Original Research Article

Genetic Association between Presenilin 2 Polymorphisms and Alzheimer's Disease and Dementia of Lewy Body Type in a Japanese Population

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Key Words

Presenilin 2 · Apolipoprotein E · Single nucleotide polymorphism · Alzheimer's disease ·
Lewy body dementia

Abstract

Background/Aims: Mutations in the presenilin 2 (*PSEN2*) gene cause familial Alzheimer's disease (AD). Common polymorphisms affect gene activity and increase the risk of AD. Nonsynonymous polymorphisms in the *PSEN2* gene showed Lewy body dementia (LBD) phenotypes clinically. Therefore, we aimed to investigate whether *PSEN2* gene polymorphisms were associated with AD or LBD. **Methods:** Seven single nucleotide polymorphisms (SNPs) of the gene were analyzed using a case-control study design comprising 288 AD patients, 76 LBD patients, and 105 age-matched controls. **Results:** Linkage disequilibrium (LD) examination showed strong LD from rs1295645 to rs8383 on the gene in our cases from Japan. There were no associations between the SNPs studied here and AD onset, and haplotypic analyses did not detect genetic associations between AD and the *PSEN2* gene. Although the number of the cases was small, the SNPs studied did not modify the risk of developing LBD in a Japanese population. **Conclusion:** The common SNPs of the *PSEN2* gene did not affect the risk of AD or LBD in a Japanese population. Because genetic variability of the *PSEN2* gene is associated with behavioral and psychological symptoms of dementia (BPSD) in AD and LBD, further detailed analyses considering BPSD of both diseases would be required.

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Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease. Genetic, metabolic, and environmental factors play an important role in the pathophysiology of sporadic AD. Presenilins are the catalytic components of the gamma-secretase complex and play an important role in the amyloid β ($A\beta$) cascade in AD [1]. Presenilin 1 (*PSEN1*) gene mutations on chromosome 14q24.3 cause autosomal dominant early-onset familial AD [1, 2]. The *presenilin 2* (*PSEN2*) gene on chromosome 1q31–q42 is a homolog of the *PSEN1* gene and shares 62% amino acid identity [1, 2]. Although *PSEN2* gene mutations are additionally reported to cause familial AD, pathogenic *PSEN2* gene mutations are rare [3]. Among the genetic risk factors, the apolipoprotein E (APOE) is recognized as an established genetic risk factor for sporadic AD [2]. Riazanskaia et al. [4] showed that the 5' regulatory region polymorphisms in the *PSEN2* gene contribute to the gene activity and risk of sporadic AD. The single nucleotide polymorphism (SNP) rs8383 on the 3' untranslated region of the gene was additionally analyzed in sporadic AD [5]. Although a few replication studies have been performed, it is currently unknown whether *PSEN2* gene polymorphisms contribute to the incidence of sporadic AD.

Lewy body dementia (LBD) is the second most common human neurodegenerative disease after AD. The pathological features of LBD are the deposition of α -synuclein in Lewy bodies and the presence of Lewy neurites in the brainstem, limbic, and cortical areas [6]. Most LBD cases show varying degrees of concurrent $A\beta$ pathology, and several lines of evidence indicate that $A\beta$ and α -synuclein may interact with each other [7, 8]. $A\beta$ deposits could cause local aggregation of α -synuclein [9, 10]. In contrast to AD, genetic studies for both familial and sporadic LBD have not been completely established [11]. The *PSEN1* mutations enhance the pathogenic phosphorylation and aggregation of α -synuclein in vivo and in vitro [12, 13]. Certain nonsynonymous *PSEN2* gene polymorphisms have clinically shown LBD or LBD-like phenotypes [3, 14]. Few studies have reported associations between the *PSEN1* gene and LBD, and to the best of our knowledge, there are no association studies for *PSEN2* and the disease [15]. In the present study, we aimed to elucidate whether *PSEN2* gene polymorphisms affect AD and LBD.

Materials and Methods

Sporadic Japanese AD cases were diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, and none of them had a familial history of AD [16]. AD cases were obtained from the Department of Psychiatry, Juntendo University Hospital; the Department of Psychiatry, Juntendo Koshigaya Hospital; the Department of Psychiatry, Jikei University Hospital, and the Department of Psychiatry, Jikei Kashiwa Hospital. LBD cases from Japan consisted of two groups: (1) LBD cases that were recruited from the PET/CT Dementia Research Center, Juntendo Tokyo Koto Geriatric Medical Center according to the diagnostic criteria by McKeith et al. [17] and (2) patients of Parkinson's disease with dementia who were recruited from the Department of Neurology, Juntendo University Hospital according to the diagnostic criteria by Emre et al. [18]. Healthy volunteers among our hospital staff with no history of dementia or other neuropsychiatric diseases were included as control cases.

