

No evidence of association between the D10S1423 locus and Alzheimer disease in Brazilian patients

Short Communication

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Summary. In a genome survey for Alzheimer's disease (AD), Zubenko et al. (1998) reported that the 234 bp allele of the D10S1423 locus was more frequent among AD cases than in controls. We have analyzed this polymorphic locus in patients and healthy controls and observed that the 226 bp allele is the most frequent allele in the D10S1423 locus in Brazilian AD patients. However, no statistically significant association between any D10S1423 allele was observed in AD patients as well as in controls.

Keywords: LOAD, D10S1423, polymorphism.

Introduction

Alzheimer's disease (AD), the most common form of dementia in the elderly, is characterized by a progressive deterioration in memory, language and other cognitive functions. The etiology of AD is complex with involvement of genetic and environmental factors. Three relatively rare genes associated with early onset AD have been identified: the amyloid precursor protein gene (APP), the presenilin 1 gene (PS1) and the presenilin 2 gene (PS2), respectively in chromosome 21, 14 and 1 (Cruets et al., 1995, 1996; Haass and De Strooper, 1999; Sisodia et al., 1999). In addition a susceptibility locus for LOAD, near the centromere of chromosome 12, was also identified (Scott et al., 2000). However, familial AD accounts for less than 1% of all cases (Kehoe et al., 1999). The majority of late onset AD (LOAD) is caused by a complex inheritance with several susceptibility genes interacting with environmental factors.

Among the susceptibility genes, the ϵ -4 allele of the apolipoprotein E (APOE) gene, at chromosome 19q13.2, has been reported in numerous studies worldwide as a risk factor associated with the disease, mainly in the late onset form (Saunders et al., 1993), which was also confirmed in the Brazilian population (Oliveira et al., 1997).

An association between a polymorphism in the transcriptional control region upstream of the serotonin transporter gene (5-HTTLPR) and psychiatry disorders including LOAD has also been reported in European and Brazilian studies (Heils et al., 1996; Lesch et al., 1996; Li et al., 1997; Oliveira et al., 1998a,b, 1999) but not for the Japanese population (Kunugi et al., 1997).

In a genome survey for novel Alzheimer disease risk loci, allelic associations with AD were identified at five other loci: D1S518, D1S547, D10S1423, D12S1045 and DXS1047 (Zubenko et al., 1998a). Among them, the most significant association were found for two loci: one X-linked 202-bp allele, at the DXS1047 locus and the 234bp allele at the D10S1423 locus on chromosome 10. The marker DXS1047 was recently confirmed to be also more frequent in Brazilian LOAD patients (Nishimura et al., 2000) although the differences were less significant than the reported by Zubenko et al. (1998a,b) in the American population. In order to verify if the D10S1423 marker was also more frequently associated with LOAD in Brazilian population, we have analyzed this marker in the same sample of affected patients.

Patients and methods

A total of 130 patients (45 males and 85 females) and 130 age-matched controls (45 males and 85 females) were included in the present investigation. The majority of patients (109) and controls (106) were Caucasians (Table 1).

The diagnosis of probable/possible Alzheimer disease in the patients was based on NINCDS-ADRAD (Mckhann et al., 1984). Their mean age was 68.7 ± 8.0 (ranging from 51 to 85 years old). The control group was selected based on the Mini Mental State Exam and/or Blessed scale (Blessed et al., 1968; Folstein et al., 1975) or depending on their educational level through familial interviews. Their mean age was 72.4 ± 9.75 (ranging from 53 to 92 years old).

DNA was extracted from blood (Miller et al., 1988), after informed consent, and the D10S1423 marker was analyzed by polymerase chain reaction (PCR) according to the method reported by Zubenko et al. (1998a).

