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Association of the CR1 polymorphism with late-onset Alzheimer's disease in Chinese Han populations: A meta-analysis

Chunhui Jin[a], Weidong Li[a,b], Jianmin Yuan[a], Wenwei Xu[a], Zaohuo Cheng[a,*]

[a] Wuxi Mental Health Center, 156 Qian Rong Road, Wuxi, 214151, PR China
[b] Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders, Ministry of Education, Shanghai Jiao Tong University, 800 Dong Chuan Road, Shanghai, 200240, PR China

HIGHLIGHTS

- The association between rs6656401 and LOAD in Chinese populations was analyzed using meta-analysis.
- The A allele of rs6656401 was associated with an increased risk of LOAD in Chinese Han populations.
- Chinese populations from different geographical areas may exhibit genetic heterogeneity of LOAD.

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ABSTRACT

It is well known that genetic variants play a critical role in the pathogenesis of Alzheimer's disease (AD). In 2009, a genome-wide association study (GWAS) demonstrated that a single nucleotide polymorphism (SNP), rs6656401, in complement receptor 1 (CR1) is significantly associated with late-onset Alzheimer's disease (LOAD) in Caucasian population. Subsequently, other researchers have attempted to validate this finding in Chinese Han populations. However, these findings in Chinese Han populations have produced both negative and positive results. To derive a more precise estimation for the relationship, we performed the present meta-analysis by analyzing three published association studies involving CR1 SNP rs6656401 through the use of the RevMan (v.5.1) program. Pooled odds ratios (ORs) were calculated for allele contrasts (A vs. G) and a dominant model [(AA + AG) vs. GG] in three studies that included 1019 cases and 1080 controls, respectively. The statistical results showed a significant difference between patients and controls for the A allele of CR1 SNP rs6656401 ($P = 0.005$). In addition, carriers of the A allele (AA + AG) of rs6656401 had a 1.69-fold increased risk for LOAD compared with non-carriers (GG) ($P = 0.01$). In conclusion, despite there are some limitations, this meta-analysis indicates that the A allele of the CR1 SNP rs6656401 is significantly associated with LOAD susceptibility in Chinese Han populations.
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1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder and leads to progressive memory loss and cognitive dysfunction in the elderly [15]. AD cases are most late-onset, and although a specific gene has not been identified as the direct cause of late-onset Alzheimer's disease (LOAD), important genetic factors are associated with the development of LOAD [17]. To date, the $\varepsilon 4$ allele of the apolipoprotein E gene (APOE) is the only well-established susceptibility gene for LOAD [2,5], but it is neither necessary nor sufficient for AD. Recently, genetic variants other than the APOE $\varepsilon 4$ allele, including complement receptor 1 (CR1), have been associated with increased LOAD risk in different ethnic populations via genome-wide association studies (GWAS) approach [6,11,16].

CR1 is a multifunctional polymorphic glycoprotein that is located at locus 1q32 on chromosome 1, and is a member of the regulators of complement reactivation (RCA) family. The extracellular portion of CR1 can be divided into 30 complement control protein repeats (CCPs), each comprised of 59–75 amino acids [10,13]. It has been postulated that CR1 is a key factor for AD pathogenesis due to its role in regulating complement activity by acting as a receptor of complement C3b protein [1]. The CR1-mediated phagocytosis may be involved in the clearance of amyloid plaques, which are an important component in AD neuropathology [18]. After the first association study was reported, several researchers attempt to replicate the finding in different populations. Thus far, three independent studies have been performed in Chinese Han populations. Li et al. failed to verify the association of SNP rs6656401 within CR1 for sporadic AD [12], but Zhang et al. [19] and Chen

* Corresponding author. Tel.: +86 510 83030359; fax: +86 510 83012201.
E-mail address: chengzaohuo@126.com (Z. Cheng).

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Table 1
Characteristics of case–control studies of association between CR1 rs6656401 polymorphism and LOAD included in the meta-analysis.