The purpose and significance of the current study was explained in detail in writing, including verbal supplementation as required, to each patient. All subjects provided their written informed consent. The study protocols were approved by the Ethics Committee of both the Juntendo University School of Medicine and the Jikei University School of Medicine.

Table 1. Subjects of the study

	Number (male:female)	Age, years (mean ± SD)	APOE ε4-positive cases, n (%)
AD	288 (123:165)	69.6 ± 9.1	134 (46.5)
LBD	76 (42:34)	70.7 ± 9.1	20 (26.3)
Controls	105 (44:61)	68.1 ± 5.1	24 (22.9)

Fig. 1. Genetic location of the six *PSEN2* SNPs.

Table 1 shows the details of the subjects in our case-control study. The mean ages of the three groups showed no statistically significant differences. DNA was extracted from white blood cells using a standard method. Seven SNPs on the *PSEN2* gene, i.e., rs1295645, rs2073489, rs11405, rs6759, rs1046240, rs1800680, and rs8383, were genotyped using TaqMan technology on an ABI7500 system (Applied Biosystems, Foster City, Calif., USA). Probes and primers were designed by the Assay-by-Design™ service of Applied Biosystems. A standard polymerase chain reaction (PCR) was performed using the TaqMan Universal PCR Master Mix reagent kit with a 10-μl volume. APOE genotypes for all the samples were determined according to a previous report [19].

Statistical Analyses for Genetic Data

Differences in the genotypic and allelic frequencies of each SNP were evaluated using a case-control study design and statistical comparison with Fisher's exact test. Linkage disequilibrium (LD) between SNPs was analyzed, and haplotype analyses were performed. LD, denoted as D' , was calculated from the haplotype frequency using the expectation-maximization algorithm. SNPs were considered to be in LD if D' was >0.75 . A case-control haplotype analysis was performed using a permutation method to obtain the empirical significance. The global p values represent the overall significance of the observed versus expected frequencies of all the haplotypes considered together using the χ^2 test. The individual haplotypes were tested for association by grouping all others together and applying the χ^2 test with one degree of freedom. p values were calculated on the basis of 10,000 replications. All the p values reported are two tailed, and statistical significance was defined as $p < 0.05$. Because the number of LBD cases was small, we could not perform haplotype analysis for LBD. Hardy-Weinberg equilibrium tests were performed in whole cases. Those analyses were performed using SNPAllyse version 7.0 Pro (Dynacom, Chiba, Japan).

Results

We performed power calculations for our AD control subjects using the power calculator (<http://www.sph.umich.edu/csg/abecasis/CaTS/>). Power was calculated under the prevalence of 0.10 using an additive or a multiplicative model based on allelic frequencies of 0.20 with an odds ratio of 1.50 and an alpha level of 0.05. Results for power analyses demon-

