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CR1 rs3818361 Polymorphism Contributes to Alzheimer's Disease Susceptibility in Chinese Population

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Abstract Recent genome-wide association studies (GWAS) reported CR1 rs3818361 polymorphism to be an Alzheimer's disease (AD) susceptibility variant in European ancestry. Three independent studies investigated this association in Chinese population. However, these studies reported weak or no significant association. Here, we reinvestigated the association using all the samples from three independent studies in Chinese population (N=4047, 1244 AD cases and 2803 controls). We also selected three independent studies in European ancestry population (N=11787, 3939 AD cases and 7848 controls) to evaluate the effect of rs3818361 polymorphism on AD risk in different ethnic backgrounds. In Chinese population, we did not identified significant heterogeneity using additive, recessive, and dominant genetic models. Meta-analysis showed significant association between rs3818361 and AD with P=6.00E-03 and P=5.00E-03. We further identified no heterogeneity of rs3818361 polymorphism between Chinese and European populations. We found that rs3818361 polymorphism contributed to AD with similar genetic risk in Chinese and European populations. In summary, this is the first study to show significant association between rs3818361 polymorphism and AD in Chinese population by a meta-analysis method. Our findings indicate that the effect of CR1 rs3818361 polymorphism on AD risk in Chinese cohorts is consistent with the increased risk observed in European AD cohorts.

Keyword Genome-wide association studies · Alzheimer's disease · Polymorphism

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Introduction

Since 2009–2013, large-scale genome-wide association studies (GWAS) reported several Alzheimer's disease (AD) susceptibility genes including CR1, BIN1, CLU, PICALM, MS4A4/MS4A6E, CD2AP, CD33, EPHA1, and ABCA7 [1–3], SORL1 [4], and TREM2 [5]. A recent large meta-analysis of AD GWAS in individuals of European ancestry identified 11 new AD genetic risk factors for AD, which include HLA-DRB5/DRB1, PTK2B, SLC24A4-0RING3, DSG2, INPP5D, MEF2C, NME8, ZCWPW1, CELF1, FERMT2, and CASS4 [3].

We previously analyzed the PICALM rs3851179 [6, 7], BIN1 rs744373 [8], CLU rs11136000 [1], rs2279590 [9], and rs9331888 [10], CD2AP rs9349407 [11], ABCA7 rs3764650 [12], and CD33 rs3865444 [13] polymorphisms, and identified significant association. In addition to these polymorphisms above, a single nucleotide polymorphism (SNP) rs3818361 in CR1 was reported to be significantly associated with AD in European ancestry with P=8.5E-08, P=9.2E-06, and P=3.7E-14 [14–16]. The following studies confirmed the influence of CR1 on clinical and pathological measures of AD [17–20]. Three candidate gene studies investigated rs3818361 polymorphism in Chinese population [21–23]. However, one study reported weak association (P=0.029 for allele test and P=0.047 for genotype test [22]) and two reported no association (P=0.07 for allele test and P=0.18 for genotype test [21], P=0.07 and P=0.26 [23]) between rs3818361 and AD in Chinese population.

It is reported that meta-analysis method combines and analyzes quantitative evidence from related studies to produce results based on a whole body of research to aggregate information in order to achieve a higher statistical power [24]. Here, we reinvestigated the association using all the samples from three independent studies in Chinese population. We also selected three independent studies in European ancestry population to evaluate the effect of rs3818361 polymorphism on AD risk in different ethnic backgrounds.

Methods and Materials

Samples

Our study included 4047 samples (1244 AD cases and 2803 controls) from previous three independent studies in Chinese population and 11787 samples (3939 AD cases and 7848 controls) from previous three independent studies in European ancestry population (Table 1).

Genetic Models

Both allele and genotype models were used to investigate the association between rs3818361 and AD. The CR1 rs3818361 polymorphism includes two alleles C and T. T is the minor allele. We assume that T is the high-risk allele and C is the lower-risk allele. We selected the additive (T allele versus C allele), recessive (TT genotype versus TC + CC genotypes), and dominant (TT + TC genotypes versus CC genotype) genetic models [25].

Quality Evaluation

Quality evaluation criteria were used to evaluate the quality of selected genetic association studies [26], which consist of ten components. Each component is scored as 1 if present or 0 if absent. The quality evaluation score was calculated by summing each component, resulting in a scoring range of 0–10 [26]. The selected studies were scored as "good" if the score was greater than or equal to 8, "mediocre" if the score was 5–7, and "poor" if the score was less than 4 [27]. Two authors performed the quality evaluation independently using the criteria proposed by Clark et al. A third author adjudicated any differences between the two authors as described in our previous study [12].

