Mol Neurobiol (2015) 52:1–7
DOI 10.1007/s12035-014-8834-2

Analyzing 54,936 Samples Supports the Association Between CD2AP rs9349407 Polymorphism and Alzheimer's Disease Susceptibility

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Received: 19 June 2014 / Accepted: 23 July 2014 / Published online: 5 August 2014

Abstract The CD2-associated protein (CD2AP) rs9349407 polymorphism was first identified to be significantly associated with Alzheimer's disease (AD) in European ancestry by genome-wide association studies (GWAS). However, the following studies reported no association in Chinese, Japanese, African-American, Canadian, and European populations. We think that these negative results may have been caused by either relatively small sample sizes compared with those used for the previous GWAS in European ancestry or the genetic heterogeneity of the rs9349407 polymorphism in different populations. Here, we reevaluated this association using the relatively large-scale samples from 15 previous studies (N= 54,936; 23,777 cases and 31,159 controls) by searching the PubMed, AlzGene, and Google Scholar databases. Using an additive genetic model, we did not identify a significant heterogeneity among the 15 studies. Using meta-analysis, we observed a significant association between the rs9349407 polymorphism and AD with P=8.78E-07, odds ratio (OR)= 1.08, 95 % confidence interval (CI) 1.05–1.12. To our knowledge, this is the first meta-analysis to investigate the

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Electronic supplementary material The online version of this article (doi:10.1007/s12035-014-8834-2) contains supplementary material, which is available to authorized users.

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association between rs9349407 polymorphism and AD in East Asian, American, Canadian, and European populations. Our analysis further supports previous findings that the CD2AP rs9349407 polymorphism contributes to AD susceptibility. We believe that our findings will be very useful for future genetic studies on AD.

Keywords CD2AP rs9349407 polymorphism · Alzheimer's disease · Genome-wide association studies · Meta-analysis

Introduction

Alzheimer's disease (AD) is a complex and the most common neurodegenerative disease in the elderly [1, 2]. It is estimated that genetic factors cause about 60–80 % of AD risk [3]. However, the specific genes influencing AD are largely unknown. Much effort has been put into identifying the genetic determinants of this disease. Genome-wide association studies (GWAS) have recently provided rapid insights into the genetics of AD and identified some common AD susceptibility variants or genes, which include complement receptor 1 (CR1); bridging integrator 1 (BIN1); clusterin (CLU); phosphatidylinositol binding clathrin assembly protein (PICALM); membrane-spanning 4-domains, subfamily A, member 4 (MS4A4)/membrane-spanning 4-domains, subfamily A, member 6E (MS4A6E); CD2-associated protein (CD2AP); CD33 molecule (CD33); EPH receptor A1 (EPHA1); and ATP-binding cassette transporter A7 (ABCA7) [4].

Two large-scale AD GWAS identified CD2AP rs9349407 polymorphism to be significantly associated with AD susceptibility in European ancestry with P=8.6E-09, odds ratio (OR)= 1.11, 95 % confidence interval (CI) 1.07–1.15 [5, 6]. These two studies show that the carriers of rs9349407 risk variant have an about 11 % additional increased risk for AD [5, 6].

Considering the different genetic architecture, AD incidence rates, and environmental exposures across different ethnic populations, it is important to investigate whether rs9349407 polymorphism is associated with AD risk in other ethnic populations. The following studies also investigated this finding in Chinese, Japanese, African-American, European-American, European, and Canadian populations (Table 1). However, these studies reported consistent and inconsistent results (Table 1).

Recent studies investigated the mechanisms of rs9349407 in AD pathogenesis and indicated that rs9349407 was associated with neuritic plaque burden [7]. Based on recent findings above, we hypothesized that these negative results may have been caused by either relatively small sample sizes compared with those used for the previous GWAS in European ancestry or the genetic heterogeneity of the rs9349407 polymorphism in different populations. Here, we reevaluated this association using the relatively large-scale samples from 15 previous studies (N=54,936; 23,777 cases and 31,159 controls) by searching the PubMed, AlzGene, and Google Scholar databases.

