Association study of three polymorphisms of TGF-β1 gene with Alzheimer’s disease

L Araria-Goumidi, J C Lambert, D M A Mann, C Lendon, B Frigard, T Iwatsubo, D Cottel, P Amouyel, M C Chartier-Harlin

**SHORT REPORT**

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**Objectives:** To explore the impact of the −800 and −509 TGF-β1 promoter polymorphisms and the +25 polymorphism on the risk of occurrence of Alzheimer’s disease in a large population of sporadic cases and controls, and on the amyloid β (Aβ) load in the brains of Alzheimer patients.

**Methods:** The TGF-β1 genotypes of the three polymorphisms were determined in 678 sporadic Alzheimer’s disease patients and 667 controls. They were also characterised, along with Aβ load, in the brains of 81 necropsy confirmed Alzheimer patients.

**Results:** No significant variations in the distribution of the genotypes and haplotypes were observed between Alzheimer patients and controls, or in the amount of Aβ deposition.

**Conclusions:** These results do not suggest an influence of genetic variability at the TGF-β1 gene locus on the occurrence of Alzheimer’s disease.

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Table 1 Genotype distribution of −800, −509, and +25 polymorphisms in a case–control population, and in relation to amyloid peptide (Aβ40, Aβ42, and total Aβ) in brains of patients with Alzheimer’s disease

<table>
<thead>
<tr>
<th></th>
<th>−800</th>
<th>−509</th>
<th>+25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ40</td>
<td>GG</td>
<td>GA</td>
<td>AA</td>
</tr>
<tr>
<td>AD patients</td>
<td>528 (83.7)</td>
<td>98 (15.5)</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>Controls</td>
<td>550 (86.1)</td>
<td>86 (13.4)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Aβ42</td>
<td>GG</td>
<td>GA</td>
<td>AA</td>
</tr>
<tr>
<td>AD patients</td>
<td>298 (41.4)</td>
<td>335 (46.5)</td>
<td>87 (12.1)</td>
</tr>
<tr>
<td>Controls</td>
<td>285 (42.0)</td>
<td>307 (45.2)</td>
<td>87 (12.8)</td>
</tr>
<tr>
<td>Total Aβ</td>
<td>15.2 (7.5)</td>
<td>14.5 (6.5)</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Values are n (%) (patients) or mean (SD) (brains).
AD, Alzheimer’s disease; Aβ, amyloid β peptide.

RESULTS
For all three polymorphisms tested, the genotype distributions in control subjects were in Hardy–Weinberg equilibrium (table 1). The allele frequencies and genotype distributions of the three TGF-β1 polymorphisms in controls were similar to those previously reported.1,11 We did not observe any differences in genotypic or allelic distributions between Alzheimer’s disease and control groups for any of the polymorphisms.

We also tested the impact of these three polymorphisms on the Aβ load in Alzheimer’s disease brains. No effect was detected for −800, −509, or +25 polymorphisms (table 1). No effect of these polymorphisms on age at onset was found in either case–control or Alzheimer brain cohorts. No difference in the distribution of estimated haplotype frequencies between patients and controls was observed. Furthermore, no particular haplotype correlated with Aβ load in Alzheimer brains (data not shown).

The linkage disequilibrium coefficients between pairs of polymorphisms were calculated. A negative sign in front of the coefficient indicates that the less frequent allele at one site is associated with the most frequent allele at the other site. As previously reported by Cambien et al,7 there was a strong negative linkage between −800 and −509 (−0.97), and between −509 and +25 (−0.94). Complete linkage disequilibrium was observed between −800 and +25 in our population.

DISCUSSION
Despite some previous evidence to the contrary, we found that genetic variability at the TGF-β1 gene locus did not appear to be associated with Alzheimer’s disease risk. TGF-β1 appears to be a potential candidate susceptibility gene for Alzheimer’s disease for the following reasons:

- In Alzheimer patients, TGF-β1 is present in senile plaques and in neurofibrillary tangles;
- TGF-β1 protein is overexpressed in Alzheimer brain tissues compared with control brain;
- Recent data on transgenic mice support the involvement of TGF-β1 in Alzheimer pathology—for example, overproduction of TGF-β1 in transgenic mice induces an Alzheimer-like cerebrovascular degeneration12; and immunoreactive astrocytes for TGF-β1 are present in cerebral Aβ deposits in mice containing the Swedish double mutation of human amyloid precursor protein 695 as transgene.

- Recent studies have shown that the TGF-β1 signalling in astrocytes promotes Aβ production and might play a critical role in the formation of amyloid plaques in the brain.7 These observations suggest that an increased level of TGF-β1 could play a significant role in neurodegeneration. These increased levels of TGF-β1 might be constitutionally associated with genetic variability at the TGF-β1 gene locus. Thus the aim of our study was to assess whether genetic variability at the TGF-β1 gene locus could be a potential risk factor for Alzheimer’s disease.

We first investigated the impact of the −509 polymorphism of the TGF-β1 gene in a large case–control population. The −509 T allele had previously been associated with higher serum concentration of TGF-β1 in a twin study, suggesting a functional role for this polymorphism in the regulation of TGF-β1 levels.11 Moreover, a weak association of the −509 T allele with Alzheimer’s disease was recently reported in an American population.12 However, while the distribution of this polymorphism was similar in our control subjects to that reported by Luedecking et al,11 we did not observe any impact of this polymorphism on the disease. Despite linkage disequilibrium reported at the TGF-β1 locus, we also tested the −800 and +25 polymorphisms in this population. The −800 and +25 polymorphisms were in strong linkage disequilibrium with −509, and not surprisingly no effect of these polymorphisms could be found in our case–control study. Moreover none of the polymorphisms tested showed an impact on Aβ load, and no haplotype appeared to influence the occurrence of Alzheimer’s disease, the age at disease onset, or the Aβ load.

In conclusion, the three polymorphisms tested in this gene do not seemed to be implicated in the development of Alzheimer’s disease.

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