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No association between presenilin 1 (PS1) intronic polymorphism and sporadic Alzheimer's disease in Koreans

K. W. Kim[1], **J. H. Jhoo**[2], **K. U. Lee**[1], **D. Y. Lee**[2], **J. H. Lee**[3], **J. Y. Youn**[2], **B. J. Lee**[4], and **J. I. Woo**[2]

[1] Neuroscience Research Institute of Medical Research Center, Seoul National University, and Clinical Research Institute of Seoul National University Hospital, [2] Neuroscience Research Institute of Medical Research Center, Seoul National University, and Department of Neuropsychiatry, Seoul National University Hospital, [3] Research Institute of Aging and Physical Culture of Medical Research Center, Seoul National University, College of Medicine, and [4] Institute of Molecular Biology and Genetics, Seoul National University, Seoul, Korea

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Summary. To investigate the possible involvement of an intronic polymorphism in the presenilin 1 (PS1) gene and its interactions with the aplolipoprotein E (APOE) or alpha-1 antichymotrypsin (ACT) polymorphisms in the manifestation of AD, we analyzed the PS1, APOE and ACT genotypes of 100 sporadic AD patients and 199 normal elderly controls in Koreans. The genotypic ($\chi^2 = 0.92$, df = 2, $P > 0.1$) and allelic ($\chi^2 = 0.01$, df = 1, $P > 0.1$) frequencies of the PS1 polymorphism in the late- and early-onset sporadic AD patients did not differ from those in the controls. And the occurrence of the APOE ε4 allele and ACT A allele did not influence the distribution of the PS1 intronic polymorphism. The PS1 intronic polymorphism didn't influence the age-at-onset of AD ($F = 0.02$, df = 2, $P > 0.1$). In conclusion, the PS1 intronic polymorphism did not modify the risk for sporadic AD, neither independently nor synergistically with the APOE ε4 allele or ACT A allele, in Koreans.

Keywords: Alzheimer's disease (AD), presenilin 1 (PS1), alpha-1-antichymotrypsin (ACT), apolipoprotein E (APOE), Koreans.

Introduction

Although the apolipoprotein E (APOE) ε4 allele is a well-established genetic risk factor for Alzheimer's disease (AD), it is neither necessary nor sufficient to cause AD (Farrer et al., 1997), and thus additional genetic or environmental factors might act independently or in concert with the APOE ε4 allele in the manifestation of AD.

Presenilin-1 gene (PS1), which accounts for about 50% of all early-onset autosomal dominant familial Alzheimer's disease (Sherrington et al., 1995), seems to be a good candidate for such a potential susceptibility gene for AD, since presenilin-1 is found to be accumulated in senile plaques (Wisniewski et al., 1995) and to play a role in the processing and trafficking of membrane-bound proteins including amyloid precursor protein (Hutton and Hardy, 1997; DeStrooper et al., 1995). In 1996, Wragg and his colleagues reported that the PS1 1/1 genotype was associated with a doubling of the risk for late-onset sporadic AD in Caucasian Americans, which was replicated soon in other independent studies from the United Kingdom (Kehoe et al., 1996; Tilley et al., 1999) and Japan (Higuchi et al., 1996; Isoe et al., 1996; Matsushita et al., 1997). The PS1 1/1 genotype seemed to be a specific risk factor for AD, since it did not associate with vascular dementia or alcohol associated dementia (Isoe et al., 1996). And the occurrence of either the APOE ε4 allele (Isoe et al., 1996; Nishiwaki et al., 1997; Ezquerra et al., 1997) or alpha-1 antichymotrypsin (ACT) A allele (Wang et al., 1998) has been reported to influence the contribution of the PS1 1/1 genotype to the development of AD.

But, since ethnic differences in the allelic frequencies of the PS1 polymorphism were evident (Wragg et al., 1996; Yasuda et al., 1999) and no association between AD and the PS1 1/1 genotype was found in African-Americans (Wragg et al., 1996) and Russians (Korovaitseva et al., 1997), the PS1-AD association may vary across racial or ethnic groups. Moreover, since the PS1-AD association was not replicated in other Caucasian populations (Scott et al., 1996, 1997; Singleton et al., 1997; Lendon et al., 1997; Mann et al., 1997; Tysoe et al., 1997; Cai et al., 1997; Sorbi et al., 1997; Perez-Tur et al., 1996; Taddei et al., 1998; Kawalska et al., 1998; Wang et al., 1998; Liao et al., 1999; Bagli et al., 1999) and Asian populations (Sodeyama et al., 1998; Hu et al., 1998; Wu et al., 1999; Yasuda et al., 1999), the PS1-AD association itself has been a matter of controversy yet and needs a further clarification.

