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Review article

Meta-analysis of the association between two neprilysin gene polymorphisms and Alzheimer's disease

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ABSTRACT

Objective: The aim of this study is to evaluate the association between two neprilysin variants (rs989692 and rs3736187) and Alzheimer's disease (AD).
Methods: All eligible studies were searched in PubMed and Embase from inception to July 2014. Data was extracted by two investigators independently. The complete overdominant model (CC + TT vs. CT) and co-dominant model (GG vs. AA and GA vs. AA) were used for rs989692 and rs3736187, respectively. A comparison of allele frequencies was also conducted.
Results: Six studies containing 2555 AD patients and 1914 controls were included for rs989692 polymorphisms. The pooled odds ratio (OR) and confidence interval (CI) suggested that rs989692 polymorphisms were not associated with AD based on the current published studies (C vs. T, OR = 1.01, 95% CI = 0.85–1.19; CC + TT vs. CT, OR = 0.89, 95% CI = 0.78–1.01). Five studies containing 2438 AD patients and 1452 controls were identified for rs3736187 polymorphisms (G vs. A, OR = 0.77, 95% CI = 0.66–0.91; GG vs. AA, OR = 0.38, 95% CI = 0.19–0.77; GA vs. AA, OR = 0.81, 95% CI = 0.61–0.99). The result showed that rs3736187 polymorphisms were likely associated with the decreased risk of AD.
Conclusions: This meta-analysis indicates that rs3736187 (A/G) polymorphisms may be a potential beneficial single nucleotide polymorphism (SNP), which are associated with a decreased risk in AD. Further larger scale studies are necessary to validate gene-to-gene interactions and to define the association of neprilysin polymorphisms with AD.

Contents

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease in the elderly, affecting about 24 million people in the world

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in 2012 [1]. The main characteristics of AD are senile plaque containing β-amyloid (Aβ), neurofibrillary tangles and neuronal loss. Numerous studies suggest that the accumulation of Aβ in the brain was the major cause of AD, which could induce inflammatory response and neuronal death [2–4]. Promoting the degradation of Aβ was supposed to be a potential strategy for the treatment of AD. Multiple Aβ-cleaving enzymes, including neprilysin (NEP), insulin-degrading enzyme (IDE), angiotensin-converting enzyme (ACE) and matrix metalloproteinase (MMP), play a vital role in the regulation Aβ level in the brain [5,6].

Neprilysin (NEP), also known as membrane metallo-endopeptidase (MME), is a type II metalloproteinase widely expressed in the neocortex and cerebral vessels. Studies showed that NEP could remove Aβ and inhibit the formation of Aβ deposition [7]. Deficit of NEP could result in the aggregation of Aβ [8]. The gene encoding human NEP is located on chromosome 3q25.1-q25.2 (MIM: 120520) and is highly polymorphic. Among the different polymorphisms in *NEP*, two SNPs, rs989692 and rs3736187, are extensively studied. Large number of studies indicated that both SNPs are considered to be associated with AD [9–13]; however, the results remain controversial, with some studies unable to identify any association between neprilysin polymorphisms and AD.

Therefore, we conducted a meta-analysis to assess the inconsistent results from published studies and clarify the association between rs989692 or rs3736187 polymorphisms and AD.

2. Methods and materials

2.1. Literature search and inclusion criteria

We performed a comprehensive search in the PubMed and Embase databases up to July 2014 and selected the original studies surveying the neprilysin polymorphisms and AD. We also searched the AlzGene database for additional articles. The following search terms were used: *neprilysin*, *NEP*, *metallo-endopeptidase*, *MME*, *polymorphism**, *variant**, *genotype*, *allele** and *Alzheimer's disease**, *Alzheimer disease**, and *AD*. The language was limited to English and Chinese. The search was restricted to human subjects.

Studies included in this meta-analysis must meet all the following inclusive selection criteria: a) evaluation of the association between *rs989692* or *rs3736187* and AD; b) conformance to Hardy–Weinberg equilibrium (HWE); c) case–control design and if there were studies having overlapped subjects, only the one with a larger sample size was selected; and d) useful data available for estimating the odds ratio (OR) with 95% confidence intervals (CIs).