Study	Subjects	*n*	Genotype (*n*, %)			Allele (*n*, %)		Genotyping	LOAD diagnosis
			AA	AG	GG	A	G		
Zhang et al. [19]	LOAD	254	2 (0.8)	14 (5.5)	238 (93.7)	18 (13.5)	490 (96.5)	MALDI-TOF MS	NINCDS-ADRDA
	Control	357	0 (0.0))	9 (2.5)	348 (97.5)	9 (1.3)	705 (98.7)		
Li et al. [12][a]	LOAD	307	1 (0.3)	2 (0.7)	304 (99.0)	4 (0.7)	610 (99.3)	PCR-RFLP	DSM-IV and NINCDS-ADRDA
	Control	380	1 (0.3)	5 (1.3)	374 (98.4)	7 (0.9)	753 (99.1)		
Chen et al. [3][b]	LOAD	458	2 (0.4)	49 (10.7)	407 (88.9)	53 (5.8)	863 (94.2)	MALDI-TOF MS	NINCDS-ADRDA
	Control	343	0 (0.0)	24 (7.0)	319 (93.0)	24 (3.5)	662 (96.5)		

Note:
[a] There are 167 early-onset Alzheimer's disease (EOAD) patients and 211 controls in total participants (474 cases and 591 controls).
[b] Genotyping success rate in LOAD patients and controls is 99.1% and 98.0%, respectively.

et al. [3] obtained consistent results with the previous GWAS analysis.

Thus, to reconcile these conflicting findings, in the present study we assessed the association between the A allele of CR1 SNP rs6656401 and LOAD susceptibility in Chinese Han populations using a meta-analysis approach with the RevMan (v.5.1) program.

2. Materials and methods

2.1. Literature search

The literature included in the meta-analysis was selected by searching the MEDLINE database update to May 2012 with the key words "*Alzheimer's disease*", "*Complement receptor 1*" and "*Chinese population*". All references in these studies were examined to identify additional work not indexed by MEDLINE. We only included published articles written in English.

2.2. Inclusion criteria

Studies included in the current meta-analysis had to meet the following criteria: (1) the study had to be focused on SNP rs6656401 within CR1 using original data and be published in a peer-reviewed journal; (2) the study had to provide sufficient data to calculate the odd ratio (OR), confidence interval (CI) and *P* value; (3) the study had to specify the genotyping methods or provide appropriate references; and (4) all clinical diagnoses of LOAD patients had to fulfill the criteria of the National Institute of Neurological and Communicative Disorders Association (NINCDS-ADRDA), and non-AD types of dementia, familial AD or other significant illness had to be excluded.

2.3. Statistical analyses

All statistical analyses were performed using the RevMan (v.5.1) program (http://www.cochrane.org/revman). To evaluate the association between polymorphism rs6656401 within the CR1 gene and LOAD, the significance of pooled OR was determined using the *Z* test. The *Q*-test and the I^2 statistic were used to investigate the degree of heterogeneity among the studies. The random effect model or fixed effect model was chosen to calculate the subtotal OR and 95% CI based on whether there was significant difference in heterogeneity among these studies. If the *Q*-test resulted in a *P*-value > 0.05, which indicated a lack of heterogeneity, the pooled OR estimate of each study was calculated by the fixed effect model (the Mantel–Haenszel method) [14]. If the *Q*-test resulted in a *P*-value < 0.05, the pooled OR estimate of each study was calculated by the random effect model (the DerSimonian and Laird method) [4].

3. Results

The detailed characteristics of the included studies are presented in Table 1. In the current meta-analysis, we evaluated whether the A allele of rs6656401 was associated with LOAD susceptibility and whether being a carrier of the A allele of rs6656401 increased the risk for LOAD. No significant difference in heterogeneity among the studies was observed in this meta-analysis [I^2 = 44% and *P* = 0.17 for A allele; I^2 = 34% and *P* = 0.22 for (AA + AG) genotype]. Thus, the fixed effect model was used to calculate the pooled OR and 95% CI. The statistical results indicated that the A allele of CR1 SNP rs6656401 is a risk factor for LOAD in Chinese Han populations (pooled OR = 1.76, 95% CI = 1.19–2.60, *P* = 0.005, Table 2 and Fig. 1). Moreover, carriers of the A allele (AA + AG) of rs6656401 had a 1.69-fold increased risk for LOAD compared with non-carriers (GG) (pooled OR = 1.69, 95% CI = 1.13–2.54, *P* = 0.01, Table 2 and Fig. 2).

4. Discussion

As mentioned above, the complement system is a factor which may be of particular importance in AD. Amyloid-β (Aβ) plaques accumulated in the AD brain are able to activate the classical complement pathway in the absence of antibodies by binding to specific sites within the collagen-like domain of C1q, a subunit of the first component of complement [7]. It has been shown that variants within the CR1 locus are strongly associated with episodic memory decline [9] and may play an important role in the clearance of Aβ plaques [18]. Therefore, previous studies suggested that CR1 might participate in the pathogenesis of AD. Although a GWAS study implicated CR1 SNP rs6656401 as a risk factor for LOAD susceptibility in a Caucasian population (OR = 1.21, 95% CI = 1.14–1.29, $P = 3.7 \times 10^{-9}$ for combined data) [11], whether the A allele of rs6656401 within CR1 is a genetic risk factor for LOAD susceptibility in a Chinese Han population remains controversial. Thus, the current meta-analysis was conducted to collectively analyze the comparative studies, thereby enlarging the sample size and statistical power to obtain a more definitive conclusion.

