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Research paper

Meta-analysis of BACE1 gene rs638405 polymorphism and the risk of Alzheimer's disease in Caucasion and Asian population

Minhua Yu, Yue Liu, Jun Shen, Dongwei Lv, Junjian Zhang*

Department of Neurology, Zhongnan Hospital, Wuhan University, No. 169, Donghu Road, 430071 Hubei, China

HIGHLIGHTS

- This is the latest meta-analysis to discuss about the risk of AD and SNP rs638405 polymorphism of BACE1 gene.
- The strengths of our analysis include the strict criteria of eligible studies and general report by additional subgroup analysis.
- We demonstrated the SNP rs638405 polymorphism of BACE1 gene displayed significant association with AD both in Asian population, Caucasion population and overall population.

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ABSTRACT

Recent studies showed the β-site amyloid precursor protein cleaving enzyme (BACE) is associated with Alzheimer's disease (AD). However, studies investigating the association of single-nucleotide polymorphism (SNP) in exon 5 of BACE1 (rs638405, C786G, Val262) with AD are controversial. Therefore we conducted this meta-analysis to clarify the association. Relevant studies were identified on PubMed, Cochrane library and CNKI from established through July 2015 according to the inclusion criteria. Odds ratios (ORs) with 95% confidence intervals (CIs) and five genetic models were applied to assess the association. A total of 13 studies composed of 2538 AD patients and 3020 controls were included in this study. Significant association of SNP rs638405 with AD was found in overall population among allelic genetic model (G vs. C: OR = 1.11, 95%CI = 1.02–1.20, P = 0.01), codominant genetic model (GG vs. CC: OR = 1.22, 95%CI = 1.04–1.44, P = 0.02) and recessive genetic model (GG vs. GC+ CC: OR = 1.25, 95%CI = 1.10–1.42, P = 0.0008). Besides, subgroup analysis indicated significant association among Asian population (allelic genetic model, G vs. C, OR = 1.18, 95%CI = 1.04–1.34, P = 0.01; codominant genetic model, GG vs. CC, OR = 1.43, 95%CI = 1.08–1.89, P = 0.01 and recessive genetic model, GG vs. GC+ CC, OR = 1.40, 95%CI = 1.09–1.78, P = 0.008) and Caucasion population (recessive genetic model, GG vs. GC+ CC, OR = 1.20, 95%CI = 1.02–1.39, P = 0.02). Our analysis demonstrated that GG genotype and G allele of BACE1 gene rs638405 probably increase the risk of AD.

1. Introduction

Alzheimer's disease is a degenerative disease characterized by a progressive decline in cognition and distinct neuropathology. One of the major hallmarks of Alzheimer's disease (AD) pathology is amyloid beta-peptide (Aβ) deposition in senile plaques and blood vessel walls in the brain. Brain Aβ is derived from the proteolytic cleavage of amyloid precursor protein (APP), which is a type-I transmembrane protein that can be cleaved by two endoproteolysis pathways. The pathway generating Aβ is initiated by β-secretase which cleaves APP at Asp1 and Glu11 of Aβ and the remaining fragment is then cleaved by γ-secretase to release Aβ [1,2]. Another non-neurotoxic pathway lies on α-secretase, it cleaves the APP within the Aβ sequence and precludes the Aβ formation. Therefore, β-secretase is an important rate-limiting enzyme of the pathway generating Aβ.

The β-site APP cleaving enzyme 1 (BACE1) is a type 1 transmembrane aspartyl protease and its synthesis can be regulated by BACE1 gene, which is located on chromosome 11q23-24, near the recently identified region associated with increased suspicion of AD. Previous studies have indicated that in the brains of patients with

Abbreviations: APP, amyloid precursor protein; BACE, β-site APP cleaving enzyme; AD, Alzheimer's disease; SNP, single-nucleotide polymorphism; Aβ, amyloid beta-peptide; HWE, Hardy-Weinberg equilibrium; ApoE, Apolipoprotein E.

* Corresponding author.
E-mail address: wdsjkx@163.com (J. Zhang).

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AD, BACE1 protein levels and enzymatic activity were significantly higher than in the control brains [3], and BACE1 was the major β-secretase for Aβ peptide generation by neurons in transgenic mice [4,5]. Animal experiment also revealed that mice deficient in BACE1 gene had normal phenotype and abolished β-amyloid generation [5]. Thus, the BACE1 gene is probably associated with risk of AD.

The single-nucleotide polymorphism (SNP) of genetic locus is very important for phenotype. There are 23 polymorphic loci in the BACE1 gene, but only a few sites may be associated with AD. A study among northern Irish population revealed that 11 polymorphic loci of BACE1 gene were not significantly associated with AD [6]. Among all of the polymorphic loci, the SNP in exon5 (rs638405) attracted researchers' attention. In the recent years, there were several studies concerning a single nucleotide polymorphism in exon5 (rs638405) of BACE1 gene and the risk of AD, however, the relationship remains inconclusive, possibly due to the limited sample size or the differences of demography. Some case-control studies reported that G allele gene may increase the risk of AD [7–10], while others indicated discrepancy [11–14]. A meta-analysis of 9 case-control studies in eight papers accounting for 1481 AD patients and 1720 controls found non-significant association between a single nucleotide polymorphism in exon 5 of BACE1 gene and the risk of AD [15]. Another meta-analysis performed by Jo et al. indicated a weak association in Asian population [13]. However, the sample size was small in previous studies and there were more case-control studies on the possible association between BACE1 gene rs638405 polymorphism and AD conducted these years. Thus here we reevaluated this relevance using the relatively large-scale samples from all available case-control studies applying five genetic models to obtain a more reliable conclusion. Besides, subgroup analysis by ethnicity (Asian population and Caucasion population) were also conducted for further studies.

