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Association of interleukin 1β polymorphisms and haplotypes with Alzheimer's disease

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ABSTRACT

Our study aimed to associate *IL-1β* and *IL-1RN* polymorphisms with AD disease in comparison with elderly control group from São Paulo — Brazil. We genotyped 199 Alzheimer's disease (AD) patients, 165 elderly control and 122 young control samples, concerning VNTR (*IL-1RN*) and −511C>T and −31T>C (*IL-1β*) polymorphisms. Our findings revealed that −511C/−31T/2-repetitions VNTR haplotype had a protective effect for AD when compared to EC ($p = 0.005$), whereas −511C/−31C/1-repetition VNTR haplotype was associated as a risk factor for AD ($p = 0.021$). Taken together, we may suggest that there is a relevant role of IL-1 genes cluster in AD pathogenesis in this Brazilian population.

1. Introduction

Alzheimer's disease (AD) is a progressive and neurodegenerative disorder that causes loss of memory, mental confusion and several cognitive disturbances. Sporadic cases frequently present late-onset disease whereas familial cases usually show early-onset disease (Khachaturian, 1985; Kay, 1986). There are evidences that at least four genes are involved in AD etiology: mutations in *APP*, *PSEN1* and *PSEN2* genes have been well documented in the literature and ε4 allele of *APOE* is considered an expressive risk factor for late-onset AD (Pericak-Vance et al., 1991; Dursun et al., 2008; Feulner et al., 2010).

The inflammatory process also seems to contribute to AD. Cytokines and other proteins associated to inflammation were found in AD patients' brains. The interleukin 1 (IL-1) is a pro-inflammatory cytokine usually produced in the brain by the microglia and seems to play an important role in the AD pathogenesis (Kornman, 2006). In humans, the interleukin 1 cytokine family consists of three genes located on the long arm of chromosome 2 that encodes for IL-1α, IL-1β and the interleukin 1 receptor antagonist (RN) in a region of approximately 430 kb (Griffin et al., 2000). Each of these genes shows single nucleotide polymorphisms (SNPs) that affect their expression by increasing either the rate of mRNA synthesis or stability.

Some findings have shown a reduced liberation of the three principal pro-inflammatory cytokines (IL-1, IL-6 and TNF) and a presence of a down-regulation system of the outlying immune response in the last phase of the disease has been proposed (Sala et al., 2003). IL1A 2,2 polymorphism has been identified as a risk factor in neuropathologically confirmed AD patients from four centers in the United Kingdom and United States (Nicoll et al., 2000). A strong association between IL1A T/T genotype with early-onset AD disease has been reported in 188 patients from Centers for Memory Disorders in Northern Italy (Grimaldi et al., 2000). Moreover, the combination of IL1A polymorphism with IL1B polymorphism at position +3953 (exon 5) increased the risk factor and modulated the age-onset of AD (Sciacca et al., 2003).

In a Japanese-American cohort of 943 men from Honolulu–Asia Aging Study, a significant association between the IL1B −511C>T and IL1RN polymorphisms with late-onset AD has been detected,

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suggesting that these variants might confer an increased risk for AD (Yucesoy et al., 2006).

Controversial findings concerning the relationship between IL1B polymorphisms and AD have been reported. A significant association of −511 TT genotype with late-onset AD has been reported in Taiwan Chineses and in Italians (Grimaldi et al., 2000; Licastro et al., 2000; Wang et al., 2005) while other studies did not reply these association findings (Ehl et al., 2003; Ma et al., 2003; Ravaglia et al., 2006; Wang et al., 2007). An association study of AD with IL-1β (−31T>C) in a Chinese population did not detect an involvement of this polymorphism in late-onset AD pathogenesis (Ma et al., 2003).

The substitution as position IL-1β (−511C>T) in the promoter region of IL-1β regulates the production of IL-1β and the *in vitro* expression of C/C genotype carriers was lower than that of C/T or T/T carriers (Santtila et al., 1998). This is consistent with the hypothesis that an increase in IL-1β expression increases the rate of Aβ deposition and cytokine-mediated inflammation in predisposed individuals.