Methods and Materials

Literature Search

Guiyou Liu searched the PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and AlzGene (http://www.alzgene.org/) databases to select all possible studies with key words including "Alzheimer's disease" and "CD2AP". The literature search was updated on June 10, 2014. Meanwhile, we used the Google Scholar (http://scholar.google.com/) to query the articles citing the studies and all references in these studies identified by the PubMed and AlzGene databases. We selected only published articles written in English.

Inclusion Criteria

We selected the studies meeting the following criteria: (1) the study was conducted by a case-control design; (2) the study evaluated the association between rs9349407 polymorphism and AD; (3) the study provided the numbers of rs9349407 genotypes or (4) the study must provide sufficient data to calculate the numbers of rs9349407 genotypes or (5) the study provided an OR with 95 % CI as well as the P value or (6) the study must provide sufficient data to calculate the OR and 95 % CI (Fig. 1).

Data Extraction

Guiyou Liu extracted the following information from each study: (1) the name of the first author, (2) the year of publication, (3) the population and ethnicity, (4) the numbers of AD cases and controls, (5) the genotype numbers of rs9349407 polymorphism in cases and controls, (6) the genotyping platform, (7) the OR with 95 % CI or (8) sufficient data to calculate the OR and 95 % CI, and (9) the inclusion criteria for Alzheimer's disease patients and controls. All relevant calculations were completed using the program R (http://www.r-project.org/).

Quality Evaluation

Here, the criteria proposed by Clark and Baudouin were used to evaluate the quality of selected genetic association studies [8]. This scoring system consists of ten components. A component of the criteria was scored as 1 if present or 0 if absent. A final quality score was obtained by summing each component, resulting in a scoring range of 0–10 for case-control association studies [8]. Selected studies were scored as "good"

Table 1 The selected studies investigating the association between rs9349407 polymorphism and AD

Study	Year	Source	Ethnicity	Case no.	Control no.	*P* value	Genotyping platform
Tan [20]	2013	China	East Asian	612	612	0.85	TaqMan
Miyashita [21]	2013	Japan	East Asian	891	844	0.38	Affymetrix GeneChip 6.0 and TaqMan
Omoumi [22]	2014	Canada	Canadian	509	433	0.56	TaqMan
Logue [23]	2011	USA	American	513	496	0.86	Illumina 610
Carrasquillo [13]	2011	Jacksonville	American	492	922	0.34	TaqMan
Carrasquillo [13]	2011	Rochester	American	313	1600	0.24	TaqMan
Carrasquillo [13]	2011	Autopsy	American	285	100	0.92	TaqMan
Carrasquillo [13]	2011	Norway	European ancestry	324	519	0.13	TaqMan
Carrasquillo [13]	2011	Poland	European ancestry	468	181	0.79	TaqMan
Carrasquillo [13]	2011	ARUK	European ancestry	639	733	0.72	TaqMan
Naj [5]	2011	ADGC—stage 1	European ancestry	8309	7366	1.17E-06	Illumina 660, 610, 550, 300, 370 and 1 M, Affymetrix 500 and 1 M
Naj [5]	2011	ADGC—stage 2	European ancestry	3531	3565	0.12	Illumina 660, 610, 550, 300, 370 and 1 M, Affymetrix 500 and 1 M
Hollingworth [6]	2011	GERAD1	European ancestry	3941	7848	1.2E-02	Illumina 660, 610, 550, 300, 370 and 1 M, Affymetrix 500 and 1 M
Hollingworth [6]	2011	EADI1	European ancestry	2025	5328	9.7E-02	Illumina 660, 610, 550, 300, 370 and 1 M, Affymetrix 500 and 1 M
Hollingworth [6]	2011	deCODE	European ancestry	925	612	4.2E-02	Illumina 660, 610, 550, 300, 370 and 1 M, Affymetrix 500 and 1 M
N=54,936				*n*=23,777	*n*=31,159		

ADGC the Alzheimer's Disease Genetic Consortium, *EADI1* European Alzheimer's Disease Initiative 1, *GERAD1* the Genetic and Environmental Risk in Alzheimer's Disease 1

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 [9]. Two authors performed the quality evaluation independently using the criteria proposed by Clark and Baudouin. A third author adjudicated any differences between the two authors.