Table 2. Genotypic and allelic frequencies of SNPs of the *PSEN2* gene

SNPs	Geno- type	AD	Controls		Allele	AD	Controls		Odds ratio (95% CI)	HWE (whole cases)
rs1295645	C/C	208 (0.72)	70 (0.67)	$\chi^2 = 0.37$ p = 0.44	C	491 (0.85)	172 (0.82)	$\chi^2 = 1.30$ p = 0.25	1.27 (0.82–1.94)	$\chi^2 = 0.004$ p = 0.86
	C/T	75 (0.26)	32 (0.30)		T	85 (0.15)	38 (0.18)			
	T/T	5 (0.02)	3 (0.03)							
rs2073489	C/C	82 (0.28)	25 (0.24)	$\chi^2 = 5.62$ p = 0.07	C	284 (0.49)	106 (0.50)	$\chi^2 = 0.10$ p = 0.75	0.95 (0.70–1.30)	$\chi^2 = 2.61$ p = 0.10
	C/T	120 (0.42)	56 (0.53)		T	292 (0.51)	104 (0.50)			
	T/T	86 (0.30)	24 (0.23)							
rs11405	C/C	143 (0.50)	48 (0.46)	$\chi^2 = 1.65$ p = 0.43	C	405 (0.70)	139 (0.66)	$\chi^2 = 1.23$ p = 0.27	1.21 (0.84–1.71)	$\chi^2 = 0.07$ p = 0.73
	C/T	119 (0.41)	43 (0.41)		T	171 (0.30)	71 (0.34)			
	T/T	26 (0.09)	14 (0.13)							
rs6759	C/C	84 (0.29)	25 (0.24)	$\chi^2 = 5.70$ p = 0.06	C	286 (0.50)	107 (0.51)	$\chi^2 = 0.11$ p = 0.75	0.96 (0.71–1.31)	$\chi^2 = 2.92$ p = 0.07
	C/T	118 (0.41)	57 (0.54)		T	290 (0.50)	103 (0.49)			
	T/T	86 (0.30)	23 (0.22)							
rs1046240	C/C	83 (0.29)	26 (0.25)	$\chi^2 = 5.25$ p = 0.07	C	285 (0.49)	108 (0.51)	$\chi^2 = 0.15$ p = 0.71	0.98 (0.73–1.32)	$\chi^2 = 2.90$ p = 0.09
	C/T	119 (0.41)	56 (0.53)		T	291 (0.51)	102 (0.49)			
	T/T	86 (0.30)	23 (0.22)							
rs8383	C/C	84 (0.29)	25 (0.24)	$\chi^2 = 5.56$ p = 0.07	C	284 (0.49)	107 (0.51)	$\chi^2 = 0.14$ p = 0.70	0.96 (0.72–1.31)	$\chi^2 = 3.58$ p = 0.06
	C/T	116 (0.40)	57 (0.54)		T	292 (0.51)	103 (0.49)			
	T/T	88 (0.31)	23 (0.22)							
SNPs	Geno- type	LBD	Controls		Allele	LBD	Controls		Odds ratio (95% CI)	
rs1295645	C/C	55 (0.72)	70 (0.67)	$\chi^2 = 1.94$ p = 0.42	C	127 (0.84)	172 (0.82)	$\chi^2 = 0.17$ p = 0.69	0.89 (0.49–1.54)	
	C/T	17 (0.22)	32 (0.30)		T	25 (0.16)	38 (0.18)			
	T/T	4 (0.06)	3 (0.03)							
rs2073489	C/C	18 (0.24)	25 (0.24)	$\chi^2 = 0.05$ p = 0.99	C	77 (0.51)	106 (0.50)	$\chi^2 = 0.03$ p = 0.99	1.01 (0.68–1.54)	
	C/T	41 (0.54)	56 (0.53)		T	75 (0.49)	104 (0.50)			
	T/T	17 (0.22)	24 (0.23)							
rs11405	C/C	38 (0.50)	48 (0.46)	$\chi^2 = 2.15$ p = 0.15	C	109 (0.72)	139 (0.66)	$\chi^2 = 1.25$ p = 0.26	0.77 (0.49–1.23)	
	C/T	33 (0.43)	43 (0.41)		T	43 (0.28)	71 (0.34)			
	T/T	5 (0.07)	14 (0.13)							
rs6759	C/C	18 (0.24)	25 (0.24)	$\chi^2 = 0.08$ p = 0.98	C	76 (0.50)	107 (0.51)	$\chi^2 = 0.03$ p = 0.86	1.04 (0.68–1.60)	
	C/T	40 (0.52)	57 (0.54)		T	76 (0.50)	103 (0.49)			
	T/T	18 (0.24)	23 (0.22)							
rs1046240	C/C	18 (0.24)	26 (0.25)	$\chi^2 = 0.09$ p = 0.96	C	76 (0.50)	108 (0.51)	$\chi^2 = 0.04$ p = 0.84	1.06 (0.70–1.58)	
	C/T	40 (0.52)	56 (0.53)		T	76 (0.50)	102 (0.49)			
	T/T	18 (0.24)	23 (0.22)							
rs8383	C/C	19 (0.25)	25 (0.24)	$\chi^2 = 0.07$ p = 0.99	C	77 (0.51)	107 (0.51)	$\chi^2 = 0.01$ p = 0.99	1.02 (0.55–1.56)	
	C/T	39 (0.51)	57 (0.54)		T	75 (0.49)	103 (0.49)			
	T/T	18 (0.24)	23 (0.22)							

CI = Confidence interval; HWE = Hardy-Weinberg equilibrium.

strated that the power ranged from 65% for the additive model to 72% for the multiplicative model.

SNP rs1800680 was not polymorphic in our cases from Japan. Figure 1 shows the genetic location of the studied SNPs. The six SNPs of the *PSEN2* gene were found to be located using Hardy-Weinberg equilibrium. LD examination showed strong LD from rs1295645 to rs8383 on the gene in our cases from Japan (table 2).

The genotypic frequencies of the six SNPs of the *PSEN2* gene are shown in table 3. There was no statistical difference between AD cases and controls for all SNPs in genotypes and alleles. The comparison between LBD and control cases also showed no statistically significant differences. The haplotypic frequencies of the AD group did not differ from those of controls (table 4).

Table 3. D' values between the SNPs of the *PSEN2* gene (whole cases)

	rs1295645 (C/T)	rs2073489 (C/T)	rs11405 (C/T)	rs6759 (C/T)	rs1046240 (C/T)	rs8383 (C/T)
rs1295645 (C/T)						
rs2073489 (C/T)	<i>-0.9663</i>					
rs11405 (C/T)	<i>0.9803</i>	<i>-0.9859</i>				
rs6759 (C/T)	<i>-0.9663</i>	<i>1</i>	<i>-0.9859</i>			
rs1046240 (C/T)	<i>-0.9663</i>	<i>1</i>	<i>-0.9859</i>	<i>1</i>		
rs8383 (C/T)	<i>0.9012</i>	<i>-1</i>	<i>0.9582</i>	<i>-1</i>	<i>0.9932</i>	

Numbers in italic font indicate statistical significance.

