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PICALM rs3851179 Variant Confers Susceptibility to Alzheimer's Disease in Chinese Population

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Abstract The association between PICALM rs3851179 variant and Alzheimer's disease (AD) has been well established by previous genome-wide association studies (GWAS) and candidate gene studies in European population. Recent studies investigated the association between PICALM rs3851179 and AD susceptibility in Chinese population. However, these studies reported consistent and inconsistent results. Here, we selected 9435 samples including 3704 AD cases and 5731 controls from previous studies and evaluated this association using a meta-analysis method for additive model. We did not observe significant genetic heterogeneity in Chinese population. Our results indicate significant association between PICALM rs3851179 and AD in Chinese population. The sensitivity analysis indicates that the association between rs3851179 and AD did not vary substantially. The regression analysis suggests no significant publication bias. In summary, this updated meta-analysis highlights the involvement of PICALM rs3851179 variant in Alzheimer's disease susceptibility in Chinese population.

Keywords Alzheimer's disease · Genome-wide association study · PICALM · rs3851179 · Chinese population

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease in the elderly population [1, 2]. It is reported that genome-wide association studies (GWAS) have been widely used to investigate the pathogenesis of AD and have yielded important new insights into the genetic mechanisms of AD [1, 3–5]. In 2009, the PICALM rs3851179 variant was originally identified to be significantly associated with AD in European population ($P = 1.30E-09$) [6]. Meanwhile, the potential association of rs3851179 with AD was also widely investigated in Chinese populations.

In 2011–2012, Yu, Li and Chen et al. analyzed 609, 1065, and 812 Chinese samples and reported no significant association between rs3851179 and AD [7–9]. In 2013, we conducted a pooled analysis of these three studies and still did not identify significant association using both genotype and allele tests [10].

In 2014, Wang et al. evaluated this association using 1509 individuals comprising two independent Chinese case-control cohorts including the cohort from Southwest China (333 AD patients and 334 cognitively healthy controls) and the cohort from East China (416 AD patients and 426 cognitively healthy individuals) [11]. In the Southwest China population, they identified that rs3851179 was significantly associated with AD [11]. They further identified significant association between rs3851179 and AD by a meta-analysis of Asian populations (Chinese and Japanese populations) [11].

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In 2015, Xiao et al. selected 459 Chinese sporadic AD patients and 751 Chinese cognitively normal controls [12]. They did not report any significant association of rs3851179 with AD ($P = 0.194$ and 0.177) [12]. In 2015, Jiao et al. screened 58 SNPs using 229 AD cases and 318 controls from mainland China [13]. Their results show no association between rs3851179 and AD with $P = 0.413$ [13].

In summary, previous and recent studies reported consistent and inconsistent results about the association between rs3851179 and AD in Chinese populations. It is still unclear whether rs3851179 contributes to AD susceptibility in Chinese population. Here, we performed an updated meta-analysis to evaluate the association between rs3851179 and AD using 9435 samples from previous studies.

Materials and Methods

Comprehensive Literature Search

We conducted a comprehensive literature search in four databases including the PubMed (http://www.ncbi.nlm.nih.gov/pubmed), AlzGene (http://www.alzgene.org/), China National Knowledge Infrastructure (CNKI, http://www.cnki.net/), and Google Scholar (https://scholar.google.com/) databases. We selected all possible studies with key words "Alzheimer's disease," "PICALM," and "China or Chinese." The literature search was updated on January 2, 2016. More detailed information about the inclusion and exclusion criteria is described in the following inclusion and exclusion criteria section.

Inclusion and Exclusion Criteria

The inclusion criteria include the following: (1) the selected studies must use a case-control design, (2) the selected studies must evaluate the association between rs3851179 and AD, (3) the selected studies must provide the number of rs3851179 genotypes or sufficient data to calculate the number of rs3851179 genotypes, or (4) the selected studies must provide an odds ratio (OR) with a 95 % confidence interval (CI) or sufficient data to calculate the OR and a 95 % CI. Any study that does not meet the inclusion criteria above is excluded.

Data Extraction

We extracted (1) the name of the first author, (2) the year of publication, (3) the population, (4) the numbers of AD cases and controls, (5) the genotype numbers of rs3851179 in cases and controls, and (6) the OR with 95 % CI or, if not provided, calculated the OR and 95 % CI.

Genetic Model

We used the additive genetic model to evaluate the association between rs3851179 and AD: the A allele versus the G allele.

Hardy-Weinberg Equilibrium Test

We evaluate the Hardy-Weinberg equilibrium (HWE) of rs3851179 in controls for each study using a chi-square test, which was conducted using R (http://www.r-project.org/). The significance threshold is 1.00E-03. A HWE test P value less than 1.00E-03 indicates significant deviation from the HWE.