Therefore, in the present study, we determined the PS1, APOE and ACT genotypes of the AD patients and normal elderly controls to examine whether the PS1 1/1 genotype increases the risk for AD and whether its interaction with the APOE ε4 allele or ACT A allele in the manifestation of AD is significant in Koreans.

Material and methods

All the AD patients and normal elderly controls were unrelated Koreans. The AD patients were enrolled at Dementia Special Clinic of Seoul National University Hospital in Seoul, Korea. The normal elderly controls were either patients' spouses or healthy blood donors recruited from three districts in Seoul (Nowongu, Seochogu and Kwanakgu). We administered standardized CERAD Clinical Assessment Battery (Morris et al., 1989) and Modified Hachinski Ischemic Score (MHIS) (Hachinski et al., 1974) not only to the patients but also to the controls. Following this evaluation, a consensus committee meeting was held to determine a diagnosis for each subject; diagnoses for dementia were according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (American Psychiatric Association, 1994)

and diagnoses for AD were according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984) with minor modification specifying the gradual onset and progression of memory loss of at least 12 months' duration as typical features of disease (Morris et al., 1989). Early-onset AD (EOAD) was defined as AD occurring in people under 65 years of age and late-onset AD (LOAD) was defined as AD arising in people over 65 years of age. Only the sporadic AD patients who did not have a relative with dementia within second degree were enlisted in the AD group. Family history was obtained by asking the next of kin whether there were at least one first or second degree relative with dementia. The committee was blinded to the APOE genotypes of the patients. Informed consent was obtained for each subject either directly or from his or her guardian.

Genomic DNA was extracted from venous blood. PS1 genotyping was performed by the methods of Wragg et al. (1996) with minor modification. The sequences of primer pair were 5′-CACCCATTTACAAGTTTAGC-3′ as the upstream primer and 5′-CACTGA TTACTAATTCAGGATC-3′ as the downstream primer. PCR was carried out in a final volume of 30 μl containing 200 ng of genomic DNA, 20 pmol of each primer, 3 μl 25 mM $MgCl_2$ and 3 μl 10X PCR reaction buffer (Tris 100 mM, pH 8.3, KCl 500 mM). An initial denaturation at 95°C for 5 min was followed by 30 cycles of annealing at 41°C for 1 min, extension at 65°C for 1 min, denaturation at 95°C for 1 min and final extension at 65°C for 10 min. APOE and ACT genotyping were done by the polymerase chain reaction and restriction fragment length polymorphism methods described by Wenham et al. (1991) and Kamboh et al. (1995), respectively.

We estimated allele and genotype frequencies by counting alleles and genotypes and calculating sample proportions. Hardy-Weinberg equilibrium was tested by Chi square analysis. Comparisons of allele frequencies and genotype frequencies were made using Chi square analysis and Fisher's exact test when appropriate. Frequencies of two-site haplotypes for the ACT and PS1 polymorphisms were estimated by maximum-likelihood methods, and linkage disequilibrium between the ACT and PS1 polymorphisms was evaluated by Chi square analysis based on difference between the observed and the expected numbers of haplotypes. Logistic regression analyses were used to calculate the odds ratios (ORs) for AD. The Wald statistic, set at a probability value of 0.05, was used as a criterion to determine whether a variable would enter the analysis. Comparison of the ages at onset among the genotypic groups were made using ANOVA.

Results

Finally 100 probable AD patients and 199 controls were enrolled in the present study. The AD group was slightly older than the control group (70.4 $\pm$ 7.6 years versus 67.0 $\pm$ 7.5 years, $P < 0.05$ by two-tailed student t test). But the AD group and control group did not differ by gender.

The distributions of the PS1, APOE and ACT genotypes were in Hardy-Weinberg equilibrium in the normal control group. But, in the AD group, although the distributions of the APOE and ACT genotypes were in Hardy-Weinberg equilibrium, the PS1 genotype was slightly out of Hardy-Weinberg equilibrium ($\chi^2 = 5.94$, df = 1, $P < 0.05$). The PS1 2/2 genotype was less prevalent and the PS1 1/2 genotype was more prevalent than expected.

