Lack of association between *PRNP* M129V polymorphism and multiple sclerosis, mild cognitive impairment, alcoholism and schizophrenia in a Korean population

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Abstract. The genetic variant at codon 129 (M129V) of the prion protein gene (*PRNP*) is considered to be a major genetic risk factor for prion diseases. In this study, we examined the possible genetic association of *PRNP**I29Val with multiple sclerosis (MS, $n = 681$), mild cognitive impairment (MCI, $n = 801$), alcoholism ($n = 761$) and schizophrenia ($n = 715$) in a Korean population, and compared the data with previous genetic association studies of the variant. The minor allele frequency of *PRNP**I29Val (MAF = 0.025) was significantly lower in Korean population ($n = 2,479$) compared to Caucasian populations ($P < 0.0001$), suggestive of a weak influence of the variant in the previous population. Statistical analysis revealed no significant association between *PRNP**I29Val and MS ($P = 0.76$), MCI ($P = 0.46$), alcoholism ($P = 0.84$) and schizophrenia ($P = 0.69$). These findings were discussed in the context of prior inconsistent reports on the role of *PRNP**I29Val polymorphism in several diseases. Results from this study may provide further evidence that *PRNP* M129V is not a genetic susceptibility factor for MS, MCI, alcoholism and schizophrenia in a Korean population.

Keywords: Prion, *PRNP* M129V, multiple sclerosis, mild cognitive impairment, alcoholism, schizophrenia

1. Introduction

The methionine/valine polymorphism at codon 129 of the prion protein gene (*PRNP*) have been known

risk factors for clinical and pathologic phenotype of both sporadic and familial forms of prion diseases [1–3], such as Creutzfeldt-Jakob disease (CJD) [4,5], Gerstmann-Sträussler-Scheinker disease (GSS), fatal familial insomnia (FFI) [6–9], Alzheimer's disease (AD), and multiple sclerosis (MS) [10]. Interestingly, we were able to observe that results from earlier association studies involving M129V polymorphism do not correspond with the findings of more recent investigations, and therefore, we would like to contend that

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more comprehensive studies are necessary to reevaluate the current findings on *PRNP**129Val, specifically with the following diseases: MS, mild cognitive impairment (MCI), alcoholism and schizophrenia.

In MS, the mechanism underlying this association can be traced to the modified prion as a factor initializing immune system reactions against myelin membrane of neuronal axons [11]. Although a previous study revealed basis for association between *PRNP**129Val polymorphism and MS [10], a contrasting report that found no association with this variant has also been presented [12]. Similarly, findings on the influence of *PRNP**129Val in the risk of AD, another neurodegenerative disorder, have been well defined despite ethnic background discrepancies. Previous studies have reported that this variant is significantly associated with AD in Dutch [13], German [14], and Polish populations [15], in contrast to the findings from studies involving Korean [16], Spanish [17], and Italian [18] populations. Furthermore, it has been known that homozygosity for codon 129 (M or V allele) is connected with early-onset AD [13,17]. Mild cognitive impairment (MCI) is a transition stage between cognitive decline of normal aging and the complications of AD. The neuropathologic mechanisms in MCI are associated with progression to AD and the mood-related depressive symptoms in the preclinical stage of the disease [19, 20]. A previous report also showed that M129V polymorphisms are associated with reduced cognitive abilities in the elderly [21]. With the previous association studies reported on *PRNP**129Val in MS, cognitive decline and AD, there is, then a need to verify the role of this variant in MS and MCI.

The M129V polymorphism has also been a recognized genetic marker for susceptibility to Creutzfeldt–Jakob disease (CJD) [4,22,23]. Often correlated with this condition is a complication of alcoholism that causes thiamine deficiency and longer disease duration among patients [24,25]. Other than this, CJD and alcoholism are quite distinct clinically. However, at this stage it may be rewarding to analyze the influence of *PRNP**129Val with alcoholism.