Table 4. A case-control haplotype analysis for the six *PSEN2* SNPs for AD and controls

Haplotype	Overall	AD	Control	Permutation p value
C-T-C-T-T-T	0.50	0.50	0.49	0.82
C-C-C-C-C-C	0.19	0.20	0.17	0.42
C-C-T-C-C-C	0.15	0.15	0.16	0.91
T-C-T-C-C-C	0.15	0.14	0.18	0.13

Rare haplotypes with frequencies >5% are not shown. Each nucleotide on the haplotypes represents SNPs in the following order from left to right: rs1295645, rs2073489, rs11405, rs6759, rs1046240, and rs8383.

Discussion

Alzheimer's Disease

To date, several genetic association studies between AD and the *PSEN2* gene have been described. After the reports of Riazanskaia et al. [4] using cases from Russia, polymorphisms on the 5' promoter region of the *PSEN2* gene were examined within several populations. Both positive and negative results were reported for regulatory region variants [20–23]. Three studies using cases from Japan have been performed to date [24–26]. These previous reports have tested whether 5' promoter, intronic, and exonic polymorphisms on the gene affect the risk of AD. The results of the current study are consistent with those of these previous three reports. No synergetic associations were found among SNPs, APOE, and the risk of AD (data not shown). However, one association study in a Han Chinese population has shown that the promoter region insertion/deletion polymorphism could be a moderate genetic risk factor for AD [27]. The meta-analytic study suggested that the insertion/deletion polymorphism did not affect AD risk [5]. A specific haplotype with four tagging SNPs (rs2073489, rs11405, rs6759, and rs1800680) of the *PSEN2* gene was found to be functionally correlated with cerebrospinal fluid Aβ42 among German patients [28]. Although rs1800680 was not polymorphic, our haplotype analyses with these tagging SNPs were found not to modify the risk of developing AD in the Japanese population.

Replication studies of the SNP rs8383 have been previously performed [5, 29]. The abovementioned meta-analysis for rs8383 showed that the polymorphism is associated with a heightened risk of AD [5]. Significant associations for the polymorphism were not detected in the current study. Our results showed that the polymorphism was in LD to the same degree

as in other SNPs and that the haplotype including rs8383 did not affect the disease within a Japanese population. The conflicting results among studies are probably indicative of genetic and ethnic heterogeneity of AD. Zhang et al. [30] have reported the influence of rs6759 and rs11405 on mRNA expression in blood lymphocytes from patients with schizophrenia. They additionally reported that rs1295645 was associated with the psychotic symptoms of patients with schizophrenia [30]. These results suggested that SNPs on the *PSEN2* gene may affect the risk of AD with such symptoms. To clarify associations between polymorphisms and AD, further studies incorporating the measurements of behavioral and psychological symptoms of dementia would be required.

Lewy Body Dementia

This is the first pilot study to clarify the genetic associations between the common SNPs of the *PSEN2* gene and LBD in a Japanese population. Although haplotypic analyses were not performed, because of the small number of cases, we failed to show a genetic association between the six SNPs and the onset of the disease. Genetic studies for LBD were not completely performed and did not detect strong risk genes such as APOE4 in AD [11, 31]. Mixed pathologies with AD and LBD are crucial, and our LBD-control cohort could not show any associations between LBD and APOE4. We additionally examined whether genotypic and allelic frequencies of the six SNPs of AD cases differ from those of LBD cases and did not identify any significant differences (data not shown).

Jayadev et al. [14] reported the phenotypes of cases with the N141I mutation of the *PSEN2* gene. The typical mutation was found in Volga German families and is known to affect the A β pathology. Most cases were accompanied by α -synuclein pathology in amygdala as revealed by brain autopsies. These findings suggested that genetic variability of the *PSEN2* gene plays an important role for mixed pathology, AD, and LBD. Other mutations, such as R62H and A85V, were additionally known to present peculiar clinical features of LBD [32, 33]. Cases with M239V mutation also indicate focal dysfunction of the posterior cortical areas, resembling the more extended parieto-occipitotemporal dysfunction [34]. In addition to cognitive symptoms, characteristic clinical phenotypes of N141I mutation were reported. Hallucinations, delusions, or psychotic symptoms were found in one third of the affected patients with the mutation [3, 14]. There are few past association studies for common polymorphisms in the gene and behavioral and psychological symptoms of LBD. Detailed investigation *PSEN2* gene polymorphisms in LBD cases showing such symptoms would result in a better understanding of the gene and LBD.

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