Heterogeneity Test

The heterogeneity test was conducted using both Cochran's Q statistic and $I^2 = {}^{(Q-(k-1))}/_{Q} \times 100\%$ [14]. Q statistic approximately follows a χ^2 distribution with k-1 degrees of freedom (k stands for the number of studies for analysis). The P value from Cochran's Q statistic <0.1 and $I^2 > 50\,\%$ indicate significant heterogeneity [14, 15].

Meta-analysis

If there was no significant heterogeneity, the pooled OR was calculated by the fixed effect model (Mantel-Haenszel). Otherwise, it is calculated by random-effects (DerSimonian-Laird). The significance of OR was determined using the Z test. All statistical methods in meta-analysis were performed using the RevMan (v.5.1) and R (http://www.r-project.org/).

Sensitivity and Publication Bias Analyses

The relative influence of each study on the pooled OR and significance were evaluated by omitting each study at a time. We used the funnel plot to evaluate the potential publication bias [16]. A regression based approach proposed by Egger is used to test for publication bias to provide statistical evidence [17]. The significance level was 0.01. All statistical tests were computed using R (http://www.r-project.org/).

Results

Comprehensive Literature Search

We got 14, 2, 2, and 3 articles from PubMed, AlzGene, CNKI, and Google Scholar databases, respectively. In the end, we excluded the overlapping studies and finally selected ten articles including 11 studies for the following meta-analysis. More detailed information is described in Fig. 1. The main characteristics of the included studies are described in Table 1.

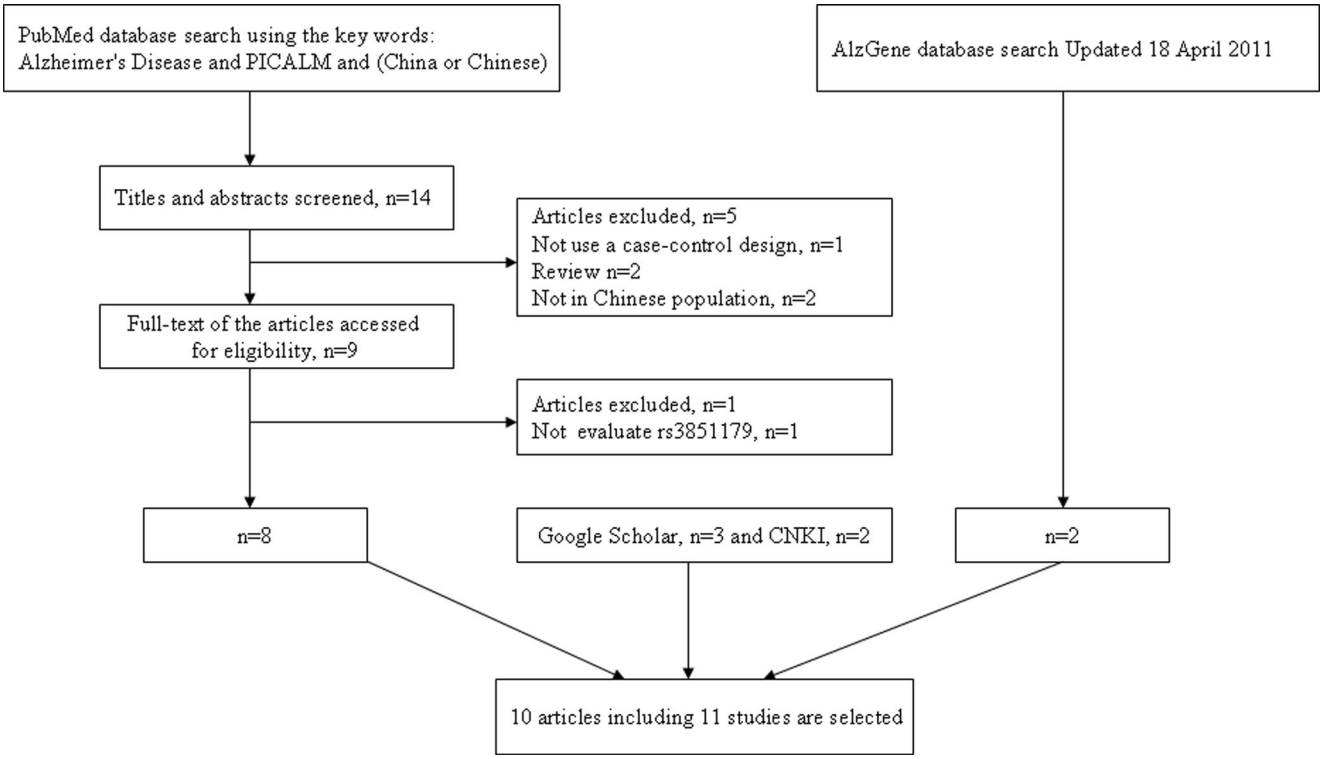

Fig. 1 Flow chart of meta-analysis for exclusion or inclusion of individual articles