Since psychiatric manifestations appear in the early phase of CJD, it has been hypothesized that the prion protein could also be involved in psychiatric disorders such as schizophrenia. In fact, reports have suggested that neurodegenerative processes emerge in the early-onset of schizophrenia spectrum disorders [26–28]. A previous study has demonstrated that methionine homozygosity at codon 129 is associated with a reduction in white matter tissue and a larger volume of cere-

brospinal fluid in schizophrenic patients [29]. This is meaningful since negative symptoms of schizophrenia include low global white matter volumes and reductions in the white matter of the specific prefrontal cortex area [30]. However, a case-control-study conducted in Caucasian patients with Schizophrenia reported that the *PRNP* SNP does not contribute to the genetic susceptibility for the disease [31]. To further clarify the role of methionine as a susceptibility genetic factor for schizophrenia, an association study between *PRNP**129Val and the disease should be carried out.

In view of the above, we conducted an extensive investigation as to the function of *PRNP**129Val in MS ($n = 681$), MCI ($n = 801$), alcoholism ($n = 761$) and schizophrenia (SC, $n = 715$) in a Korean population. Results from this study would provide further insights into the conflicting findings on the role of *PRNP**129Val polymorphism in several neuropsychiatric diseases.

2. Subjects, materials and methods

Description of the study subjects has been reported in previous studies which vary only in the number of samples as summarized in: MS, MCI [32], alcoholism [33] and schizophrenia [34]. Briefly, the following subjects were included in the current study: 681 for the MS study (200 cases and 481 controls); 801 for the MCI study (320 cases and 481 controls); 761 for the alcoholism study (540 cases and 223 controls); and 715 for the schizophrenia study (348 cases and 367 controls). For MS and MCI studies, we used 481 shared controls consisted of healthy and old-age individuals of Korean ethnicity who, at the moment, were not diagnosed with MS and MCI. The control group for alcoholism composed of healthy male employees of Hangang Sacred Heart Hospital who were mostly non-drinkers as revealed by a drinking habit questionnaire. An exclusion criterion was having first-degree relatives with major psychiatric disorders. Similarly, healthy employees of Hangang Sacred Heart Hospital and Center for Health Promotion of Seoul National University Hospital made up the control group for schizophrenia association study. To ensure that the participants did not have an ongoing or previous psychiatric illness, each control subject was evaluated by a trained clinician using the Structured Clinical Interview for DSM-IV, non-patient edition (SCID-NP). This study incorporated large sample sizes for each studied group, which are most effective in detecting simple gene changes. The research

Table 1
Association analysis of *PRNP* M129V with neuropsychiatric diseases in a Korean population

Disease	Genotype	Case	Control*	OR	HWE
Multiple sclerosis	MM	187 (93.5%)	455 (94.6%)	1.28 (0.27–6.19)	0.76
	MV	13 (6.5%)	26 (5.4%)		
	VV	0 (0.0%)	0 (0.0%)		
Mild cognitive Impairment	MM	306 (95.6%)	455 (94.6%)	0.76 (0.36–1.57)	0.46
	MV	14 (4.4%)	26 (5.4%)		
	VV	0 (0.0%)	0 (0.0%)		
Alcoholism	MM	514 (95.2%)	213 (95.5%)	1.08 (0.51–2.27)	0.84
	MV	26 (4.8%)	10 (4.5%)		
	VV	0 (0.0%)	0 (0.0%)		
Schizophrenia	MM	329 (94.5%)	347 (94.6%)	0.87 (0.43–1.75)	0.69
	MV	19 (5.5%)	19 (5.2%)		
	VV	0 (0.0%)	1 (0.3%)		

Logistic regression analyses were performed for odds ratios and corresponding *P*-value of the co-dominant model controlling for age (continuous value) and sex (male = 0, female = 1) as covariates.

OR: odds ratio; HWE: *P*-values of deviation from Hardy-Weinberg equilibrium.

*For association studies of mild cognitive impairment and multiple sclerosis, shared controls (*n* = 481) were used for comparison.

protocols were approved by the Institutional Review Board of each hospital, and informed consents were obtained from each subject.

Genotyping of *PRNP**129Val polymorphism was performed using the TaqMan method [35]. To determine if the individual variants were in Hardy-Weinberg equilibrium, χ^2 tests were carried out. Logistic regression analyses controlling for age as covariate were used to calculate odds ratios and *P*-values for case-control analysis.

