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

Ihn-Geun Choi\textsuperscript{a,1}, Sung-II Woo\textsuperscript{b,1}, Ho Jin Kim\textsuperscript{c,1}, Dai-Jin Kim\textsuperscript{d,1}, Byung Lae Park\textsuperscript{e,1}, Hyun Sub Cheong\textsuperscript{e}, Charisses Flerida A. Pasaje\textsuperscript{f}, Tae Joon Park\textsuperscript{f}, Joon Seol Bae\textsuperscript{f}, Young Gyu Chai\textsuperscript{g} and Hyoung Doo Shin\textsuperscript{e,f,\*}

\begin{itemize}
  \item \textsuperscript{a}Department of Neuropsychiatry, Hallym University, Han-Gang Sacred Heart Hospital, Seoul, Korea
  \item \textsuperscript{b}Department of Neuropsychiatry, Soonchunhyang University Hospital, Seoul, Korea
  \item \textsuperscript{c}Department of Neurology, National Cancer Center, Gyeonggi-do, Korea
  \item \textsuperscript{d}Department of Psychiatry, Holy Family Hospital, College of Medicine, Catholic University of Korea, Korea
  \item \textsuperscript{e}Department of Genetic Epidemiology, SNP Genetics, Inc., WooLim Lion's Valley, Seoul, Korea
  \item \textsuperscript{f}Department of Life Science, Sogang University, Seoul, Korea
  \item \textsuperscript{g}Division of Molecular and Life Sciences, Hanyong University, Ansan, Korea
\end{itemize}

Abstract. The genetic variant at codon 129 (M129V) of the prion protein gene (\textit{PRNP}) is considered to be a major genetic risk factor for prion diseases. In this study, we examined the possible genetic association of PRNP*129Val 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*129Val (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*129Val 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*129Val 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 (\textit{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
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 homozygosis 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 cerebrospinal 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 \( P \)-values 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, \( \chi^2 \) 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

| 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 | 0.01 | [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            | 239 (0.42) | 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

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