



## SCIENTIFIC CORRESPONDENCE

# The association of the short variant of the 5-HTTLPR polymorphism and the apoE $\epsilon 4$ allele does not increase the risk for late onset Alzheimer's disease

SIR — Alzheimer's disease (AD), the most common form of dementia in the elderly, is a complex disorder characterized by a progressive deterioration in memory, language and other cognitive functions. In addition to the genetic contribution, environmental factors such as the educational level or the occurrence of head injuries have been implicated also in the development of late onset AD (LOAD).<sup>1</sup>

LOAD appears to be influenced by multiple susceptibility loci whose combined effects contribute to the development of this disorder. Among these, the  $\epsilon 4$  allele of the apolipoprotein E (APOE) gene, at chromosome 19, has been reported in numerous studies worldwide as a risk factor associated mainly with the late onset AD form,<sup>2</sup> which was also confirmed in the Brazilian population.<sup>3</sup>

More recently, an association between a polymorphism in the transcriptional control region upstream of the serotonin transporter gene (5-HTT) and LOAD has been found in European patients<sup>4</sup> and confirmed by us in a Brazilian sample of AD patients.<sup>5</sup> It has been demonstrated that the long (L) and short (s) variants of this 5-HTT gene-linked polymorphic region (5-HTTLPR) have different transcriptional activities. That is, the short variant s of this polymorphism reduces the transcriptional efficiency of the 5-HTT gene promoter resulting in decreased 5-HTT expression and 5-HT uptake in lymphocytes.

In order to assess if there is an interaction between this polymorphism s and the ApoE  $\epsilon 4$  allele, we have analyzed 61 patients with probable/possible diagnosis of AD (mean age  $70.7 \pm 8.42$  years, ranging from 55 to 92) and 64 normal control subjects (mean age  $76.89 \pm 10.26$  years, ranging from 50 to 98). Determination of

the APOE and 5HTTLPR polymorphisms was done as reported previously.<sup>6,7</sup>

As shown in Table 1, the preliminary  $\chi^2$  tests on  $2 \times 2$  contingency tables confirmed that the frequency of individuals with the APOE  $\epsilon 4$  allele, the s allele or the APOE  $\epsilon 4 + s$  alleles is significantly greater among AD patients than among controls. On the other hand, the estimated relative risks that a person carrying the  $\epsilon 4$  or the  $\epsilon 4 + s$  alleles will develop Alzheimer disease were very similar (3.72 and 3.58, respectively). In addition, the approximate 95% confidence intervals of these estimates showed extensive overlapping.

The 5-HTTLPR polymorphism has been studied in several psychiatric and personality conditions (affective disorders, obsessive compulsive disorder, panic disorder, schizophrenia and autistic disorder) with some contradictory findings. Two independent recent studies<sup>4,8</sup> reported that the frequency of the low-activity short variant s of the 5-HTTLPR polymorphism was higher among European patients with affective disorders and LOAD than in normal controls.

Our previous data suggest that this polymorphism does not seem to play a major role in the genetics of bipolar and schizophrenic disorders<sup>9</sup> but was significantly more frequent in LOAD than in control Brazilian subjects.<sup>5</sup> In addition, results from the present study support the recent report of Li *et al*<sup>4</sup> who found no significant association between the APOE  $\epsilon 4$  allele and the short variant s of the 5-HTTLPR polymorphism among Caucasian AD patients from England. That is, the present data suggest that the association of these two polymorphic alleles does not seem to represent an increased risk factor for LOAD in Brazilian patients. However, since the ethnic background may influence the degree of penetrance of susceptibility genes,<sup>10</sup> it will be important to confirm such findings in different populations from various ethnic backgrounds.

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**Table 1** Frequencies of individuals with alleles  $\epsilon 4$ , s and  $\epsilon 4 + s$  in Alzheimer disease (AD) patients and normal controls and estimated relative risks

Alleles	AD	Controls	$\chi^2$	Relative risks
$\epsilon 4$	35/61 = 0.574	17/64 = 0.266	10.97**	3.72 (1.75–7.89)
s <sup>a</sup>	48/61 = 0.787	35/64 = 0.547	7.02*	3.06 (1.39–6.71)
$\epsilon 4$ and s <sup>a</sup>	26/61 = 0.410	11/64 = 0.172	8.51*	3.58 (1.57–8.16)

\* $P < 0.01$ ; \*\* $P < 0.001$ .

<sup>a</sup>At least one allele s.



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