The distributions of the PS1 genotypes and alleles of the AD group and control group are presented in Table 1. The PS1 1 allele frequency of the normal elderly controls in Korean was 0.631, which was comparable to that in other Asian populations (Wu et al., 1999; Higuchi et al., 1996). We failed

Table 1. The distribution of the PS1 genotypes and alleles in the AD group, EOAD group, LOAD group and control group

	AD						Control	
	All		EOAD		LOAD		All	
	N	(%)	N	(%)	N	(%)	N	(%)
PS1 genotypes								
1/1	34	(34.0)	12	(29.3)	22	(37.3)	73	(36.7)
1/2	58	(58.0)	25	(61.0)	33	(55.9)	105	(52.8)
2/2	8	(8.0)	4	(9.7)	4	(6.8)	21	(10.6)
Total	100		41		59		199	
PS1 alleles								
1	126	(63.0)	49	(59.8)	77	(65.3)	251	(63.1)
2	74	(37.0)	33	(40.2)	41	(34.7)	147	(36.9)
Total	200		82		118		398	

to detect a significant difference in genotypic frequencies ($\chi^2 = 0.92$, df = 2, $P > 0.1$) and allelic frequencies ($\chi^2 = 0.01$, df = 1, $P > 0.1$) of PS1 between the AD group and control group. No overexpression of the PS1 1/1 genotype and PS1 1 allele was found either when we analyzed the LOAD patients and EOAD patients separately.

We stratified the PS1 genotypes based on the presence or absence of the APOE ε4 allele to evaluate the possible interaction between them (Table 2). As expected, the APOE ε4 allele was more prevalent in the AD group than in

Table 2. The distribution of the PS1 genotypes and alleles stratified by the occurrence of the APOE ε4 allele

	APOE ε4 (−)				APOE ε4 (+)			
	AD		Control		AD		Control	
	N	(%)	N	(%)	N	(%)	N	(%)
PS1 genotypes								
1/1	21	(35.6)	62	(37.6)	13	(31.7)	11	(32.4)
1/2	34	(57.6)	85	(51.5)	24	(58.5)	20	(58.8)
2/2	4	(6.8)	18	(10.9)	4	(9.8)	3	(8.8)
Total	59		165		41		34	
PS1 alleles								
1	76	(64.4)	209	(63.3)	50	(61.0)	42	(61.8)
2	42	(35.6)	121	(36.7)	32	(39.0)	26	(38.2)
Total	118		330		82		68	

Table 3. The distribution of the PS1 genotypes and alleles stratified by the occurrence of the ACT A allele

	ACT A (+)				ACT A (−)			
	AD		Control		AD		Control	
	N	(%)	N	(%)	N	(%)	N	(%)
PS1 genotypes								
1/1	26	(37.7)	42	(32.8)	8	(25.8)	31	(43.7)
1/2	37	(53.6)	71	(55.5)	21	(67.7)	34	(47.9)
2/2	6	(8.7)	15	(11.7)	2	(6.5)	6	(8.5)
Total	69		128		31		71	
PS1 alleles								
1	89	(64.5)	155	(60.5)	37	(59.7)	96	(67.6)
2	49	(35.5)	101	(39.5)	25	(40.3)	46	(32.4)
Total	138		256		62		142	

the control group ($\chi^2 = 25.59$, df = 1, $P < 0.01$). But no significant overrepresentations of the PS1 1 allele and PS1 1/1 genotype were found in both the APOE ε4-positive and APOE ε4-negative subjects.

Then we stratified the PS1 genotypes by the ACT genotypes (Table 3). There were no significant difference in genotypic frequencies ($\chi^2 = 0.71$, df = 2, $P > 0.1$) and allelic frequencies ($\chi^2 = 0.61$, df = 1, $P > 0.1$) of the ACT polymorphism between the AD group and control group. No significant overrepresentations of the PS1 1 allele and PS1 1/1 genotype were found in the ACT A-positive subjects. In the ACT A-negative subjects, the PS1 1/1 genotype tended to be underrepresented in the AD patients compared to the controls (25.8% vs. 43.7%), but the difference was not statistically significant ($\chi^2 = 2.88$, df = 2, $P = 0.09$). We also performed two-site haplotype analysis (Table 4). No linkage disequilibrium was observed in either the AD patients or controls ($P > 0.1$). There were no significant differences in the distribution of two-site haplotypes between the AD patients and controls ($\chi^2 = 4.51$, df = 3, $P > 0.1$).

In logistic regression analyses, the occurrence of the APOE ε4 allele was the only significant predictor (Wald = 6.06, df = 1, $P = 0.01$), and the age- and sex-adjusted OR for subjects with one or two copies of the APOE ε4 alleles was 3.43 (95% CI = 1.94–6.04). But, neither the PS1 genotype (Wald = 3.12, df = 2, $P > 0.1$) nor the occurrence of ACT A allele (Wald < 0.01, df = 1, $P > 0.1$) met the criteria for entry into the regression equation. And the interaction terms of the PS1 genotype with the occurrence of the APOE ε4 allele (Wald = 1.96, df = 2, $P > 0.1$) and the occurrence of the ACT A allele (Wald = 3.07, df = 2, $P > 0.1$) were not significant predictors, either.