3. Results

We genotyped 2,479 samples from our existing case/control studies of multiple sclerosis (cases/controls = 200/481), mild cognitive impairment (cases/controls = 320/481), alcoholism (cases/controls = 540/223) and schizophrenia (cases/controls = 348/367). For association studies of mild cognitive impairment and multiple sclerosis, shared controls (*n* = 481) were used for comparison. Table 1 shows the allele and genotype frequencies. The genotype distributions in all studied groups were in Hardy-Weinberg equilibrium. Statistical analysis revealed no significant difference between the allele and genotype frequencies of the controls for each studied group and MS (*P* = 0.76), MCI (*P* = 0.46), alcoholism (*P* = 0.84) and SC (*P* = 0.69) in a Korean population. The minor allele frequency (MAF) of *PRNP**129Val in a Korean population (*n* = 2,816) was 0.026.

A summary of *PRNP**129Val frequency among different ethnic groups is presented in Table 2. The MAF

of *PRNP**129Val in Asian populations (freq. = 0.01–0.03) is generally much lower than in Caucasian populations (freq. = 0.24–0.39) (*P* < 0.0001, data not shown). Lastly, we showed a summary on worldwide genetic association studies of *PRNP**129Val in Table 3.

4. Discussion

Genetic associations of *PRNP**129Val with the risk of several diseases other than CJD are of interest but are still up for debate (Table 3). Several studies reported statistically significant association with this variant and AD [15], late-onset AD [36], early-onset AD [13,37], temporal lobe epilepsy in an Italian population (TLE) [38], MS [10], and cognitive performance and impairment [21,37,39], as opposed to studies that found no association with M129V polymorphism and Parkinson's disease (PD) [40,41], TLE in a Hans Chinese population [42] and MS [12]. Although it is hard to decipher the reason behind the discrepancies among previous studies on the effect of this important *PRNP* variant on neuropsychiatric diseases, the relatively low sample sizes (cases or controls) and/or marginal significances in previous studies could be plausible explanations. In addition, the large difference in frequency between Asian populations (freq. = 0.02–0.03) and Caucasian populations (freq. = 0.24–0.39) may also influence the previous results.

The mechanisms underlying the association between MS and schizophrenia and *PRNP**129Val have been described by previous studies emphasizing on the *PRNP* biology relevant to the pathophysiology of the diseases.

Table 2
Genotype frequency of M129V polymorphism of codon 129 in the prion gene (*PRNP*) in various populations

Population	Total	Genotype			Allele		Reference
		MM N(freq.)	MV N(freq.)	VV N(freq.)	M	V	
Korean	2,816	2,671 (0.95)	144 (0.05)	1 (0.00)	0.974	0.026	This study
Chinese (Hans)	558	540 (96.77)	18 (0.03)	0	0.98	0.02	[42]
Taiwanese	100	97 (0.97)	3 (0.03)	0	0.99	0.02	[43]
Korean	236	223 (0.95)	13 (0.05)	0	0.97	0.03	[44]
Japanese	466	436 (0.94)	30 (0.06)	0	0.97	0.03	[45]
Danish	352	131 (0.37)	168 (0.48)	53 (0.15)	0.61	0.39	[46]
Finnish	1957	969 (0.49)	818 (0.42)	170 (0.09)	0.70	0.30	[47]
Turkish	100	57 (0.57)	34 (0.34)	9 (0.09)	0.74	0.26	[48]
Icelandic	208	97 (0.47)	93 (0.45)	18 (0.08)	0.69	0.31	[49]
Slovakian	613	295 (0.48)	265 (0.43)	53 (0.09)	0.70	0.30	[50]
Irish/N. Irish	353	129 (0.37)	186 (0.53)	38 (0.10)	0.63	0.37	[47]
UK	406	164 (0.41)	196 (0.48)	46 (0.11)	0.65	0.36	[47]
French	161	63 (0.39)	82 (0.51)	16 (0.10)	0.65	0.35	[47]
Spanish	546	231 (0.42)	239 (0.44)	76 (0.14)	0.64	0.36	[47]
Austrian	300	129 (0.43)	146 (0.49)	25 (0.08)	0.67	0.33	[39]
Italian	186	84 (0.45)	75 (0.40)	27 (0.15)	0.65	0.35	[51]
Cretan	205	117 (0.57)	77 (0.38)	11 (0.05)	0.76	0.24	[52]