In the present study, we investigated a possible association among the interleukin 1 β (−511C>T and −31T>C) and the interleukin 1 receptor antagonist with late-onset AD and controls.

2. Materials and methods

2.1. Subjects

Peripheral blood samples were obtained from 199 AD patients, 165 elderly control (EC) and 122 young control (YC) individuals. The three subject groups had similar ethnic origins, being 95% with major European origin, 2.5%, with Japanese origin and 2.5% with mixture origin. The mean age and standard deviation of the samples were 75.31 ± 7.92 years for AD group composed by 69 men and 130 women; 71.67 ± 8.13 years for EC group composed by 55 men and 110 women and 20.76 ± 1.63 for YC group composed by 42 men and 80 women. AD patients were selected according to NINCDS-ADRDA criteria for probable AD (Morris, 1993). Vascular dementia was excluded by a Hachinski score of 5 or higher and by neuroimaging (Hachinski et al., 1975). Patients and controls were from São Paulo City and all subjects gave informed consent to participate in this study that was approved by the local ethics committee.

2.2. Genotyping

Genomic DNA was extracted from blood samples using QIAamp DNA Blood Midi Kit QIAGEN™ (Qiagen, Germany), following manufacturer's instructions. Genotypes were determined by a polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP).

2.2.1. IL1β −31T>C

The 240 base pairs (bp) fragment was amplified from genomic DNA using the oligonucleotides ST 5′-AGAAGCTTCCACCAATACT -3′ and AC 5′-TAGCACCTAGTTGTAAGGA-3′ (22). PCR conditions involved an initial denaturation of 94 °C/5 min followed by 27 cycles of 94 °C/45 s, 53 °C/45 s, 72 °C/1 min and a final extension period at 72 °C/7 min. The amplification products (240 bp) were digested with *Alu*1 (Fermentas, USA) and visualized in 3% agarose gel, stained with ethidium bromide and analyzed on Alpha Imager 2200 (Alpha Innotech Corporation™).

2.2.2. IL1β −511C>T

IL-1β (−511C>T) genotypes were determined with a PCR and RFLP. The 189 bp fragment was amplified from genomic DNA using the oligonucleotides F 5′-CTGCATACCGTATGTTCTCTGCC-3′ and R 5′-GGAATCTTCCCACTTACAGATGG-3′ (23). PCR conditions involved an initial denaturation of 94 °C/5 min followed by 30 cycles of 94 °C/30 s, 60 °C/30 s, 72 °C/30 s and a final extension period at 72 °C/5 min. The amplification products (189 bp) were digested with *Ava*I (Fermentas, USA) and visualized in 2% agarose gel, stained with ethidium bromide and analyzed on Alpha Imager 2200 (Alpha Innotech Corporation™).

2.2.3. IL1RN/VNTR

Fragments containing variable number of identical tandem repeat of 87 bp were amplified using the primers flanking the region: RNa 5′ TCCTGGTCTGCAGGTAA 3′ and RNb 5′ CTCAGCAACACTCCTAT 3′ (24). Amplification was performed under the following conditions: at 94 °C for 5 min; 40 cycles at 94 °C for 30 s, 60 °C for 30 s, 72 °C for 30 s, followed by one cycle at 72 °C for 5 min and cooling at 4 °C. PCR products of 410 bp (allele 1, four repeats of the 86 bp region), 240 bp (allele 2, two repeats), 500 bp (allele 3, five repeats), 325 bp (allele 4, three repeats) and 595 bp (allele 5, six repeats).

2.3. Statistical analysis

Allele frequencies were calculated by allele counting as described by Emery (Emery, 1986). Hardy–Weinberg equilibrium was evaluated using χ^2 test. To assess the association between allele and morbidity, logistic regression analysis was performed, which considered morbidity as a dependent variable and allele, age and sex as covariates in the model. Odds ratios (OR) with 95% confidence intervals (CI) were also calculated using SPSS® 18.0. For VNTR polymorphism, only subjects with genotypes 1/1, 1/2 and 2/2 were included in the analysis. For genotype distributions only two groups: I/I and non-I/I (I/II + II/II) genotypes were analyzed, due to the expected small number of subjects. Linkage disequilibrium (LD) and haplotype association analysis with morbidities were performed by Haploview software (Barrett et al., 2005). Expectation–Maximization algorithm was used to estimate haplotype frequencies and to verify the association between haplotypes and morbidities. χ^2 test was used to compare haplotypes frequencies of cases and controls concerning the morbidities studied. Statistical significance was accepted at $p<0.05$.

