of amyloid deposits and no association with the apoE4 allele [20].

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