ApoE ε4 is not associated with posictal confusion in patients with mesial temporal lobe epilepsy with hippocampal sclerosis

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ApoE; Temporal lobe epilepsy; Gene; Polymorphism

Summary A previous report found an association between ApoE isoforms and postictal confusion in medically intractable temporal lobe epilepsy (TLE). We performed a molecular epidemiology study in an independent sample of 77 TLE patients. We failed to replicate the original allelic association between ApoE ε4 allele and postictal confusion in our population ($\chi^2 = 1.67$; d.f. = 1; $p = 0.2$). Thus, the association between ApoE ε4 allele and postictal confusion still needs to be fully investigated in different and independent populations.

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Introduction

The role of apolipoprotein E (ApoE) gene variation in different neurological diseases has been extensively investigated (Laskowitz and Vitek, 2007). Two single nucleotide polymorphisms result in three different protein isoforms (Strittmatter et al., 1993). Of them, ApoE ε4 isoform seems to be functionally deficient (Mahley et al., 2006). This deficiency might result in a failure of different neuronal repairing processes that could be involved in the pathophysiology of diverse neurological diseases such as Alzheimer (Ye et al., 2005), traumatic brain injury (Ariza et al., 2006), multiple sclerosis (Burwick et al., 2006) and temporal lobe epilepsy (TLE) (Busch et al., 2007).

TLE is a heterogeneous disorder with complex genetics in which variants in putative genes could be acting as susceptibility factors and modifiers of the phenotypic features (Tan et al., 2006; Kauffman et al., 2008). Recently, Chapin et al. (2008) reported the association between ApoE ε4 alleles and postictal confusion in a sample of TLE patients. Association studies have been proposed as a method to dissect the genetic basis of these complex disorders. However, they have not produced consistent results; initial positive associa-

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We failed to show an allelic association between ApoE /H9255/US allele and postictal confusion in our population (d.f. = 1; p = 0.2). Moreover, we found that patients with an e4 allele were less likely to experience postictal confusion. Specifically, of the 23 individuals with ApoE e4 allele and postictal confusion still present in the sample sized as ours might be reduced because of insufficient power to detect a true association.

In conclusion, we agree with Chapin et al. that the association between ApoE e4 allele and postictal confusion still need to be fully investigated in different and independent populations.

**Materials and methods**

**Patients**

Between August 2003 and July 2005, we recruited 102 consecutive mesial temporal lobe epilepsy with hippocampal sclerosis (MTE-HS) patients from the Epilepsy Clinic at the Neurology Division of the Ramos Mejía Hospital in Buenos Aires, Argentina. The study was reviewed and approved by the local ethics committee and a written informed consent was obtained from each patient prior to any sample recovery. All patients had a comprehensive diagnostic evaluation, including detailed seizure history and neurological examination, neuropsychological testing, optimized MRI study, and surface EEG. Long-term video-EEG monitoring was performed in a subset of patients. Data from all these patients was consistent with the diagnosis of typical MTE-HS. The subjects were interviewed about ethnic background. We paid special attention to the nationalities of parents and grandparents of the subjects included. From a subset of 77 patients we could analyze the presence of postictal confusion, coding and defining it in a similar way than Chapin et al. (2008). The results obtained in this sample of 77 patients are presented here.

**Genotyping and statistical analysis**

Genomic DNA was isolated from whole blood using a Flexigene kit, as described by the manufacturer (Qiagen, Hilden, Germany). ApoE status was determined by PCR-RFLP, as previously described (Busch et al., 2007). The genotyping reactions were performed in a blinded manner to clinical features. We used the same statistical analysis that Chapin et al. (2008).

**Results**

The distribution of ApoE genotypes was consistent with what is typically observed in the general population and is opposite to what was reported by Chapin et al. (2008). Therefore, addressing the necessity to replicate positive findings in order to confirm or refute previously published associations, we present the results of an independent replication study of the association between ApoE e4 allele and postictal confusion in a sample of TLE patients from Argentina.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Frequency of patients with and without an ApoE e4 allele who did and did not exhibit postictal confusion, $\chi^2 = 1.67$; d.f. = 1; $p = 0.2$.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Postictal confusion</td>
</tr>
<tr>
<td>ApoE</td>
<td>No</td>
</tr>
<tr>
<td>e4</td>
<td>29</td>
</tr>
<tr>
<td>+e4</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
</tr>
<tr>
<td>--e4 = participants without an e4 allele; +e4 = participants with at least one e4 allele.</td>
<td></td>
</tr>
</tbody>
</table>

**Discussion**

Recently, Chapin et al. (2008) found an association between ApoE e4 isoforms and postictal confusion in a sample of TLE patients. However, we failed to replicate these findings in an independent population of MTE-HS patients.

We agree with these authors that ApoE e4 isoforms might be modulating the clinical features of TLE, such as postictal confusion, because of their probable lower ability to repair neuronal damage (Laskowitz and Vitek, 2007). Therefore, we expected a confirmation of the original findings. However, replication failure frequently occurs in the field of complex genetics. This situation could be caused by several factors, that have been discussed extensively in previous studies (Colhoun et al., 2003). Among these factors, we think there are two that are the most probable. First, ethnic-geographic differences between the populations could be considered as a cause. Apart from the percentage of refractory patients, the samples investigated differ mainly in their ethnic origin. Common diseases, as well as their clinical variability, might arise from the interaction of several genes with additional environmental influences (Lander, 1996). These different genes have probable populational differences in their susceptibility alleles prevalences, which can lead to the discrepancy observed when independent populations are investigated. Second, it is possible that the originally reported findings represent false-positives because of chance. In order to control for this factor, some researchers suggested accepting only highly conservative p-values to reject the null hypothesis of no association (Colhoun et al., 2003). A p-value of 0.036 is above what is currently recommended for genetic association studies (Tan et al., 2004).

Alternatively, the genetic effect in the first positive study could be biased upward as it was suggested as a common phenomenon by some authors (Lohmueller et al., 2003). In this scenario, the chances of replication in a sample sized as ours might be reduced because of insufficient power to detect a true association.

In conclusion, we agree with Chapin et al. that the association between ApoE e4 allele and postictal confusion still need to be fully investigated in different and independent populations.

**References**

ApoE variants and Postictal confusion in patients with mesial temporal lobe epilepsy