3. Results

Genotype frequencies are presented in Table 1. Minor allele frequencies of −511C>T, −31T>C and VNTR polymorphisms were 0.441, 0.455 and 0.257, respectively. All polymorphisms were within the Hardy–Weinberg equilibrium in the whole population (df = 1) (Table 1).

Using haploview software, we observed that −511C>T and −31T>C polymorphisms were in linkage disequilibrium (D′ = 0.7336) as well

Table 1
Genotype distribution of −511C>T, −31T>C and VNTR polymorphisms and Hardy–Weinberg Equilibrium (HWE) results, in all analyzed groups.

Polymorphism	Genotypes	Groups N (%)			HWE
		AD	EC	YC	^{2} (p)
−31T>C	C/C	57 (28.9)	54 (33.2)	45 (38.1)	2.16
	C/T	93 (47.2)	81 (49.6)	48 (40.7)	(p = 0.142)
	T/T	47 (23.9)	28 (17.2)	25 (21.2)	
	Total	197	163	118	
−511C>T	C/C	38 (20.2)	24 (15.8)	24 (21.6)	1.613
	C/T	107 (56.9)	84 (55.3)	48 (43.2)	(p = 0.203)
	T/T	43 (22.9)	44 (28.9)	39 (35.2)	
	Total	188	152	111	
VNTR	2/2	10 (5.3)	18 (11.8)	8 (7.2)	1.737
	1/2	73 (38.8)	54 (35.6)	36 (32.4)	(p = 0.188)
	1/1	105 (55.9)	80 (52.6)	67 (60.4)	
	Total	188	152	111	

AD: Alzheimer's disease group; EC: elderly control group; YC: Young control group.

Table 2
Haplotype association composed by *IL1*β −511C>T, −31T>C and VNTR polymorphisms between AD patients and Elderly Controls (EC).

−511C>T	−31T>C	VNTR	Haplotype frequency	OR (95% CI)	p
C	T	1	0.395	1.00	–
C	T	2	0.073	0.26 (0.10–0.66)	0.005*
C	C	1	0.072	2.42 (1.15–5.09)	0.021*

OR: odds ratio; CI: confidence interval.
*p statistically significant.

Table 3
Haplotype association composed by *IL1b* −511C>T, −31T>C and VNTR polymorphisms between AD patients and Young Controls (YC).

−511C>T	−31T>C	VNTR	Haplotype frequency	OR (95% CI)	p
T	C	1	0.402	1.00	–
T	C	2	0.1507	1.80 (1.01–3.20)	0.05
C	C	1	0.0777	2.81 (1.13–7.02)	0.028*

OR: odds ratio; CI: confidence interval.
*p statistically significant.

as −31T>C with VNTR (D′ = 0.37) and −511C>T with VNTR (D′ = 0.336).

Tables 2 and 3 shows the haplotype composed by IL1 beta −511C>T, −31T>C and VNTR polymorphisms frequencies, the calculated Odds Ratio, the 95% Confidence Interval and p value related to comparison between AD patients and Controls . Thus, haplotype −511C, −31T and VNTR2 showed a protective effect to AD in relation to Elderly Group. On the other hand, haplotype −511 C, −31 C, VNTR1 has been considered a risk factor associated to AD in relation do Elderly Group (p − 0.021, OR = 2.41, 95% CI: 1.15–5.09) as well as and in relation to Young controls (p − 0.028, OR = 2.81, 95% CI: 1.13–7.02).

Table 4 indicates studies of the IL-1β −511C>T, −31C>T and IL1RN polymorphisms/haplotypes and yours effects in AD.

4. Discussion

To our knowledge, there are no reports concerning association study of *IL1beta* polymorphisms and haplotypes with AD in the Brazilian population.