Table 2
Summary ORs and 95% CI of CR1 rs6656401 polymorphism and LOAD.

Analysis model	Comparisons	OR	95% CI	*P* value
A vs. G	Total (3)	1.76	1.19–2.60	0.005
(AA + AG) vs. GG	Total (3)	1.69	1.13–2.54	0.01

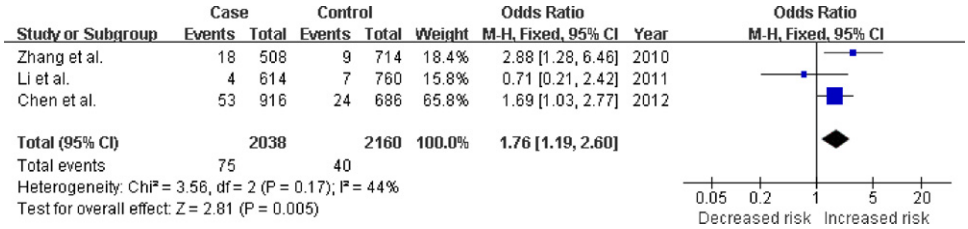

Fig. 1. Forest plot for the association between the A allele of rs6656401 within CR1 and LOAD risk. Each study is shown by the point estimate of OR with 95% CI.

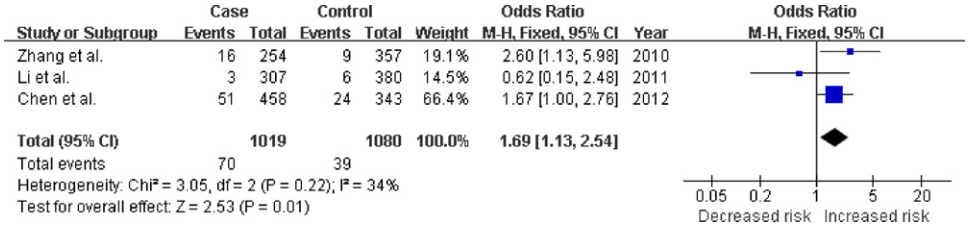

Fig. 2. Forest plot for the association between (AA + AG) combined genotype of rs6656401 within CR1 and LOAD risk. Each study is shown by the point estimate of OR with 95% CI.

The present findings suggest that CR1 SNP rs6656401 confers a LOAD susceptibility in a Chinese Han population; this finding is consistent with those reported by Lambert et al. [11]. However, some limitations in the current meta-analysis should be considered. First, the number of current studies on SNP rs6656401 in Chinese Han cohorts is relatively small. A previous meta-analysis indicated that genetic variants within the CR1 locus were associated with AD in Caucasians but not in other ethnic population [8]. The participants in current meta-analysis are from Shanghai, Shandong, and Hong Kong. The inconsistent results of these studies suggested that Chinese populations from differently geographical areas might also exhibit genetic heterogeneity of LOAD. Therefore, investigations involving more subjects on a large scale and a more reliable meta-analysis are necessary. Second, it is well known that AD is a neurodegenerative disease with a very complex pathogenesis; in addition to genetic factors, environmental factors may also modify the effects of CR1 SNP in Chinese AD. Last but not least, rs6656401 is located in the intronic region of the CR1 gene. Although the SNP may indirectly influence the function of the protein encoded by CR1 through linkage disequilibrium or affect gene expression through influencing alternative splicing of RNA, the genetic SNP in the intronic region does not affect the sequence of amino acids and protein structure of the target gene. Thus, the functional locus and specific functions of the CR1 polymorphism for LOAD require further study to acquire more direct evidence.

5. Conclusion

Taken together, we provide important evidence to support a highly significant association between the A allele of CR1 SNP rs6656401 and an increased risk for the development of LOAD in Chinese Han populations. Nevertheless, the functional significance of the CR1 polymorphism is currently unknown. To better understand the association between the CR1 polymorphism and the mechanism for AD, further research with larger cohorts should be performed, and it is important to examine how the CR1 variants interact with other risk loci to influence LOAD risk.

Conflict of interest

We have no any actual or potential conflict of interest, including any financial personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, our work.

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