Mol Neurobiol (2014) 50:757–764
DOI 10.1007/s12035-014-8670-4

Analyzing Large-Scale Samples Confirms the Association Between the ABCA7 rs3764650 Polymorphism and Alzheimer's Disease Susceptibility

Guiyou Liu · Fujun Li · Shuyan Zhang · Yongshuai Jiang · Guoda Ma · Hong Shang · Jiafeng Liu · Rennan Feng · Liangcai Zhang · Mingzhi Liao · Bin Zhao · Keshen Li

Received: 7 December 2013 / Accepted: 28 February 2014 / Published online: 19 March 2014
© Springer Science+Business Media New York 2014

Abstract Large-scale genome-wide association studies (GWAS) have revealed that the ABCA7 rs3764650 polymorphism (or its proxies, namely rs115550680, rs3752246, and rs4147929) is associated with Alzheimer's disease (AD) susceptibility in individuals of Caucasian ancestry. The following studies have investigated this finding in Chinese (N=633 and N=1,224), Japanese (N=1,735), Korean (N=844), African American (N=5,896), and Canadian (N=1,104) populations. However, these studies reported a weak or negligible association. 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 individuals of Caucasian ancestry or the genetic heterogeneity of the rs3764650 polymorphism (or its proxies) in different populations. Here, we reevaluated the association between rs3764650 and AD using large-scale samples from 18 previous studies (N=79,381—30,590 cases and 48,791 controls) by searching PubMed, AlzGene, and Google Scholar databases. Using allele, dominant, recessive, and additive models, we did not identify significant heterogeneity among the 18 studies. We observed a significant association between rs3764650 and AD using the allele (P=1.76E−26, odds ratio (OR)=1.21, 95 % confidence interval (CI) 1.17–1.26), dominant (P=4.00E−04, OR=1.17, 95 % CI 1.07–1.28), recessive

Guiyou Liu, Fujun Li, and Shuyan Zhang contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s12035-014-8670-4) contains supplementary material, which is available to authorized users.

G. Liu · G. Ma · K. Li
Institute of Neurology, Guangdong Medical College, Zhanjiang 524001, China

G. Liu (✉)
Genome Analysis Laboratory, Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences, Xiqi Dao 32, Tianjin Airport Economic Area, Tianjin 300308, China
e-mail: liuguiyou1981@163.com

F. Li
Department of Anesthesiology, The First Affiliated Hospital, Harbin Medical University, Harbin, China

S. Zhang · H. Shang
Department of Neurology, The Forth Affiliated Hospital of Harbin Medical University, Harbin, China

Y. Jiang · M. Liao
College of Bioinformatics Science and Technology, Harbin Medical University, Harbin, China

J. Liu
Department of Neurology, The First Hospital of Harbin, Harbin, China

R. Feng
Department of Nutrition and Food Hygiene, School of Public Health, Harbin Medical University, Harbin, China

L. Zhang
Department of Statistics, Rice University, Houston, TX, USA

B. Zhao · K. Li (✉)
Key Laboratory of Aging-Related Cardio-Cerebral Diseases of Guangdong Province, Affiliated Hospital of Guangdong Medical College, Zhanjiang, China
e-mail: keshenli2012@163.com

(P=3.00E−03, OR=1.43, 95 % CI 1.13–1.81), and additive models (P=3.00E−03, OR=1.49, 95 % CI 1.16–1.91). Collectively, our analysis further supports previous findings that the ABCA7 rs3764650 polymorphism is associated with AD susceptibility. We believe that our findings will be very useful for future genetic studies on AD.

Keywords ABCA7 rs3764650 polymorphism · Alzheimer's disease · Genome-wide association studies

Introduction

Studies from the World Health Organization have demonstrated that Alzheimer's disease (AD) is a complex and common neurodegenerative disease in the elderly that causes more than 50–75 % of dementia types [1]. It is estimated that genetic factors underlie approximately 60–80 % of AD risk [2]. To identify common AD genetic variants, large-scale genome-wide association studies (GWAS) have been conducted in individuals of Caucasian ancestry, revealing nine AD susceptibility genes, namely CR1, BIN1, CLU, PICALM, MS4A4/MS4A6E, CD2AP, CD33, EPHA1, and ABCA7 [3–7]. Among these loci, a single nucleotide polymorphism (SNP), rs3764650 in ABCA7, was found to be significantly associated with AD (P=5.00E−21, odds ratio (OR)=1.23, 95 % confidence interval (CI) 1.17–1.28, minor allele=C) [4]. This study indicated that European carriers of the rs3764650 risk variant (C) had an additional 23 % increased risk for AD [4].

