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BIN1 gene rs744373 polymorphism contributes to Alzheimer's disease in East Asian population

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HIGHLIGHTS

- We evaluated association between rs744373 polymorphism and AD.
- Pooled analysis was used to investigate the association.
- Meta-analysis was used to investigate the association.
- This is the first study to show significant association in East Asian population.

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ABSTRACT

Large-scale genome-wide association studies (GWAS) identified BIN1 gene rs744373 polymorphism to be significantly associated with Alzheimer's disease (AD) in Caucasian ancestry. Recently, this polymorphism was also investigated in East Asian population. However, no study reported significant association. We consider that the failure to replicate significant association between rs744373 polymorphism and AD may be caused by the relatively small sample size. In this research, we evaluated this association using pooled samples from previous studies (n = 4982, 1437 AD cases and 3545 controls). Two methods including pooled analysis and meta-analysis were used to investigate the association. Using the pooled analysis, we observed significant association between rs744373 polymorphism and AD by both genotype test (P = 3.94E−03, 4.59E−03 and 1.04E−02) and allele test (P = 1.12E−03, OR = 1.16, 95% CI 1.06–1.28). Interestingly, the meta-analysis confirmed this association with P = 8.00E−03 (OR = 1.14, 95% CI 1.03–1.25) and P = 2.00E−02 (OR = 1.16, 95% CI 1.02–1.32). We also evaluated the effect of rs744373 polymorphism on AD risk in different ethnic backgrounds and found that rs744373 polymorphism contributed to AD with similar genetic risk in East Asian and Caucasian populations. To our knowledge, this is the first study to show significant association between rs744373 polymorphism and AD in East Asian population.

1. Introduction

Alzheimer's disease (AD) is a complex neurodegenerative disease in the elderly [13]. Recently, genome-wide association studies (GWAS) have been widely used to identify the common AD susceptibility genes or loci. In addition to the known apolipoprotein E (APOE) gene, recent GWAS have identified nine additional AD susceptibility genes or loci, which include CR1, BIN1, CLU, PICALM, MS4A4/MS4A6E, CD2AP, CD33, EPHA1 and ABCA7 [4,5,9,11,14]. Among these loci, a single nucleotide polymorphisms (SNPs) rs744373 in BIN1 gene were identified to be significantly

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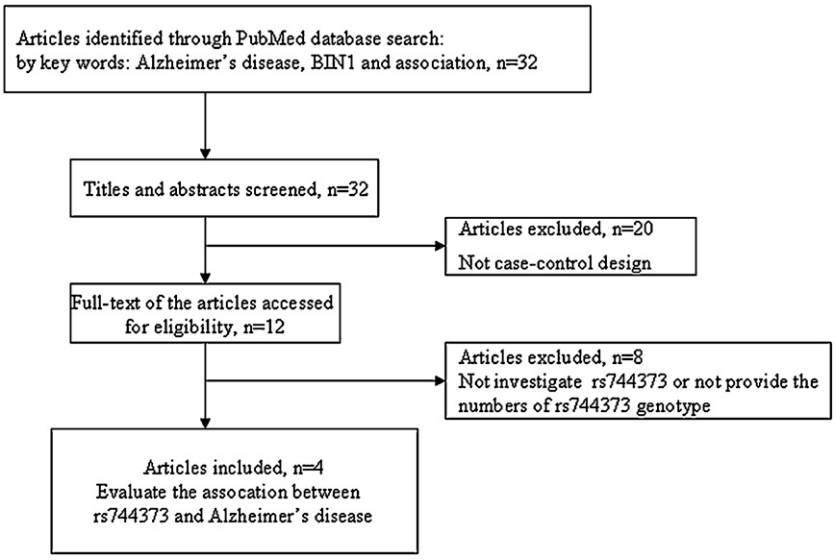

Fig. 1. Flow chart of meta-analysis for exclusion or inclusion of individual articles.

associated with AD in Caucasian ancestry with $P = 1.59E{-}11$ [14], $P = 3.16E{-}10$ [6], $P = 2.6E{-}14$ [5], $P = 2.13E{-}09$ [1], $P = 2.9E{-}07$ [10] and $P = 1.1E{-}04$ [3].