2. Materials and methods

2.1. Literature search strategy

We searched the PubMed, Cochrane Library, and Chinese National Knowledge Infrastructure (CNKI) from established to July 2015 to select all possible studies with key words including "Alzheimer's disease" or "Alzheimer's dementia" or "AD"; "β-site APP cleaving enzyme" or "BACE". Only articles published in English and Chinese were considered.

2.2. Inclusion criteria

We selected the studies meeting the following criteria: (1) the studies conducted by a case-control design, (2) the studies evaluated the association between rs638405 polymorphism and risk of AD, (3) the studies provided the numbers of rs638405 genotypes, (4) the studies provided an odd ratio (OR) with 95% confidence interval (CI) as well as P value, (5) the studies of human research. Additionally, we excluded reviews, editorials, and letters without sufficient data.

2.3. Data extraction

The following information from each study were extracted independently: (1) the name of the first author, (2) the year of publication, (3) the country where the study was performed and the ethnicity of population, (4) the diagnostic criteria of AD, (5) the methods for genotyping, and (6) the total number of AD group and control group, and the frequencies of every genotype.

2.4. Meta-analysis

The association between AD and BACE1 gene rs638405 was estimated by calculating the pooled OR and its corresponding 95% CI. The significant levels for heterogeneity were defied to be with $P < 0.05$ and $I^2 > 50\%$. If there was no significant heterogeneity among the included studies, the pooled OR was calculated using the fixed effect model; otherwise, the OR was calculated by random effect model. The satisfaction of the Hardy-Weinberg equilibrium (HWE) among genotype values in control group was also checked. For genotypic comparison, to dissect the association patterns, the allelic (G vs. C), dominant (GG + GC vs. CC), recessive (GG vs. GC+ CC), codominant (GG vs. CC, GC vs. CC) models were applied in the investigation of the disease association. Meanwhile, we used funnel plots to evaluate the potential publication bias and we performed the sensitivity analysis. All statistical tests for heterogeneity and meta-analysis were computed using RevMan 5.1 software.

3. Results

3.1. Characteristics of studies

After searching all literatures on the electronic databases, 13 studies were identified according to the inclusion and exclusion criteria [7–14,16–20]. The study identification and selection progression is described in Fig. 1. Totally, 13 studies containing 2538 AD patients and 3020 controls and their main characteristics are shown in Table 1. Among the 13 studies, 4 studies were conducted in China, 3 in USA, 1 in Spain, 1 in France, 1 in Switzerland, 1 in Korea, 1 in England and 1 in Germany. Both of the populations were Asian or Caucasion. The genotype distribution in the controls of all studies were in agreement with HWE. The Newcastle-Ottawa Scale (NOS) was applied to quality assessment of all included studies and the scores ranged of 5–7. All data had been reported in Table 1.

3.2. Meta-analysis results

We evaluated the genetic heterogeneity of rs638405 polymorphism among all the selected studies applying five genetic models: allelic (G vs. C), dominant (GG + GC vs. CC), recessive (GG vs. GC+ CC), and codominant (GG vs. CC, GC vs. CC) model. We did not identify significant heterogeneity among these studies using these five different models (G vs. C: $P = 0.47$, $I^2 = 0\%$; GG vs. CC: $P = 0.34$, $I^2 = 10\%$; GC vs CC: $P = 0.05$, $I^2 = 42\%$; GG + GC vs. CC: $P = 0.09$, $I^2 = 37\%$; GG vs. GC + CC: $P = 0.79$, $I^2 = 0\%$). Therefore, fixed-effect model was used in all populations and showed that SNP rs638405 was associated with an increased risk of AD in allelic model (G vs. C: $P = 0.01$, OR = 1.11, 95%CI 1.02–1.20), codominant model (GG vs. CC: $P = 0.02$, OR = 1.22, 95%CI 1.04–1.44) and recessive model (GG vs. GC+ CC: $P = 0.0008$, OR = 1.25, 95%CI 1.10–1.42). Detailed results of the three genetic models are described in Fig. 2. Other two genetic models (GG + GC vs. CC and GC vs. CC) did not show any significant association with AD ($P > 0.05$, see Table 2).

3.3. Subgroup analysis

To further assess the potential effects of racial difference on the association between BACE1 gene rs638405 polymorphism and AD risk, we conducted a subgroup analysis and pooled the OR and 95% CI from the subgroups of ethnicity, Asian population and Caucasion population. A total of 8 studies involving 1545 AD patients and 1924 controls were Caucasion population and the other 5 studies involving 993 AD patients and 1096 controls were Asian population. Fixed-effect model was used in Caucasian population and Asian population, showed that SNP rs638405 was associated with an increased risk of AD in three genetic models (G vs. C: $P = 0.01$,