In addition to the rs3764650 polymorphism, three other polymorphisms in ABCA7, rs115550680 (P=2.20E−09, African American) [8], rs3752246 (P=5.00E−07, European), [7] and rs4147929 (P=1.10E−15, European) [9], have been reported. Evidence from the HapMap Reference Sample (African Americans in southwest USA) showed that rs115550680 is in high linkage disequilibrium (LD) with rs3764650 and rs3752246 ($0.8<D'<0.9$) [8]. Using 1,000 Genomes data (YRI) in SNP Annotation and Proxy Search (SNAP) [10], a web-based tool for the identification and annotation of proxy SNPs, we found that rs3764650 was in LD with rs115550680 (D'=1). rs3764650 was in LD with rs3752246 (D'=0.70 for CEU; D'=0.80 for CHB+JPT) and rs4147929 (D'=0.81 for CEU; D'=0.83 for CHB+JPT). LD also exists between rs3752246 and rs4147929 (D'=0.94 for CEU; D'=0.96 for CHB+JPT).

Recent studies that investigated the genetic mechanisms of ABCA7 in AD pathogenesis have indicated that ABCA7 plays an important role in AD risk in individuals of European ancestry [11–13]. AD GWAS and candidate gene studies have also investigated ABCA7 polymorphisms (especially rs3764650) in other populations (Chinese, Japanese, Korean, African American, and Canadian) [14–19]. However, these studies reported a weak or negligible association between rs3764650 and AD. We hypothesized that these negative results were due to relatively small sample sizes compared with those used in previous GWAS studies in individuals of European ancestry or the genetic heterogeneity of the rs3764650 polymorphism in different populations. Here, we reevaluated the association between the rs3764650 polymorphism (or its proxies, namely rs115550680, rs3752246, and rs4147929) and AD using relatively large-scale samples from previous studies (N=79,381—30,590 cases and 48,791 controls), which may be helpful for revealing significant disease associations.

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 the key words "Alzheimer's disease," "ATP-binding cassette, sub-family A (ABC1), member 7," or "ABCA7." The literature search was updated on January 18, 2014. To compile additional studies, we used Google Scholar (http://scholar.google.com/) to query articles citing the initial studies and all references in these studies identified by PubMed and AlzGene. We only selected published articles written in English.

Inclusion Criteria

We selected studies meeting the following criteria: (1) the study was conducted by a case-control design, (2) the study evaluated the association between the rs3764650 polymorphism (or one of its proxies) and AD, (3) the study provided the number of rs3764650 (or its proxies) genotypes or sufficient data to calculate the number of rs3764650 (or its proxies) genotypes, and (4) the study provided an OR with a 95 % CI or sufficient data to calculate the OR and a 95 % CI.

Data Extraction

Guiyou Liu and Yongshuai Jiang 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 genotyping platform; (6) the number of rs3764650 (or its proxies) genotypes or if not provided, calculated the number of rs3764650 (or its proxies) genotypes; and (7) the OR with 95 % CI or if not provided, calculated the OR and 95 % CI. All relevant calculations were completed using R (http://www.r-project.org/).

Quality Evaluation

Here, the criteria proposed by Clark et al. were used to evaluate the quality of selected genetic association studies [20]. 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 [20]. 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 [21]. 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.

Genetic Models

We used allele, dominant, recessive, and additive models for our meta-analysis. The ABCA7 rs3764650 polymorphism has two alleles, C and A. C is the minor allele. We assumed that C was the high-risk allele and that A was the lower risk allele. The four models can be described as follows: the allele model (C allele versus A allele), the dominant model (CC+CA versus AA), the recessive model (CC versus CA+AA), and the additive model (CC versus AA) [22].

Heterogeneity Test

We evaluated genetic heterogeneity among the included studies using Cochran's Q test, which approximately follows a χ^2 distribution with $k-1$ degrees of freedom (where k is the number of studies analyzed). Another statistic, $I^2 = {}^{(Q-(k-1))}/_{Q} \times 100\%$, was also used. I^2 ranges from 0 to 100 % [23]. Low, moderate, large, and extreme heterogeneity corresponded to I^2 values of 0–25, 25–50, 50–75, and 75–100 %, respectively [23]. Heterogeneity was considered significant when $P<0.01$ and $I^2>50$ %.

