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The association between the methionine/valine (M/V) polymorphism (rs1799990) in the *PRNP* gene and the risk of Alzheimer disease: An update by meta-analysis ☆

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ABSTRACT

Background: The M/V polymorphism in the *PRNP* gene has been extensively examined for the association to the risk of Alzheimer disease (AD); however, results from different studies have been inconsistent. The aim of this study is to evaluate the association between the M/V polymorphism in the *PRNP* gene and the risk of AD.
Methods: A meta-analysis was carried out to analyze the association between the M/V polymorphism in the *PRNP* gene and the risk of AD.
Results: A total of 4228 cases and 4324 controls in 16 case–control studies were included in the meta-analysis. The results indicated that the variant V allele carriers (VV + MV) had a 13% decreased risk of AD, when compared with the homozygote MM (VV + MV vs. MM: OR = 0.87, 95% CI = 0.79–0.96, $P = 0.004$). In the subgroup analysis by ethnicity, significant decreased risks of AD were found in the Caucasian V allele carriers (OR = 0.85, 95% CI = 0.77–0.94, $P = 0.002$), but not in Asian V allele carriers (OR = 1.11, 95% CI = 0.78–1.57, $P = 0.57$). In the subgroup analysis by age of onset, significant decreased risks of AD were associated with V allele carriers in late-onset Alzheimer disease (OR = 0.76, 95% CI = 0.62–0.93, $P = 0.007$) but not in early-onset Alzheimer disease (OR = 0.86, 95% CI = 0.70–1.06, $P = 0.17$).
Conclusions: Our results suggest that the M/V polymorphism in the *PRNP* gene contributes to the susceptibility of Alzheimer disease.

1. Introduction

Alzheimer disease (AD) is characterized by progressive cognitive decline usually beginning with impairment in the ability to form recent memories, but inevitably affecting all intellectual functions and leading to complete dependence for basic functions of daily life, and premature death [1]. The global prevalence of dementia has been estimated to be as high as 24 million, and is growing everyday and predicted to double every 20 years until at least 2040 [2]. Moreover, Alzheimer disease is the most common type of dementia, and almost 70% of dementia cases were attributed to AD [3]. However, the etiology of the AD is still unclear. Previous studies have indicated that AD is a complex disorder with multiple determinants that include vascular risk factors, diabetes, hypertension, smoking, obesity and genetic variations [2]. Numerous studies have focused on the association between host genetic variants and AD susceptibility, and the *PRNP* gene has been identified as one AD susceptible gene.

The *PRNP* gene is located on 20p13, and encodes a prion protein [4,5]. The protein is mainly expressed in the brain, and is associated with a variety of cognitive deficiencies and neurodegenerative diseases, including AD [6–8]. Several studies had reported that a functional polymorphism in the *PRNP* gene might be a risk factor for AD. This polymorphism is based on the presence of a valine (V) and replacing a methionine (M) at codon 129, and is named M/V polymorphism (rs1799990). A large number of studies have investigated the association between the M/V polymorphism in the *PRNP* gene and the risk of AD. However, the results were inconclusive and inconsistent. In several European studies, statistically significant associations were reported [9–11], however, other studies failed to find significant associations [12–14]. In 2006, Bo et al. performed a case–control and meta-analysis to assess the association between this polymorphism and the risk of AD [15]. They suggested that the MM genotype and M allele might represent risk factors for AD. However, the results should be updated. First, only six case–control studies were included in that study. A small number of studies might have low power to reveal a reliable association. Second, gene polymorphism can vary substantially between different ethnic populations and age of onset; this was not analyzed in the previous study. Thirdly, in the past few years, more studies concerning the

☆ Summary at a glance: this meta-analysis investigated the association between the methionine/valine (M/V) polymorphism (rs1799990) in the *PRNP* gene and the risk of Alzheimer disease. This polymorphism is associated with decreased risk of AD in Caucasians.

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association between the M/V polymorphism in the *PRNP* gene and the risk of Alzheimer disease had been published in different populations, and these data should also be included. Thus, we carried out a meta-analysis that included the latest data to investigate in particular the association between the M/V polymorphism in the *PRNP* gene and the risk of AD. Our purpose was also to investigate ethnicity-specific and age of onset-specific AD risk. This is, to our knowledge, the most comprehensive meta-analysis regarding the association between the M/V polymorphism in the *PRNP* gene and the risk of Alzheimer disease.

2. Subjects and methods

2.1. Study identification and selection

A literature search in PubMed, EMBASE, Wanfang and Chinese National Knowledge Infrastructure databases was carried out to identify studies investigating the association between the M/V polymorphism in the *PRNP* gene and the risk of Alzheimer disease (last updated in May 2012). The search terms were used as follows: 'Alzheimer disease' or 'AD' in combination with 'polymorphism' or 'variant' or 'mutation', and in combination with 'prion protein gene' or '*PRNP*'. All studies had to meet the following inclusion criteria: (a) articles had to evaluate the association between the methionine/valine (M/V) polymorphism in the *PRNP* gene and the risk of Alzheimer disease; (b) the design had to be a case–control study based on unrelated individuals; (c) the genotype distributions were available for both cases and controls. The following exclusion criteria were also applied: (a) study design was based on family or sibling pairs; (b) genotype frequencies were not reported; (c) abstracts, reviews and overlapped studies; (d) genotype distribution in the control population was not in accord with Hardy–Weinberg equilibrium.