HWE, Heterogeneity, and Meta-analysis

With the significance level $P < 1.00E-03$, we do not identify significant deviation from the HWE (a HWE P value less than 1.00E-03). The heterogeneity test showed no significant genetic heterogeneity of rs3851179 polymorphism in Chinese population with $P = 0.55$ and $I^2 = 0\,\%$. We calculated the overall OR by the fixed effect model. Our results showed significant association between rs3851179 and AD with $P = 5.20E-03$, OR = 0.92, and 95 % CI 0.86–0.97. Detailed results are described in Fig. 2.

Sensitivity Analysis and Publication Bias Analysis

Using sensitivity analysis, we identified that the association between rs3851179 and AD did not vary substantially by excluding any one study (Table 2).

The funnel plot is symmetrical inverted funnel (Fig. 3). The regression analysis provides statistical

Table 1 Eleven selected studies investigating the association between rs3851179 and AD

Study	Population	Case #	Control #	HWE in control	Case genotypes			Control genotypes		
					AA	AG	GG	AA	AG	GG
Chen 2012 [9]	South China	248	406	0.91	77	210	170	56	163	122
Ding 2012 [27]	South China	266	343	0.88	9	19	23	28	100	84
Hui 2014 [28]	Northern China	415	426	0.60	34	139	75	61	186	159
Jiao 2015 [13]	South China	229	318	NA	NA	NA	NA	NA	NA	NA
Li 2011 [8]	South China	51	212	0.0014	55	258	161	74	321	196
Liao 2014 [29]	South China	239	207	1	69	250	214	273	856	673
Liu 2014 [30]	Southwest China	333	334	0.78	23	133	83	41	100	66
Wang 2014 [11]	East China	533	1802	0.22	55	198	162	57	214	155
Wang 2014 [11]	Southwest China	474	591	0.0035	54	143	136	46	190	98
Xiao 2015 [12]	South China	459	751	NA	NA	NA	NA	NA	NA	NA
Yu 2011 [7]	Northern China	457	341	0.64	26	126	114	44	164	135
All	China	3704	5731							

NA not publicly available, *HWE* Hardy-Weinberg equilibrium

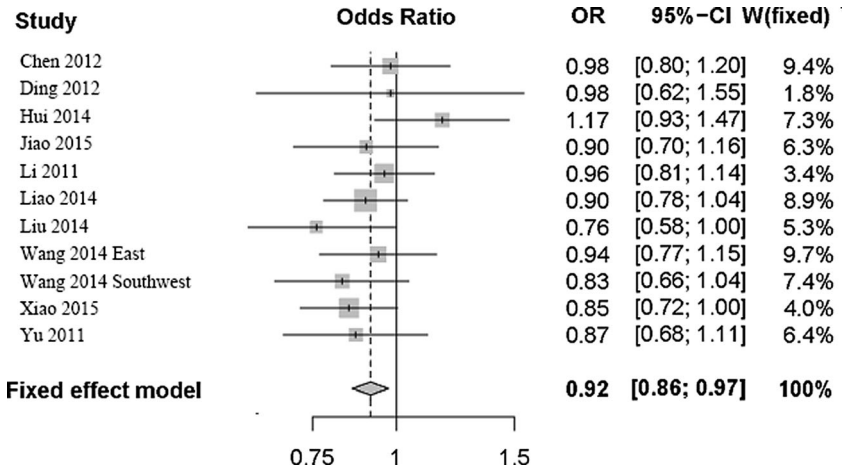

Fig. 2 The forest plot for the meta-analysis of the association between rs3851179 and AD using the additive genetic model

evidence, suggesting no significant publication bias for additive model (regression $P = 0.94$).

Discussion

The association between PICALM rs3851179 and AD has been well established by previous GWAS and candidate gene studies in European population. Meanwhile, the potential role of PICALM in aging and AD was widely investigated. It is reported that PICALM is associated with an earlier age at midpoint of cognitive decline [18]. It is well known that the β-amyloid (Aβ) peptides are involved in the pathogenesis of AD [19]. PICALM could regulate amyloid precursor protein internalization and subsequent Aβ generation [20]. In the hippocampus, it is reported that PICALM knockdown can decrease soluble and insoluble Aβ levels and amyloid plaque load and PICALM overexpression can increase Aβ levels and amyloid plaque load [20].

Evidence shows that PICALM rs3851179 polymorphism plays a significantly protected role against rapid AD progression [21]. Parikh et al. evaluated the association between rs3851179 and PICALM expression in three cell lines including microvessels, neurons, and astrocytes [22]. The results showed that PICALM was expressed robustly in microvessels and moderately in other cell types [22]. The rs3851179 protective allele (A) is associated with modestly increased PICALM expression [22].