Meta-analysis

If there was no significant heterogeneity among the selected studies, the pooled OR was calculated using the fixed effect model (Mantel-Haenszel). For all other cases, the pooled OR was calculated using the random-effect model (DerSimonian-Laird). A Z test was used to determine the significance of the OR. All statistical tests for heterogeneity and the meta-analysis were computed using the R Package (meta: Meta-Analysis with R, http://cran.r-project.org/web/packages/meta/index.html) or RevMan (v.5.1) software (http://ims.cochrane.org/revman/download).

Sensitivity Analyses and Publication Bias Analyses

For sensitivity analyses, we evaluated the relative influence of each study by omitting each study, one at a time. In addition, we used funnel plots to evaluate potential publication bias [24]. Begg's and Egger's tests were used to evaluate the asymmetry of the funnel plots [24].

Results

Literature Search and Quality Evaluation

A total of 48 articles were identified using PubMed, AlzGene, and Google Scholar. In the end, nine articles describing 18 independent studies were included for 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 did not identify significant heterogeneity among the included studies using the allele model ($P=0.02$ and $I^2=45.9$ %). We then calculated the overall OR with the fixed effect model and found a significant association between the rs3764650 polymorphism and AD ($P=1.76E-26$, OR=1.21, 95 % CI 1.17–1.26, minor allele=C). More detailed results are provided in Fig. 1.

In addition to the allele model, we used dominant, recessive, and additive models to investigate the association between the rs3764650 polymorphism and AD. Because all three models require the exact number of original genotypes, we selected only 6 of 18 studies for our further analysis. There was no significant heterogeneity among selected studies using the dominant model ($P=0.09$ and $I^2=47$ %), recessive model ($P=0.18$ and $I^2=34$ %), or additive model ($P=0.21$ and $I^2=30$ %). Furthermore, a meta-analysis revealed significant associations using the dominant model ($P=4.00E-04$, OR=1.17, 95 % CI 1.07–1.28), recessive model ($P=3.00E-03$, OR=1.43, 95 % CI 1.13–1.81), and additive model ($P=3.00E-03$, OR=1.49, 95 % CI 1.16–1.91). More detailed results are provided in Fig. 2.

Subgroup Analysis

The frequency of rs3764650 is variable among different populations. Only 6 of 18 studies were selected for further analysis using the dominant, recessive, and additive models. We then conducted a subgroup analysis using the allele model in East Asian and Caucasian populations. There was no significant heterogeneity in the East Asian ($P=0.85$ and $I^2=0$ %) or

Table 1 Main characteristics of the individual studies included in the meta-analysis

Study	Population	Ethnicity	No. of cases	No. of controls	Genotyping platform	SNP	Genotype
Tan et al. [14]	Chinese	East Asian	612	612	TaqMan	rs3764650	Yes
Liu et al. [15]	Chinese	East Asian	350	283	PCR and DNA sequencing	rs3764650	Yes
Chung et al. [16]	Korean	East Asian	290	554	SNPtype, TaqMan, and SNaPshot	rs3764650	NA
Miyashita et al. [17]	Japanese	East Asian	891	844	Affymetrix GeneChip 6.0 and TaqMan	rs3764650	NA
Omoumi et al. [18]	Canadian	Canadian	580	524	TaqMan	rs3764650	Yes
Reitz et al. [8]	African American	African	1,968	3,928	Illumina 660, Omni Express, 1 M, 610, 300, 370	rs115550680	NA
Lambert et al. [5]	France	Caucasian	2,025	5,328	Illumina 610	rs3764650	NA
Harold et al. [6]	UK/Ireland	Caucasian	2,226	4,704	Illumina 610, 550, and 300	rs3764650	Yes
Harold et al. [6]	Germany	Caucasian	555	824	Illumina 610, 550, and 300	rs3764650	Yes
Harold et al. [6]	USA	Caucasian	551	960	Illumina 610, 550, and 300	rs3764650	Yes
Hollingworth et al. [4]	ADNI	Caucasian	151	177	Illumina 610	rs3764650	NA
Hollingworth et al. [4]	GERAD2	Caucasian	3,262	3,320	Sequenom	rs3764650	NA
Hollingworth et al. [4]	deCODE	Caucasian	925	612	Illumina 300 and CNV370	rs3764650	NA
Hollingworth et al. [4]	AD-IG	Caucasian	709	971	Illumina 610 and 550	rs3764650	NA
Hollingworth et al. [4]	EADI1	Caucasian	2,751	2,620	Sequenom	rs3764650	NA
Hollingworth et al. [4]	CHARGE	Caucasian	1,239	10,813	Illumina CNV370, 550 and Affymetrix 500+50 k	rs3764650	NA
Hollingworth et al. [4]	MAYO2	Caucasian	2,490	4,114	TaqMan	rs3764650	NA
Hollingworth et al. [4]	ADGC	Caucasian	9,015	7,603	Illumina 660, 610, 550, 300, 370, and 1 M; Affymetrix 500 and 1 M	rs3764650	NA
All=79,381			30,590	48,791			