Genetic Model

Here, we selected the additive genetic model for further meta-analysis. The CD2AP rs9349407 polymorphism has two alleles including C and G. C is the minor allele. We assume that C

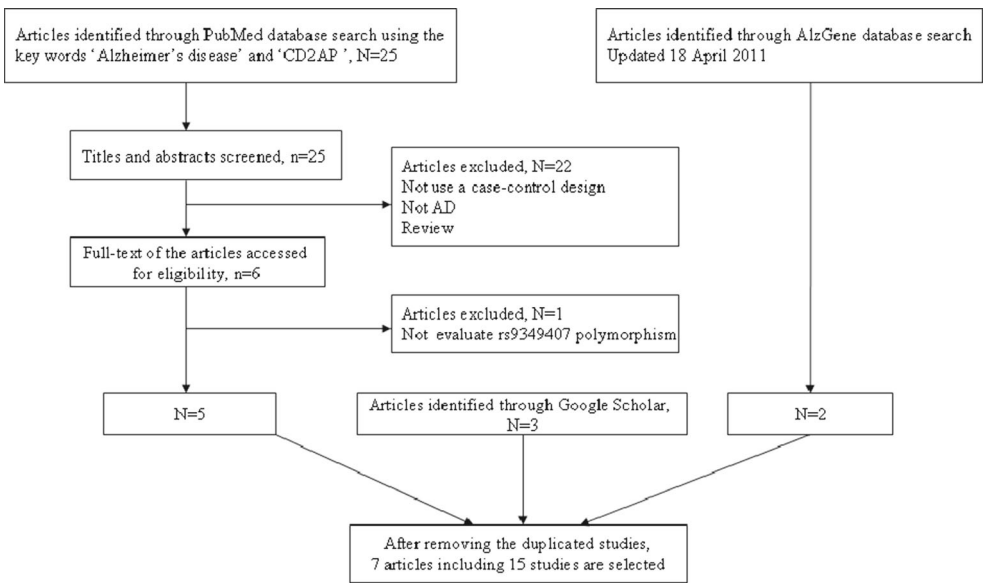

Fig. 1 Flow chart of meta-analysis for exclusion or inclusion of individual articles

is the high-risk allele and G is the lower-risk allele. The additive model can be described as C allele versus G allele [10].

Heterogeneity Test

We evaluated the genetic heterogeneity among the studies included using Cochran's Q test, which approximately follows a χ^2 distribution with k-1 degrees of freedom (k stands for the number of studies for analysis). $I^2 = {}^{(Q-(k-1))}/_{Q} \times 100\%$, which ranges from 0 to 100 %, was also used [11]. Low, moderate, large, and extreme heterogeneity corresponded to 0–25, 25–50, 50–75, and 75–100 %, respectively [11]. The significance levels for heterogeneity are defined to be with $P<0.01$ and $I^2>50$ %.

Meta-Analysis

If there is no significant heterogeneity among the included studies, the pooled OR is calculated by the fixed effect model (Mantel-Haenszel); otherwise, the OR is calculated by random effect model (DerSimonian-Laird). Z test is used to determine the significance of OR. All statistical tests for heterogeneity and meta-analysis were computed using R package for meta-analysis (http://cran.r-project.org/web/packages/meta/index.html).

Sensitivity and Publication Bias Analyses

We evaluated the relative influence of each study by omitting each study at a time. Meanwhile, we used funnel plots to evaluate the potential publication bias [12]. Begg's and Egger's tests were used to evaluate the asymmetry of the funnel plot [12]. The significance level for publication bias test is 0.01.

Results

Literature Search

Twenty-five, two, and three articles were identified through PubMed, AlzGene, and Google Scholar search, respectively. Finally, after excluding those studies with overlapping samples, seven articles including 15 independent studies were included for our following analysis. More detailed information about the inclusion or exclusion of selected studies and quality evaluation is provided in the supplementary materials. The main characteristics of the included studies are described in Table 1.

Heterogeneity Test and Meta-analysis

We evaluated the genetic heterogeneity of rs9349407 polymorphism among the selected studies. We did not identify a significant heterogeneity among these studies with $P=0.098$ and $I^2=33.8$ %. We further calculated the overall OR by the fixed effect model. Our results showed a significant association between rs9349407 polymorphism and AD with $P=$ 8.78E-07, OR=1.08, 95 % CI 1.05–1.12. Detailed results are described in Fig. 2.