Heterogeneity Test

Genetic heterogeneity among the selected studies is evaluated using Cochran's Q test and $I^2 = {}^{(Q-}\ (k-1))/\ Q \times 100\%$ statistic. Cochran's Q test approximately follows a χ^2 distribution with $k-1$ degrees of freedom (k stands for the number of studies for analysis). I^2 ranges from 0 to 100 %, 0–24 % = no heterogeneity, 25–49 % = moderate heterogeneity, 50–74 % =large heterogeneity, and 75–100 % = extreme heterogeneity. $P<0.01$ from Cochran's Q test and $I^2>50\%$ was considered to indicate statistically significant heterogeneity.

Meta-analysis

The pooled odds ratio (OR) is calculated by the fixed effect model (Mantel-Haenszel). Z test is used to determine the significance of OR. All statistical tests were computed using RevMan (v.5.1).

Sensitivity Analysis

We omit each study at a time to assess the influence of each individual study on the pooled OR.

Table 1 The selected studies investigating the association between rs3818361 and AD using a case-control design

Study	Quality score	Population	Ethnicity	Case no.	Control no.	Case genotypes			Control genotypes		
						TT	CT	CC	TT	CT	CC
Chen 2012 [22]	8	China	Chinese	455	340	51	214	190	27	147	166
Liao 2014 [23]	8	China	Chinese	535	2106	78	241	216	246	988	872
Zhang 2010 [21]	8	China	Chinese	254	357	38	118	98	38	161	158
Harold 2009 [15]	9	UK/Ireland	European	2226	4836	87	712	1427	157	1367	3312
Harold 2009 [15]	9	Germany	European	554	824	35	182	337	40	260	524
Harold 2009 [15]	9	USA	European	1159	2188	52	401	706	90	678	1420
All N=15834				N=5183	N=10651						

The quality score of included studies was scored based on the criteria developed by Clark et al. [26] to evaluate the quality of genetic association studies.

Publication Bias Analysis

A funnel plot from Egger et al. is commonly used to check for the existence of publication bias [28, 29]. A regression-based approach proposed by Egger is used to test for publication bias to provide statistical evidence, with a $P<0.01$ indicating that there was a significant publication bias [30]. All statistical tests were computed using *R*.

Results

Heterogeneity Test and Subgroup Meta-analysis

We first performed a subgroup analysis in Chinese and European populations, respectively. In Chinese population, we did not identify significant heterogeneity using additive (P=0.41 and I^2 = 0 %), recessive (P=0.84 and I^2 = 0 %), and dominant (P=0.32 and I^2 = 13 %) genetic models. Meta-analysis showed significant association between rs3818361 and AD with P=6.00E-03 and P=5.00E-03 for additive and recessive genetic models but suggestive association for dominant genetic model with P=5.00E-02.

In European population, we did not identify significant heterogeneity using additive (P=0.87 and I^2 = 0 %), recessive (P=0.81 and I^2 = 0 %), and dominant (P=0.82 and I^2 = 13 %) genetic models. Meta-analysis showed significant association between rs3818361 and AD with P=1.36E-05 and P=1.24E-05 for additive and dominant genetic models but no association for recessive genetic model with P=7.00E-02. More detailed results were described in Figs. 1, 2, and 3.

We further found that rs3818361 polymorphism contributed to AD with similar genetic risk in Chinese and European populations with OR=1.16 and 1.16, OR=1.36 and 1.19, and OR=1.15 and 1.20 for additive, recessive, and dominant genetic models. More detailed results are described in Figs. 1, 2, and 3.

Heterogeneity Test and Meta-analysis in Pooled Population

We further evaluated the genetic heterogeneity of rs3818361 polymorphism between Chinese and European populations. We did not identify significant heterogeneity using additive (P=0.84 and I^2 = 0 %), recessive (P=0.91 and I^2 = 0 %), and dominant (P=0.71 and I^2 = 0 %) genetic models. Meta-analysis showed significant association between rs3818361 and AD with P=2.47E-07, P=1.00E-03, and P=2.03E-06 for additive, recessive, and dominant genetic models. More detailed results were described in Figs. 1, 2, and 3.

Sensitivity Analysis

We identified that the association between rs3818361 polymorphism and AD did not vary substantially, which suggested that the results from this meta-analysis were stable.

Publication Bias Analysis

The funnel plots of the selected studies investigating the association between rs3818361 and AD are symmetrical inverted funnels (Fig. 4). Egger's test provides statistical evidence of symmetry with P=0.637, P=0.235, and P=0.977 for additive, recessive, and dominant genetic models, respectively. These results indicated no evidence of publication bias.