Recently, rs744373 polymorphism was also investigated in East Asian population. Tan et al. analyzed 1224 individuals (612 AD cases and 612 controls) in Chinese population. However, they did not reported any significant association using allele test ($P = 0.217$) and genotype test ($P = 0.547$, 0.263 and 0.397 for dominant, recessive and additive logistic genetic models) [15]. Ohara et al. analyzed 825 AD cases and 2934 controls in Japanese population. However, the study did not report significant association ($P = 0.06$) using logistic regression analysis under an additive genetic model [12].

We consider that the failure to replicate significant association between rs744373 polymorphism and AD may be caused by the relatively small sample size. In this research, we evaluated this association using pooled samples from the two studies ($n = 4982$, 1437 AD cases and 3545 controls), which we think may have greater power to detect significant association between rs744373 polymorphism and AD. Two methods including pooled analysis and meta-analysis were used to investigate the association between rs744373 polymorphism and AD.

2. Materials and methods

2.1. Literature search and inclusion criteria

We searched PubMed database to select all possible studies using the following key words: 'Alzheimer's disease' and 'BIN1'. The literature search was updated on 1/20/2013. As the involvement of rs744373 polymorphism in AD has been well established in Caucasian ancestry, here, we aim to replicate this finding in Asian population. Meanwhile, in order to compare the effect of rs744373 polymorphism on AD risk in different ethnic backgrounds, we also selected previous studies investigating the rs744373 polymorphism in Caucasian ancestry. We included those studies meeting the following criteria: (1) the study evaluated the association between rs744373 polymorphism and AD by a case–control design; (2) the study provided the numbers of rs744373 genotype data. In the end, we selected two independent studies in East Asian population and two independent studies in Caucasian population (Fig. 1).

2.2. Data extraction

For the case–control genetics studies, the following information was extracted from each study: (1) the name of the first author; (2) the year of publication; (3) the ethnicity of the studied population; (4) the number of rs744373 genotypes in cases and controls (Table 1).

2.3. Evaluating the population stratification by genetic heterogeneity test

In order to evaluate the potential population stratification, we test the genetic heterogeneity of rs744373 polymorphism in different ethnic backgrounds using Cochran's Q test, which approximately follows a χ^2 distribution with $k-1$ degrees of freedom (k is the number of studies included) [7]. The null hypothesis for the Cochran's Q test is that there is no difference between the five studies ($\alpha = 0.01$). Another statistic $I^2 = ((Q-(k-1))/Q) \times 100\%$ was also used. I^2 ranges from 0 to 100%. $I^2 = 0$–25%, 25–50%, 50–75% and 75–100% means low, moderate, large and extreme heterogeneity, respectively [7]. We conducted Cochran's Q test using RevMan (v.5.1) software (http://www.cochrane.org/revman).

2.4. Pooled analysis of rs744373 polymorphism in East Asian population

If there was no significant genetic heterogeneity of rs744373 polymorphism in Chinese and Japanese populations (P value > 0.01 for Cochran's Q test and $I^2 < 50\%$), we performed a pooled analysis. Chi-square test was used to investigate the Hardy–Weinberg equilibrium (HWE) of rs744373 polymorphism and the association between rs744373 polymorphism and AD in pooled dataset. All the chi-square tests for pooled analysis were conducted using the program R (http://www.r-project.org/).

2.5. Meta-analysis of rs744373 polymorphism in East Asian population

As the pooled analysis may not adjust the numbers of cases and controls used in Chinese and Japanese populations, we then performed a meta-analysis of rs744373 polymorphism in East Asian population. For meta-analysis, odds ratio (OR) was calculated