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Research Report

Lack of association between the polymorphisms of β-site APP-cleaving enzyme 2 (BACE2) 5′-flanking region and sporadic Alzheimer's disease

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ABSTRACT

Amyloid β-peptide (Aβ) plays a central role in the pathogenesis of Alzheimer's disease (AD). Aβ is produced by sequential cleavage of the amyloid precursor protein (APP) by two enzymes referred to as β- and γ-secretase. β-secretase is of more importance, as it catalyses the rate-limiting step in the production of Aβ. Although β-site APP-cleaving enzyme 1 (BACE1) is known to cleave APP at the β-secretase site as required for the generation of Aβ, the role of its homologue BACE2 is controversial. For seeking the correlation of the BACE2 promoter with sporadic AD (SAD), we performed a case-control study in a Chinese Han population. In the study, we sequenced the 2641 bp fragment of the 5′-flanking region of BACE2 gene and found three polymorphisms which are -320C/- (rs11316732), -1541A/T (rs9975138) and -1904C/T (rs28656880). Definitive genotyping these markers and apolipoprotein E (APOE) polymorphism were surveyed using restriction enzyme digestion and direct sequencing in 359 SAD patients and 334 controls. We failed to find any association between these three polymorphisms and SAD even after statistical adjustment for age, gender and APOEε4 status. Our data do not support that there is a linkage between the 5′-flanking region polymorphisms of BACE2 and SAD in the Chinese Han population.

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of progressive dementia in the elderly. It is characterized by the cortical and subcortical accumulation of proteinaceous deposits called senile plaques (Selkoe, 1999). Although the aetiology of AD remains unknown, a large amount of evidence suggests that amyloid β-peptide (Aβ) deposition is a critical feature in the brain during the deterioration of AD (Jucker et al., 2006). A key component of senile plaques is Aβ which is generated from the amyloid precursor protein (APP) by sequential action of β- and γ-secretase (Selkoe, 2001; Walter et al., 2001; Annaert and De Strooper, 2002). Because β-secretase catalyses the rate-limiting step in the production of Aβ, it is of central importance and was thus identified as β-site APP-cleaving enzyme 1 (BACE1) 9 years ago (Hussain et al., 1999; Sinha et al., 1999; Vassar et al., 1999; Yan et al., 1999; Cai et al., 2001; Luo et al., 2001). Soon afterwards, its homologue BACE2 was discovered (Acquati et al., 2000; Solans et al., 2000; Farzan et al., 2000).

A complex interaction between genetic and environmental factors contributes to the pathologic process of this disease.

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Although apolipoprotein E (APOE) ε4 allele was proved a major risk factor for sporadic AD (SAD), it is just responsible for partial cases, the rest of which remain elusive in their genetic susceptibilities (Poirier et al., 1993; Saunders et al., 1993; Strittmatter et al., 1993). As APOEε4 is neither sufficient nor necessary to cause the disease, it is likely that other genetic risk factors exist. Numerous AD loci have been suggested by previous studies, but one of the most promising loci, on the basis of several linkage studies, is on chromosome 21q (Heston et al., 1991; Pericak-Vance et al., 1991; Kehoe et al., 1999; Wavrant-De et al., 1999; Olson et al., 2001).

The BACE2 gene has been determined to be located on the long arm of chromosome 21. Several studies have shown that elevated expression of BACE2 appears to be associated with the earlier onset of dementia in patients with Down syndrome (Motonaga et al., 2002; Barbiero et al., 2003). The exons and partial introns in the gene have been screened in previous studies. Some results indicated that there is a weak association between BACE2 polymorphisms and SAD (Myllykangas et al., 2005); while others did not (Nowotny et al., 2001; Gold et al., 2003). It is possible that non-screened regions may be associated with the development of SAD. For this hypothesis, we analyzed BACE2 gene 5′-flanking region polymorphisms and its role in the development of SAD.

2. Results

We sequenced the 2641 bp fragment of the 5′-flanking region of BACE2 in 20 individuals and found three polymorphisms which are -320C/- (rs11316732), -1541A/T (rs9975138) and -1904C/T (rs28656880). Definitive genotyping of -1541A/T, -1904C/T and APOE polymorphism were performed using restriction enzyme digestion. However, -320C/- was directly sequenced for the definitive genotyping. Allelic and genotype frequencies of BACE2 5′-flanking region in SAD patients and controls were reported in Table 1. The distributions of the allelic and genotype frequencies were in Hardy–Weinberg equilibrium both in SAD patients and controls.

No significant differences were detected for the three BACE2 single nucleotide polymorphisms (SNPs) between SAD patients and controls. As expected, the presence of the APOEε4 in the total SAD patient was significantly higher than that in the control (28% vs. 8.4%, $p=0.0000$). However stratification of both case and control groups by APOEε4 also failed to reveal any association between the gene polymorphism and SAD (Table 1).

The results remained no differences after gender, age and APOE adjustment by logistic regression (Table 2). Linkage

Table 1 – Distribution of the polymorphisms in SAD patients and controls

	Genotype					Allele		
	Total	CC(%)	C–(%)	–(%)	P	C(%)	–(%)	P
-320C/-								
SAD	359	208(57.9)	128(35.7)	23(6.4)	0.50	544(75.8)	174(24.2)	0.40
Control	334	207(62.0)	105(31.4)	22(6.6)		519(77.7)	149(22.3)	
APOE(–)								
SAD	220	128(58.2)	78(35.5)	14(6.4)	0.66	334(75.9)	106(24.1)	0.49
Control	294	182(61.9)	93(31.6)	19(6.5)		457(77.7)	131(22.3)	
APOE(+)								
SAD	86	45(52.3)	33(38.4)	8(9.3)	0.94	123(71.5)	49(28.5)	0.71
Control	27	15(55.6)	10(37.0)	2(7.4)		40(74.1)	14(25.9)	
	Total	AA(%)	AT(%)	TT(%)	P	A(%)	T(%)	P
-1541A/T								
SAD	359	214(59.6)	125(34.8)	20(5.6)	0.98	553(77.0)	165(23.0)	0.87
Control	334	197(59.0)	118(35.3)	19(5.7)		512(76.6)	156(23.4)	
APOE(–)								
SAD	220	134(60.9)	76(34.5)	10(4.5)	0.88	344(78.2)	96(21.8)	0.66
Control	294	175(59.5)	103(35.0)	16(5.4)		453(77.0)	135(23.0)	
APOE(+)								
SAD	86	50(58.1)	29(33.7)	7(8.1)	0.35	129(75.0)	43(25.0)	0.68
Control	27	13(48.1)	13(48.1)	1(3.7)		39(72.2)	15(27.8)	
	Total	TT(%)	CT(%)	CC(%)	P	T(%)	C(%)	P
-1904C/T								
SAD	359	102(28.4)	184(51.3)	73(20.3)	0.58	388(54.0)	330(46.0)	0.32
Control	334	87(26.0)	169(50.6)	78(23.4)		343(51.3)	325(48.7)	
APOE(–)								
SAD	220	64(29.1)	118(53.6)	38(17.3)	0.31	246(55.9)	194(44.1)	0.26
Control	294	81(27.6)	146(49.7)	67(22.8)		308(52.4)	280(47.6)	
APOE(+)								
SAD	86	27(31.4)	43(50.0)	16(18.6)	0.23	97(56.4)	75(43.6)	0.12
Control	27	4(14.8)	16(59.3)	7(25.9)		24(44.4)	30(55.6)	