"Yes" indicates the genotype numbers are available; NA indicates the genotype numbers are not available

ADNI the Alzheimer's Disease Neuroimaging Initiative, *GERAD2* the Genetic and Environmental Risk in Alzheimer's Disease 2, *AD-IG* German Alzheimer's Disease Integrated Genome Research Network, *ADGC* the Alzheimer's Disease Genetic Consortium, *CHARGE* the Cohorts for Heart and Aging Research in Genomic Epidemiology, *EADI1* European Alzheimer's Disease Initiative 1

Caucasian (P=0.65 and I^2=0 %) populations. A subsequent meta-analysis revealed significant associations in the East Asian (P=0.029, OR=1.09, 95 % CI 1.01–1.19) and Caucasian (P=6.95E−22, OR=1.22, 95 % CI 1.17–1.28) populations.

Sensitivity Analyses and Publication Bias Analyses

We found that the association between rs3764650 and AD did not vary substantially when excluding any one study using the four models (data not shown). However, by excluding the study from Logue et al. (African American) [19] using the allele model, the heterogeneity decreased from P=0.02 and I^2=45.9 % to P=0.46 and I^2=0 %. The four plots were symmetrical inverted funnels (Figs. 3 and 4), suggesting that there was no significant publication bias for the allele model (Begg's test, P=0.65, and Egger's test, P=0.65), dominant model (Begg's test, P=0.25, and Egger's test, P=0.25), recessive model (Begg's test, P=0.99, and Egger's test, P=0.99), or additive model (Begg's test, P=1, and Egger's test, P=1). The findings from the sensitivity analyses and publication bias analyses indicated that our results were robust.

Discussion

A previous GWAS showed that rs3764650 was significantly associated with AD [4]. Recent studies have investigated the genetic mechanisms of ABCA7 in AD pathogenesis and indicated that ABCA7 plays an important role in AD risk. Vasquez et al. demonstrated that the rs3764650 polymorphism T allele, which is associated with an increased risk of AD, is correlated with increased ABCA7 expression in human brain samples and that ABCA7 expression is increased in AD individuals [11]. Shulman et al. conducted an investigation of 725 subjects, followed by a targeted validation of 114 subjects, and found that ABCA7 (rs3764650; P=0.02) was associated with neuritic plaque burden [12]. Karch et al. measured the influence of the rs3764650 polymorphism and ABCA7 expression levels on clinical and pathological measures of AD in brain tissue from the parietal lobe of both AD