Discussion

Original GWAS identified significant association between rs3818361 and AD in European ancestry [14–16]. Three independent studies investigated the rs3818361 polymorphism in Chinese population and reported a weak or negligible association between rs3818361 and AD. Growing evidence confirmed the influence of CR1 on clinical and pathological measures of AD [17–20]. Considering the important role of CR1

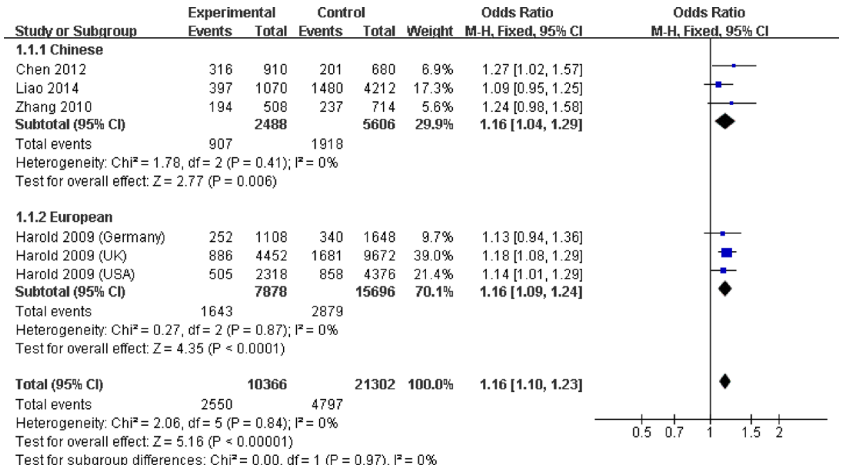

Fig. 1 The forest plot for the meta-analysis of the association between rs3818361 and AD using an additive genetic model

in AD, we reevaluated this association using large-scale samples from six independent studies in Chinese and European populations. Our results showed significant association between rs3818361 polymorphism and AD in Chinese population. We found no heterogeneity of rs3818361 polymorphism between Chinese and European populations.

Recent therapeutic strategies for treating AD mainly focused on reducing brain amyloid burden [18]. The influence of CR1 on clinical and pathological measures of AD cases and controls was also investigated. The results indicated that the higher expression of CR1 was associated with more advanced cognitive decline [19]. Chibnik et al. analyzed 1666 non-demented subjects to evaluate the associations between CR1 rs3818361 and rate of change in cognitive function [20]. The results showed that CR1 was associated with amyloid plaque burden and age-related cognitive decline [20]. Sweet et al. investigated 1831 non-demented subjects from Cardiovascular Health Study to determine the effects of CR1 on age and rate of decline. The results also indicated significant association between CR1 and more rapid cognitive decline [17].

In addition to rs3818361 polymorphism, CR1 rs6656401 polymorphism was also identified to be significantly associated with AD in European ancestry [14, 31]. Evidence showed that the OR was highest for the rs6656401 and rs3818361AA haplotype compared to the GG haplotype (OR=1.22, *P*= 3.10E-10) [14]. Lambert et al. recently conducted a large, two-stage meta-analysis of AD GWAS in individuals of European ancestry [3]. They identified CR1 rs6656401 and rs3818361 polymorphisms to be significantly associated with AD reaching genome-wide significance with *P*=5.70E-24 and 5.40E-14 [3]. We previously analyzed rs6656401 polymorphism in Asian and European populations. We did not identify significant heterogeneity [32]. We identified significant association between rs6656401 polymorphism and AD with *P*=1.82E-26 [32]. We further performed a subgroup analysis in East Asian population. We did not identify significant heterogeneity and found significant association between

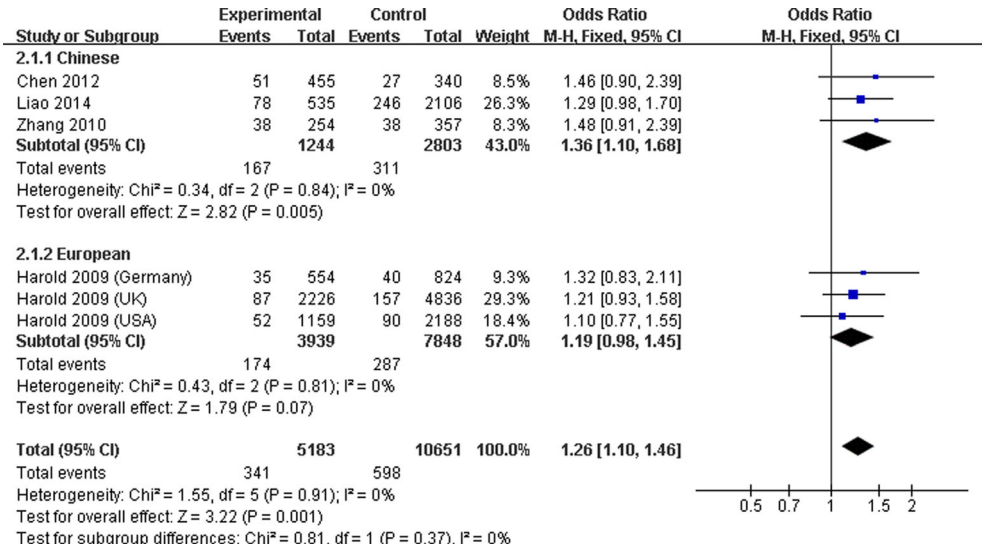

Fig. 2 The forest plot for the meta-analysis of the association between rs3818361 and AD using a recessive genetic model