Sensitivity Analysis and Publication Bias Analysis

By excluding any one study, we identified that the association between rs9349407 polymorphism and AD did not vary substantially (detailed data not shown). Take Naj et al. (Alzheimer's Disease Genetic Consortium (ADGC)—stage 1) [5], for example, as it includes more sample than other studies. After excluding this study, we did not identify a significant heterogeneity among other studies using the additive model ($P=0.2566$ and $I^2=18$ %). Meta-analysis using the fixed effect model showed a significant association between rs9349407 polymorphism and AD ($P=8.60$E-03, OR=1.05, 95 % CI 1.00–1.10). The funnel plots are symmetrical inverted funnels for models (Fig. 3), suggesting no significant publication bias for the additive model (Begg's test, $P=0.02$ and Egger's test, $P=0.02$).

Discussion

Recent GWAS identified rs9349407 polymorphism to be significantly associated with AD in European ancestry [5, 6]. The following studies investigated this association and reported inconsistent results. We think that these inconsistent results may have been caused by either relatively small sample sizes compared with those used for the previous GWAS in European ancestry or the genetic heterogeneity of rs9349407 polymorphism in different populations.

Shulman et al. investigate whether AD susceptibility loci from GWAS affect neuritic plaque pathology [7]. They performed a candidate polymorphism analysis in a joint clinicopathologic cohort, including 725 deceased subjects from the Religious Orders Study and the Rush Memory and Aging Project, followed by targeted validation in an independent neuroimaging cohort, including 114 subjects from multiple clinical and research centers. Their results indicated that rs9349407 was associated with neuritic plaque burden [7]. This finding enhances the understanding of AD risk factors by relating validated susceptibility alleles to increased neuritic plaque pathology [7].

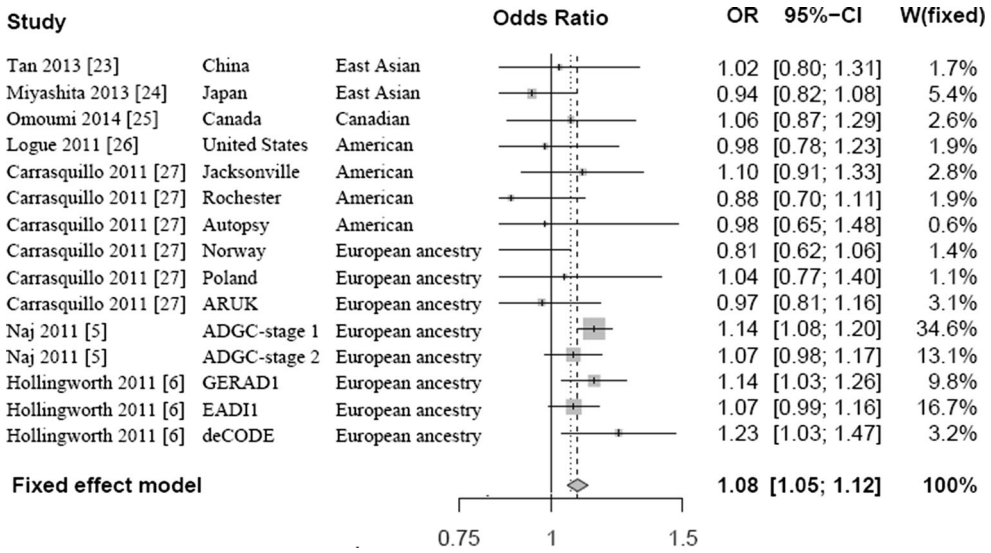

Fig. 2 Forest plot for the meta-analysis of the rs9349407 polymorphism using additive model. *fixed* fixed effect model, *CI* confidence interval

Considering the important role of rs9349407 polymorphism in AD, we reevaluated this association using the relatively large-scale samples from 15 studies. We did not identify a significant heterogeneity of rs9349407 polymorphism pooled populations. We observed a significant association between the rs9349407 polymorphism and AD in pooled populations. The sensitivity analysis and publication bias analysis indicated that our results were robust and no publication bias was observed.