Recently, Zhao et al. identified reduced expression of PICALM in AD and found that PICALM deficiency diminished Aβ clearance across the murine blood-brain

Table 2 Sensitivity analysis with each study omitted in meta-analysis

Study omitted	Heterogeneity test		Meta-analysis		
	I^2 (%)	P	OR	95 % CI	P
None	0	0.55	0.92	0.86–0.97	0.0052
Chen 2012 [9]	0	0.52	0.91	0.85–0.97	0.0041
Ding 2012 [27]	0	0.47	0.91	0.86–0.97	0.0050
Hui 2014 [28]	0	0.91	0.90	0.84–0.96	0.0010
Jiao 2015 [13]	0	0.46	0.92	0.86–0.98	0.0075
Li 2011 [8]	0	0.49	0.91	0.85–0.97	0.0049
Liao 2014 [29]	0	0.46	0.92	0.86–0.99	0.0162
Liu 2014 [30]	0	0.65	0.93	0.87–0.99	0.0165
Wang 2014 [11]	0	0.46	0.91	0.86–0.97	0.0062
Wang 2014 [11]	0	0.53	0.92	0.87–0.98	0.0142
Xiao 2015 [12]	0	0.54	0.93	0.87–0.99	0.0254
Yu 2011 [7]	0	0.47	0.92	0.86–0.98	0.0094

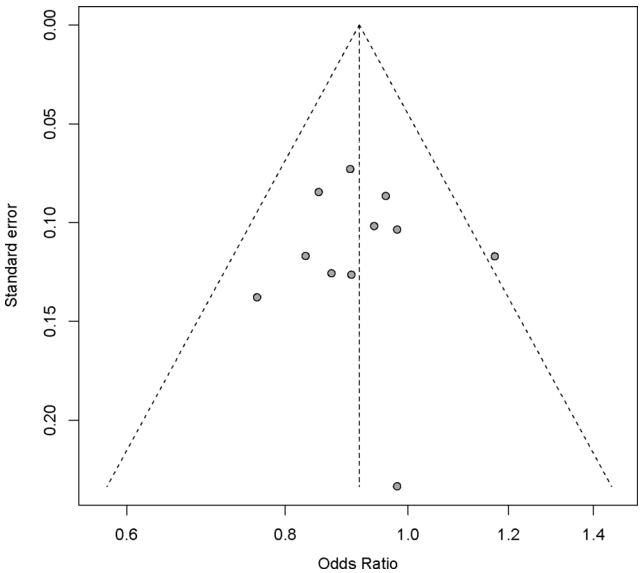

Fig. 3 The funnel plots for publication bias analysis of the selected studies investigating the association between rs3851179 and AD using the additive genetic model. The *x-axis* stands for the ORs and the *y-axis* is the standard error for each of the 11 studies. A linear regression based approach proposed by Egger et al. is used to evaluate the asymmetry of the funnel plot

barrier (BBB) and accelerated Aβ pathology [23]. By PICALM re-expression, this situation will be further reversed [23]. Using inducible pluripotent stem cell-derived human endothelial cells, Zhao et al. further showed that rs3851179 protective allele (A) regulated increased PICALM expression and enhanced Aβ clearance [23]. They conclude that PICALM regulates Aβ BBB transcytosis and clearance, which has implications for Aβ brain homeostasis and clearance therapy [23]. Moreau et al. show that PICALM modulates autophagy activity and tau accumulation [24].

Evidence also shows that in case-control association studies, a deviation from HWE in cases may indicate a genetic association. Here, HWE test was only used in controls but not AD cases [25, 26]. Until recently, there are several studies evaluating the potential association between rs3851179 and AD in Asian or Chinese populations, such as three studies from Yu, Li, and Chen et al. [7–9], our previous studies using the pooled samples from these three studies above [10, 14], Wang et al. [11], Xiao et al. [12], and Jiao et al. [13]. There is a major difference between our study and previous studies. This difference is that all above studies evaluate the association between rs3851179 and AD. However, all these studies reported consistent and inconsistent association results.

Here, based on the inconsistent results reported by recent studies in Chinese population, we performed an updated meta-analysis using 7678 individuals from Chinese population. Our results showed no significant genetic heterogeneity of rs3851179 polymorphism in Chinese population. Meta-analysis using the fixed effect model further showed significant association between rs3851179 and AD in Chinese population. The sensitivity analysis indicates that the association between rs3851179 and AD did not vary substantially. The regression analysis suggests no significant publication bias using the additive model. In summary, this updated meta-analysis highlights the involvement of PICALM rs3851179 variant in Alzheimer's disease susceptibility in Chinese population.

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Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflicts of interest.

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