**P*—values of Chi-square tests compared to Korean population.

Table 3
Distribution and association of *PRNP* M129V with neuropsychiatric diseases in various populations

Disease	Population	Control			Case			Association	Ref.
		N	A (Met)	G (Val)	N	A (Met)	G (Val)		
Multiple sclerosis (MS)	Korean	481	0.973	0.027	200	0.967	0.033	NS	This Study
Mild cognitive impairment (MCI)		481	0.973	0.027	320	0.978	0.022	NS	
Alcoholism		223	0.022	0.027	540	0.967	0.024	NS	
Schizophrenia		367	0.0971	0.029	348	0.973	0.027	NS	
Alzheimer's disease (AD)	Korean	236	0.975	0.025	271	0.970	0.030	NS	[44]
	Korean	217	0.972	0.028	297	0.963	0.037	NS	[16]
	Japanese	466	0.970	0.030	548	0.965	0.035	NS	[45]
	Italian	124	0.675	0.325	195	0.685	0.315	NS	[53]
	US(Caucasian)	58	0.735	0.265	109	0.705	0.295	NS	[18]
	Italian	318	0.675	0.325	258	0.675	0.325	NS	
	US	415	0.710	0.290	281	0.710	0.290	NS	[15]
	Polish	107	0.636	0.364	88	0.705	0.295	<i>P</i> = 0.005	
	Dutch	282	0.650	0.350	44	0.625	0.375	NS	[13]
	Italian	201	0.705	0.295	212	0.765	0.235	NS	[55]
	Spanish	268	0.630	0.370	278	0.655	0.345	NS	[17]
Alzheimer's disease (AD), early onset	Polish	194	0.645	0.355	53	0.680	0.320	NS	[36]
					113	0.725	0.275	<i>P</i> = 0.05	
Schizophrenia	German	401	0.667	0.333	327	0.683	0.317	NS	[31]
	Spanish	502	0.653	0.347	411	0.652	0.348	NS	[56]
Parkinson's disease (PD),	Caucasian	125	0.612	0.388	54	0.667	0.333	NS	[40]
Multiple system atrophy (MSA)					63	0.635	0.365	NS	
Temporal lobe epilepsy (TLE)	Italian	272	0.719	0.280	289	0.660	0.340	<i>P</i> = 0.03	[38]
Idiopathic Parkinson's disease (IPD)	Finnish	131	0.676	0.324	142	0.669	0.331	NS	[41]
	Greek	125	0.636	0.364	133	0.673	0.327	NS	
	US (Caucasian)	142	0.676	0.324	125	0.696	0.304	NS	
Creutzfeldt – Jakob disease (CJD)	German	722	0.640	0.360	582	0.780	0.220	<i>P</i> < 0.001	[22]

Despite that, there have been contradicting reports on the association of the variant with the mentioned diseases. This event demonstrates the need to further elucidate the involvement of the *PRNP* codon 129 polymorphism with the risk of MS and schizophrenia. In addition, since it has been known that polymorphisms

of *PRNP* contribute to the genetic determinants of CJD and AD, it may also be rewarding to study alcoholism and MCI in this context considering that these conditions are often correlated with the latter diseases respectively.

In summary, we investigated the influence of

PRNP*129Val in MS, MCI, alcoholism and schizophrenia in a Korean population ($n = 2,479$). We also presented a summary on previous genetic association studies of the PRNP variant. Despite the large sample sizes utilized in this study, statistical analyses did not reveal significant interaction between the PRNP polymorphism and MS, MCI, alcoholism and schizophrenia.

Our findings provide more evidence that PRNP*129Val is not a genetic susceptibility factor for MS, MCI, alcoholism and schizophrenia in a Korean population. These results confirm some of the previous reports on this variant as presented in the literature. To our knowledge, few studies have extended the study of M129V polymorphism to MCI, and alcoholism.

Conflicts of interest

We have no conflicts of interest with this study.

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