IL1 have been found to be related to susceptibility and to pathogenic activities in the central nervous system and in many other immune-mediated disorders, such as AD, Parkinson's, temporal lobe epilepsy, schizophrenia, febrile convulsions and others (Mrak and Griffinbc, 2001). Each one of our studied polymorphisms of IL 1beta did not show association with AD in relation to Elderly and Young Controls, but our findings agreed partially with results from Polish (Klimkowicz-Mrowiec et al., 2009) and Chinese populations where IL1 beta (−511C>T) and (−31T>C) were not respectively associated with AD late-onset (Ma et al., 2003). Furthermore our findings also partially agreed with those from Bosco et al. from an Italian population (Bosco et al., 2004) who reported a protective effect of allele 2 of IL1RN in 152 sporadic AD with dementia grade ≥6 according to Reisberg score in relation to 136 age-matched controls.

Therefore we may suggest that this cluster is effectively involved in AD late-onset pathogenesis in Brazilian population.

Probably IL1 up regulates expression and processing of APP, which may influence A-beta load (beta-amyloid immunoreactivity) in the brain of AD patients. It is also possible that the increased risk found in previous studies could be caused by linkage disequilibrium with other yet to be identified polymorphism in the IL-1 α and β cluster in chromosome 2q14, present in some populations.

Likewise, IL-1β elevated the levels of sAPP in the culture medium of primary neurons in a dose-dependent fashion (Liu et al., 2011). In addition to inducing IL-1β expression and release, sAPP and Aβ also stimulate microglia to release biologically relevant levels of glutamate and its cooperative excitatory amino acid D-serine (Wu et al., 2004, 2007).

The imbalance in the IL-1β/IL-1RN ratio may result in elevated IL-1 responses and a more severe inflammation. An increased serum level of IL1 beta has been proposed as a stage marker of the ongoing brain neurodegeneration since aging, mild cognitive impairment and AD (Forlenza et al., 2009).

Excess production and secretion of IL-1β elevates neuronal expression of the precursors of each of the changes characteristic of AD. These neurodegeneration-related precursors include β-amyloid precursor protein (βAPP), which may lead in vivo to deposition of Aβ (Sheng et al., 1996a, 1996b) and further induction of IL-1β (Barger and Harmon, 1997); ApoE, which is present in plaques (Sheng et al., 1996a, 1996b) and necessary for the accumulation of Aβ deposits (Bales et al., 1999); and hyperphosphorylated tau (Strittmatter et al., 1994), the principal component of neurofibrillary tangles. IL-1 also induces α-synuclein (Griffin et al., 2006), the Lewy body precursor.

Therefore, taking together our findings with those from literature we can suggest that IL-1 gene cluster polymorphisms may play a relevant role in the susceptibility to Alzheimer´s disease in Brazilians.

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Table 4
Summary of 8 case–control studies and one meta-analysis study of the IL-1β −511C>T, −31C>T and IL1RN polymorphisms/haplotypes and yours effects in AD.

Authors	*Polymorphism/**Haplotypes			IL1β Levels	Association with AD/effect
	−511C>T	−31C>T	IL1RN		
Present study	** C	** T	** 2	–	Yes/protective effect to AD in relation to Elderly Group
	** C	** C	** 1	–	Yes/risk factor associated to AD in relation do Elderly Group
Klimkowicz-Mrowiec et al. (2009)	* C>T	–	–	–	No
Ma et al. (2003)	* C>T	* C>T	–	–	No
Bosco et al. (2004)	* C>T	–	* 2	–	Yes/protective effect of allele 2 in relation to age-matched controls
Bi et al. (2004)	–	–	*1>2	–	No
Forlenza et al. (2009)	–	–	–	↑	Yes/a stage marker of the ongoing brain neurodegeneration
Déniz-Naranjo et al. (2008)	* T	–	–	–	Yes/−511T polymorphism is an independent risk factor for AD
Di-Bona et al. (2008) meta-analysis with 16 case–control study	* T	–	–	–	Yes/−511 TT genotype on the risk of AD for Caucasian and non-Caucasian populations
Wang et al. (2005)	* T	–	–	–	Yes/−511TT genotype is a risk factor for AD in Chinese and Taiwan patients

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