Results

Out of the six alleles segregating at this locus, the 226bp allele was the most frequent both in patients (39.7% for both sexes, 33.3% for males and 42.9%

Table 1. Demographic characteristics of AD and control groups

	AD patients (n = 130)	Control group (n = 130)
Sex (male/female)	45/85	45/85
Mean age (years)	68.7 ± 8	72.3 ± 9.75
Ethnic composition (C/O*)	109/21	106/24

C Caucasian, O others

Table 2. Allele and genotype frequencies of D10S1423 in patients with Alzheimer's disease and controls

Alleles	Males AD p \pm s.e. (p)	Females AD p \pm s.e. (p)	Total p \pm s.e. (p)	Males controls p \pm s.e. (p)	Females controls p \pm s.e. (p)	Total p \pm s.e. (p)
1 (238 pb)	6 (0.067 \pm 0.0263)	9 (0.053 \pm 0.01717)	15 (0.058 \pm 0.0144)	7 (0.078 \pm 0.0282)	16 (0.094 \pm 0.0224)	23 (0.088 \pm 0.0176)
2 (234 pb)	14 (0.156 \pm 0.0381)	27 (0.159 \pm 0.0280)	41 (0.158 \pm 0.02259)	12 (0.133 \pm 0.0358)	31 (0.182 \pm 0.02961)	43 (0.165 \pm 0.0230)
3 (230 pb)	29 (0.322 \pm 0.0492)	44 (0.259 \pm 0.0335)	73 (0.28 \pm 0.0278)	22 (0.244 \pm 0.0452)	33 (0.194 \pm 0.0303)	55 (0.212 \pm 0.0253)
4 (226 pb)	30 (0.333 \pm 0.0496)	73 (0.429 \pm 0.0379)	103 (0.397 \pm 0.03033)	35 (0.389 \pm 0.0513)	62 (0.365 \pm 0.03691)	97 (0.374 \pm 0.0491)
5 (222 pb)	4 (0.044 \pm 0.0217)	7 (0.041 \pm 0.0152)	11 (0.042 \pm 0.01248)	7 (0.078 \pm 0.0282)	11 (0.065 \pm 0.01886)	18 (0.069 \pm 0.0157)
6 (198 pb)	7 (0.078 \pm 0.0282)	10 (0.059 \pm 0.0180)	17 (0.065 \pm 0.0153)	7 (0.078 \pm 0.0282)	17 (0.10 \pm 0.0230)	24 (0.092 \pm 0.0179)
Total	90	170	260	90	170	260

for females) as well as in controls (37.4% for both sexes, 38.9% for males and 36.5% for females). However, as seen in Table 2, no statistically significant association between any D10S1423 allele and LOAD was observed when both sexes were analyzed together ($\chi^2 = 7.328$, d.f. = 5; $P = 0.197$) or separately among AD patients and controls ($\chi^2 = 2.748$, d.f. = 5, $P = 0.739$ and $\chi^2 = 2.289$, d.f. = 5, $P = 0.808$, respectively).

Discussion

Zubenko et al. (1998a, 1999) reported an association between the 234bp allele at D10S1423 and AD. According to these authors, patients with AD who carried this allele, manifested substantial reductions in dopamine levels in all six cortical regions examined. In discordance with their study, the 226bp and not the 234bp allele was the most frequent among Brazilian AD patients although the difference was not statistically significant. In addition, the results of our investigation showed that no allele at the D10S1423 locus differed significantly between patients and controls. It is possible that it is necessary to have very large samples in order to detect any difference. This has already been shown for the serotonin (5-HTTLPR) polymorphism and psychiatric disorders where the association of the shorter allele and bipolar disorder was significant only after assembling samples from three independent European centers (Collier et al., 1996).

Interestingly, Kehoe et al. (1999) also reported a full genome scan for AD and found two peaks on the chromosome 10. However, these two regions do not correspond to the D10S1423 marker which illustrates again differences in population studies.

More recently, a study of Daw et al. (2000), suggests that several genes that have not yet been localized may play a larger role than does ApoE in AD indicating that the search for novel susceptibility genes should continue. In addition, apparent contradictions among different reports may be the reflect of gene-environment interactions, supporting the importance of replication studies in different populations.

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