The PS1 genotype didn't influence the age-at-onset of AD ($F = 0.02$, df = 2, $P > 0.1$). The mean age-at-onset of the AD patients with 1/1, 1/2 and 2/2

Table 4. Two-site haplotype frequencies at the PS1 and ACT loci

		AD (N = 100)	Control (N = 199)
Genotypes			
ACT A/A	PS1 1/1	5 (5.0%)	8 (4.0%)
	PS1 1/2	8 (8.0%)	13 (6.5%)
	PS1 2/2	2 (2.0%)	5 (2.5%)
ACT A/T	PS1 1/1	21 (21.0%)	34 (17.1%)
	PS1 1/2	29 (29.0%)	58 (29.1%)
	PS1 2/2	4 (4.0%)	10 (5.0%)
ACT T/T	PS1 1/1	8 (8.0%)	31 (15.6%)
	PS1 1/2	21 (21.0%)	34 (17.1%)
	PS1 2/2	2 (2.0%)	6 (3.0%)
Haplotype			
A*1		0.268	0.231
A*2		0.153	0.156
T*1		0.363	0.399
T*2		0.218	0.214

genotype were 66.6 ± 9.6 years old, 66.8 ± 0.3 years old and 65.9 ± 9.3 years old, respectively.

Discussion

In contrast to a series of previous reports (Wragg et al., 1996; Kehoe et al., 1996; Tilley et al., 1999; Higuchi et al., 1996; Isoe et al., 1996; Matsushita et al., 1997), the PS1 intronic polymorphism was not associated with the risk for sporadic AD, and its genetic interaction with the APOE ε4 allele in the manifestation of AD was not significant either in the present study.

Since association studies are sensitive to variations in allele frequencies and the PS1 allele frequencies vary substantially depending on the ethnic background (Yasuda et al., 1999), the racial or ethnic difference may contribute to the discrepancy of the results. But the PS1-AD association was not consistently replicated even within the populations with the same ethnic origin like Japanese (Sodeyama et al., 1998; Yasuda et al., 1999; Isoe et al., 1996; Higuchi et al., 1996; Matsushita et al., 1997; Nishiwaki et al., 1997) or Chinese (Hu et al., 1998; Wu et al., 1999). And the frequency of the PS1 1 allele in our Korean elderly controls was comparable to those of Chinese and Japanese (Yasuda et al., 1999). Thus the ethnic difference does not seem to be the main source of the discrepancy.

The differences in defining phenotypes, i.e. AD and normal elderly, may also contribute to the above conflicting results. But neuropathological findings confirmed the high accuracy of diagnosis through CERAD clinical evaluation (Gearing et al., 1995), and no significant increase in the risk for AD by the presence of the PS1 1/1 genotype was found in autopsy-confirmed AD cases (Tysoe et al., 1997; Sodeyama et al., 1998) either. And we tried to exclude the subjects with age-associated cognitive decline or very mild AD by enrolling

only the cognitively normal elderly as controls. Thus the results of the present study rejecting the PS1-AD association are not likely to be false negative findings caused by erroneous diagnoses.

Finally, the PS1 polymorphism may be in linkage disequilibrium with another biologically relevant genetic variations within the PS1 gene. Actually the PS1 polymorphism exists in an intron, and the exon 8 of the PS1 gene, which is located just next to the intron in which the PS1 polymorphism is located, is the site for the most prominent cluster of mutations leading to EOAD (Alzheimer's disease collaborative group, 1995; Sherrington et al., 1995).

The interaction between the PS1 and ACT in the manifestation of AD was also reported. Wang and coworkers reported that A*1 haplotype carrying the ACT A allele and PS 1 allele was more frequent in AD patients than controls (0.310 vs. 0.251; $P = 0.018$) (Wang et al., 1998). But in the present study, we couldn't find a significant overrepresentation of A*1 haplotype in the AD patients (0.268 vs. 0.231, $P > 0.1$). Since the locations of the ACT gene and PS1 gene somewhat different, i.e. the PS1 gene at 14q24.3 (Sherrington et al., 1995) and ACT gene at 14q32.1 (Chandra et al., 1983), and no linkage disequilibrium was observed in either AD patients or controls, these conflicting results may be attributable to the difference in the ACT A allelic frequencies. In the study reported by Wang et al. (1998), the ACT A allele itself was overrepresented in AD patients compared with controls. But in our sample, its frequency did not differ by diagnosis.

In conclusion, the PS1 intronic polymorphism did not modify the risk for sporadic AD, neither independently nor synergistically with the APOE ε4 allele or ACT A allele in Koreans.

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Authors' address: Dr. J. I. Woo, Department of Neuropsychiatry, Seoul National University, College of Medicine and Seoul National University Hospital, 28 Yongon-dong, Chongno-gu, Seoul, Korea 110-744, e-mail: jiwoomd@plaza.snu.ac.kr