2.2. Extraction of data

Two reviewers independently collected the data and reached a consensus on all items. The following items were extracted from each study if available: first author's surname, publication year, original country, ethnicity, sample size, genotyping method, definition of AD, total number of cases and controls, and genotype distribution in cases and controls.

2.3. Statistical methods

The strength of the association between the M/V polymorphism in the *PRNP* gene and the risk of Alzheimer disease was assessed by OR with the corresponding 95% CI. The genetic model evaluated for pooled OR was as follows: VV + MV versus MM. OR were analyzed by a fixed-effects model or a random-effects model according to the heterogeneity. Heterogeneity among studies was assessed by a χ^2-based Q statistic and was considered statistically significant at P value$<$0.10. When the P value$\geq$0.10, OR was pooled according to the fixed-effect model; otherwise, a random-effects model was used. The significance of OR was demonstrated by the Z test. When the P value$<$0.05, OR was considered as statistically significant. To evaluate the ethnicity-specific and age of onset-specific effects, subgroup analyses were performed by ethnicity and age of onset. Subgroup analyses were investigated in a sufficient number of studies (more than three case–control studies). Other genetic models (VV vs. MV + MM, VV vs. MM, MV vs. MM, V vs. M) were also used to assess the association with the risk of AD.

Asymmetry funnel plots were used to assess potential publication bias. The Begg's test and Egger's test were also used to statistically assess publication bias.

Hardy–Weinberg equilibrium was tested by Pearson χ^2 test. Meta-analysis was performed using Reman4.2 and STATS11.0 software.

3. Results

3.1. Study selection process and characteristics

A total of 281 results were identified after an initial search from the selected electronic databases (Fig. 1). After reading the titles and abstracts, 257 articles were excluded for not being relevant to the *PRNP* gene and Alzheimer disease risk, or abstracts and review. After reading the full texts of the remaining 24 articles, two studies which did not concern the M/V polymorphism in the *PRNP* gene were excluded. Consequently, 22 articles were left for data extraction. Three articles did not report usable data and were excluded. One article reported two cohorts. Each of the cohorts was considered as a separate case–control study. Thus, a total of 21 case–control studies in 18 articles were identified. Among 21 case–control studies, genotype frequencies for the control group in two studies were not consistent with HWE, and data in three studies was overlapping or duplicated. Finally, a total of 16 case–control studies in 15 articles that met inclusion criteria were identified [5,9–22]. Four case–control studies were performed on Asians. Twelve case–control studies were performed on Caucasians. The characteristics of each case–control study were listed in Table 1. The genotype and allele distributions for each case–control study were listed in Table 2.

3.2. Quantitative data synthesis

3.2.1. All studies

As shown in Fig. 2, the heterogeneity of VV + MV vs. MM for all 16 studies was assessed, and the value of χ^2 was 18.27 with 15 degrees of freedom and p = 0.25 in a fixed-effects model. The I^2, which is another index of the test of heterogeneity, was 17.9%, suggesting a moderate heterogeneity. Thus, we chose the fixed-effects model to synthesize the data. Overall, OR was 0.87 (0.79, 0.96), and the test for overall effect *Z* value was 2.86 (P = 0.004) for VV + MV vs. MM model (Fig. 2). The results suggested a significant association between the M/V polymorphism in the *PRNP* gene and the risk of Alzheimer disease. Summary results of all comparisons were listed in Table 3.

3.2.2. Subgroup analyses

Subgroup analyses were performed by ethnicity and the age of onset. Because the conclusion may be weakened by a small number of case–control studies, only those ethnicities with more than three case–control studies were analyzed in the subgroup analysis. In the subgroup analysis by ethnicity, decreased risks were identified among Caucasians (VV + MV vs. MM, OR = 0.85, 95% CI = 0.77–0.94, P = 0.002), but not in Asians (VV + MV vs. MM, OR = 1.11, 95% CI = 0.78–1.57, P = 0.57) (Fig. 3). In the subgroup analysis by age of onset, significant decreased risks were found among late-onset Alzheimer disease (VV + MV vs. MM, OR = 0.76, 95% CI = 0.62–0.93, P = 0.007) but not in early-onset Alzheimer disease (VV + MV vs. MM, OR = 0.86, 95% CI = 0.70–1.06, P = 0.17) (Fig. 4). Summary of results of other comparisons were listed in Table 3.

3.3. Publication bias

Publication bias was assessed by the Begg's funnel plots and Egger's test. The shape of the Begg's funnel plots seemed symmetric in the VV + MV vs. MM comparative genetic model (Fig. 5). The Egger's test was performed to provide statistical evidence of funnel