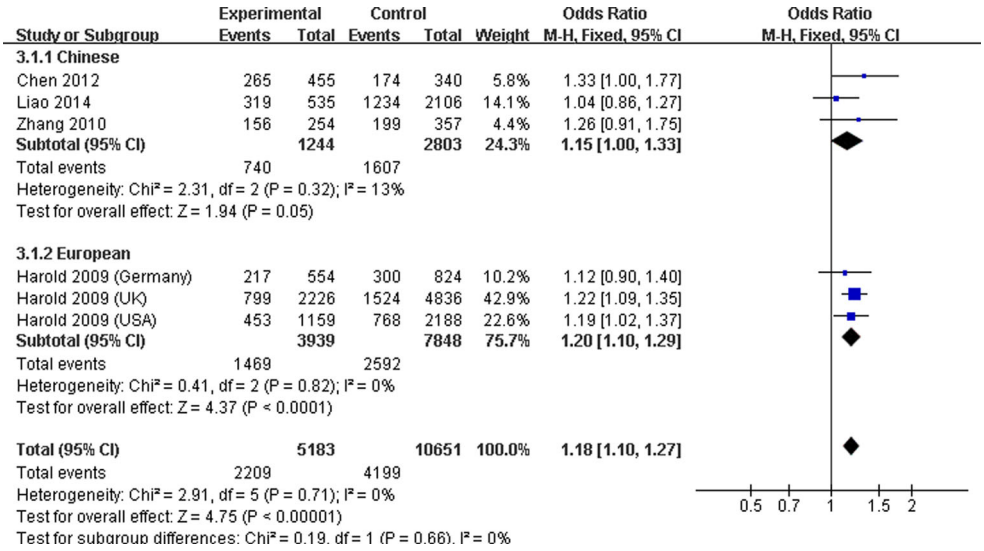

Fig. 3 The forest plot for the meta-analysis of the association between rs3818361 and AD using a dominant genetic model

rs6656401 polymorphism and AD in East Asian population [32].

In addition to the rs6656401 and rs3818361 polymorphisms, we previously analyzed PICALM rs3851179, BIN1 rs744373, and CLU rs11136000 and rs2279590 polymorphisms [1, 6–9]. We found that there was no significant genetic heterogeneity of these polymorphisms in Asian and European populations. We further analyzed relatively large-scale samples and reported significant association between these common variants and AD in Asian populations [1, 6–9].

Our study also has some limitations. In our research, we performed a publication bias analysis. However, it cannot adjust all the biases. Sampling bias and geographical bias analyses may be very helpful. Future studies are required to replicate our findings. In summary, our findings indicate that the effect of CR1 rs3818361 polymorphism on AD risk in Chinese cohorts is consistent with the increased risk observed in European AD cohorts. To our knowledge, this is the first study to show significant association between rs3818361 polymorphism and AD in Chinese population by a meta-analysis method.

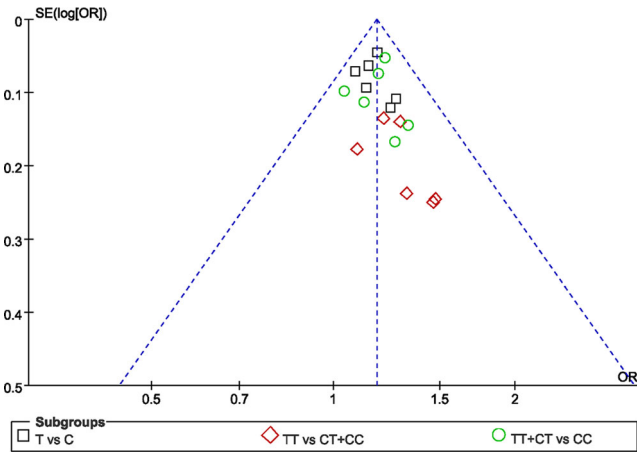

Fig. 4 The funnel plots for publication bias analysis of the selected studies investigating the association between rs3818361 and AD

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Conflict of Interest The authors declare no conflict of interest.

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