2.2. Data extraction and outcome measures

For each study, information was recorded including first author, year of publication, country of origin, ethnicity of population, study design, definition of Alzheimer's disease, number of patients and controls, genotyping methods and genotype distributions. Data were extracted independently by two investigators (Guo Xingzhi and Tang Peng) using a standardized data extraction form. Agreement was reached after discussion for conflicting data with a third author (Li Rui), and then extracted data were typed into an excel file by another author (Hou Chen).

2.3. Assessment of risk of bias

The Newcastle–Ottawa Scale (NOS) was conducted to assess the risk of bias [14]. This scale evaluates quality of observational studies from three aspects, including selection (0–4 points), exposure (0–3 points) and comparability (0–2 points). A score of 1 is deducted when one point is unmatched and high scores indicate better quality. Two authors (Liu Peng and Liu Yue) independently estimated the risk of bias.

2.4. Statistical analysis

The association between the NEP gene polymorphism at rs989692 or rs3736187 and AD was estimated by calculating pooled ORs with 95% CIs. According to the recently suggested guidelines for analysis of genetic association data [15], we adopted the most probably appropriate genetic model for both SNPs. The allele model and complete overdominant model were performed for rs989692, whereas allele model and codominant model were performed for rs3736187. The Cochran Q test and I-squared test were conducted to assess the statistical heterogeneity ($P < 0.1$ was considered significant). A fixed-effects model (Mantel–Haenszel method) [16] or random-effects model (DerSimonian and Laird method) [17] was applied according to the presence ($P < 0.1$) or absence ($P > 0.1$) heterogeneity. Sensitive analysis was used to assess the stability of the results by sequentially excluding one publication at a time. Begg's and Egger's tests were applied to assess the publication bias. All statistical analyses and graphics were conducted in Stata 12.0 and Revman 5.2 software. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Selection of eligible studies

A total of 94 potential studies were identified by the initial search in PubMed and Embase databases, and 25 duplicate studies were excluded After reviewing titles and abstracts, 53 studies were excluded for they were reviews or not relevant to our analysis. Sixteen potentially relevant articles were reviewed for full-text analysis (Fig. 1). Ten studies were excluded: 9 articles for other diseases or SNPs and one with overlapped data [18]. One additional study with available data was identified in the AlzGene database and included in the analysis [19]. Thus, a total of 7 studies were included in final meta-analysis and four of them evaluated both rs989692 and rs3736187 polymorphisms [9–13, 19,20].

3.2. Study characteristics

The detailed characteristics of each included studies were presented in Table 1. These studies were published from 2004 to 2014. All articles were case–control studies. Six studies defined AD according to the NINCDS–ADRDA criteria and the DSM-IV criteria, and only Miners et al. used the CERAD criteria for AD diagnosis [13]. Among the included studies, four of them evaluated both rs989692 and rs3736187 polymorphisms [9,10,13,20].

For the rs989692 polymorphism, all the six studies were performed in Caucasians and 2555 AD patients and 1914 normal controls were included [9,10,12,13,19,20]. The study of Helisalmi et al. screened the mutations in APP, PSEN-1 or PSEN-2 genes, but none of the mutations were found [9].

For the rs3736187 polymorphism, finally five studies were included in our meta-analysis with 2438 AD patients and 1452 normal controls [9–11,13,20]. Four studies were conducted in Caucasians, and only one was performed in Asia [11].

3.3. Quantitative data synthesis

The result for the rs989692 polymorphism was presented in Fig. 2. Compared to the T allele, the C allele had no significant association with AD susceptibility for both models (C vs. T, OR = 1.01, 95% CI = 0.85–1.19; CC + TT vs. CT, OR = 0.89, 95% CI = 0.78–1.01). A fixed-effects model was conducted for the complete overdominant model (CC + TT vs. CT) without significant heterogeneity, whereas a random-effects model was used for the allele model which had a significant heterogeneity. Thus, the sensitivity analyses were applied to explore the potential sources of heterogeneity. Exclusion of the