Recently, Carrasquillo et al. performed a meta-analysis to investigate the association between rs9349407 polymorphism and AD. Our study is different from the previous study conducted by Carrasquillo et al. [13]. Carrasquillo et al. used the samples from three articles [5, 6, 13]. Here, we selected seven articles and performed an updated analysis. To our knowledge, this is the first meta-analysis to investigate the association between rs9349407 polymorphism and AD in East Asian, American, Canadian, and European populations. Our analysis further supports previous findings that the rs9349407 polymorphism is associated with AD susceptibility. We believe that our findings will be very useful for future genetic studies on AD.

In addition to the CR1 rs9349407 polymorphism, common variants in another eight AD susceptibility genes were also reported in European population. Interestingly, these variants were successfully replicated by analyzing large-scale dataset, such as PICALM rs3851179, BIN1 rs744373, CLU rs11136000 and rs2279590, ABCA7 rs3764650, and CR1 rs6656401 polymorphisms [4, 11, 14–18]. These results indicate that analyzing relatively large-scale samples is effective to identify the significant association between these common variants and AD.

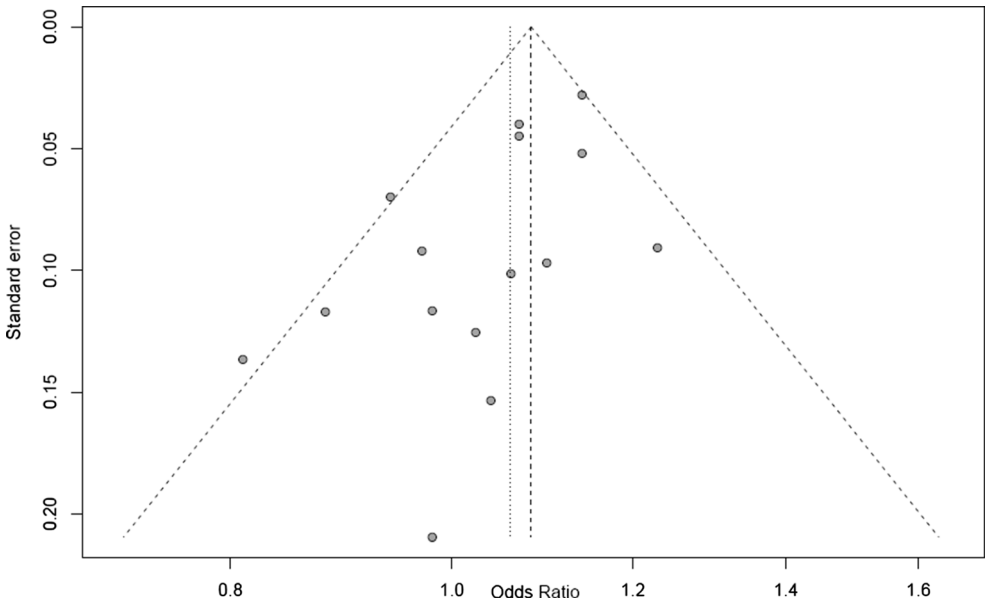

Fig. 3 The funnel plot for publication bias analysis of rs9349407 polymorphism using additive model

Despite these interesting results, there is also a limitation in our study. Here, we investigated the association between CD2AP rs9349407 polymorphism and AD using the additive model. It is reported that most meta-analyses used an additive genetic model [19]. In general, this model performs well when the true underlying genetic model is uncertain [19]. It was also important to analyze the association using dominant model and recessive model [10]. However, the dominant and recessive models required exact genotype numbers of all studies used in our analysis. We attempted to obtain these genotype numbers but were not successful. Future studies using genotype data are required to replicate our findings.

Acknowledgments This work was supported by funding from the National Nature Science Foundation of China (grant numbers 81300945, 31301938, 31200934, 31171219, 81271213, 81070878, 81271214, and 81261120404), the Natural Science Foundation of Guangdong Province, China (No. S2012010008222), and the Science and Technology Innovation Fund of Guangdong Medical College (No. STIF 201101).

Conflict of Interest The authors declare no conflict of interest.

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