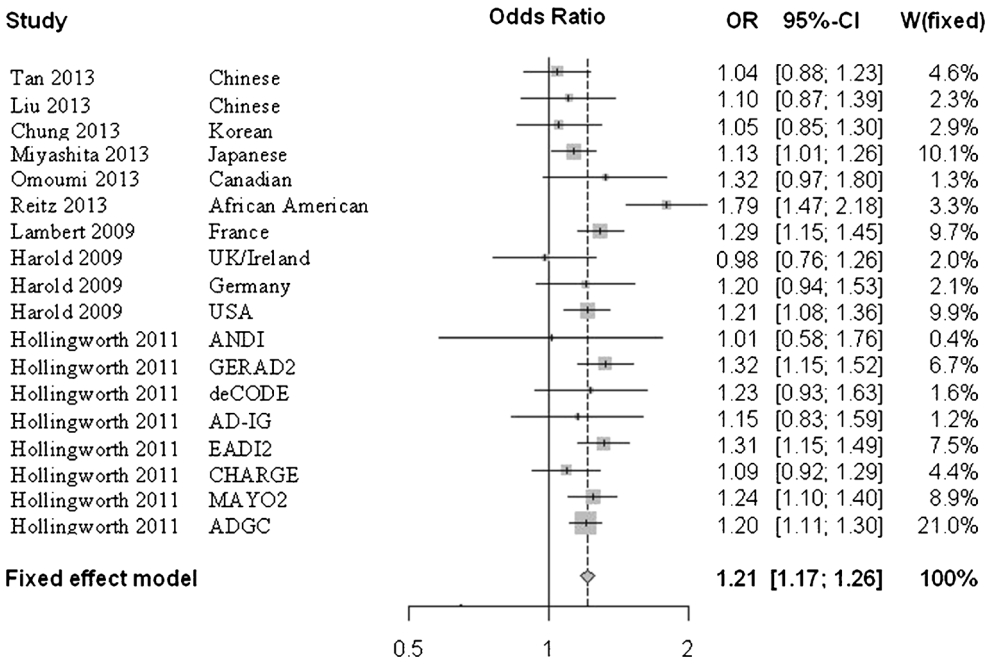

Fig. 1 Forest plot for the meta-analysis of the rs3764650 polymorphism using the allele model. *M-H* Mantel-Haenszel, *Fixed* fixed effect model, *CI* confidence interval

cases and age-matched, cognitively normal controls [13]. Their results showed that the minor allele of rs3764650 C was associated with age at onset and disease duration. ABCA7 expression levels were associated with a clinical dementia rating, with higher expression being correlated with more advanced cognitive decline [13].

Here, due to the weak or negligible association between rs3764650 and AD reported by previous studies in Chinese, Japanese, Korean, African American, and Canadian populations, we reevaluated the association using large-scale samples. We observed that there was no significant heterogeneity among the selected studies using our four models. Our results revealed

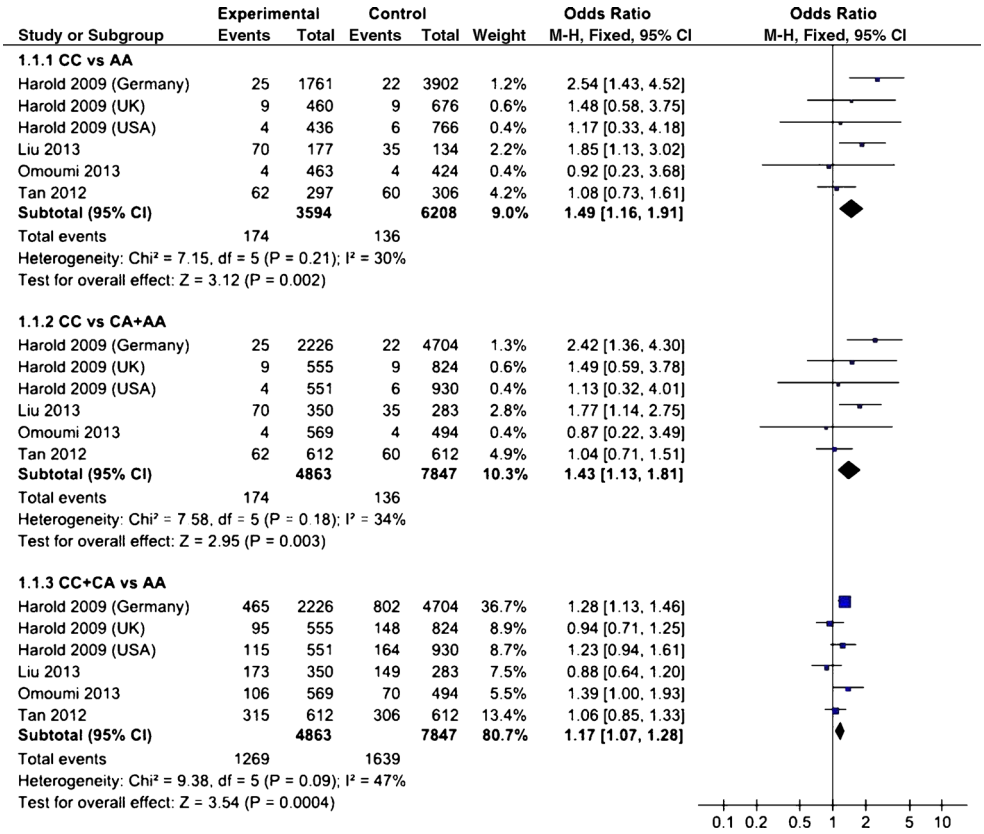

Fig. 2 Forest plot for the meta-analysis of the rs3764650 polymorphism using recessive, dominant, and additive models. *M-H* Mantel-Haenszel, *Fixed* fixed effect model, *CI* confidence interval

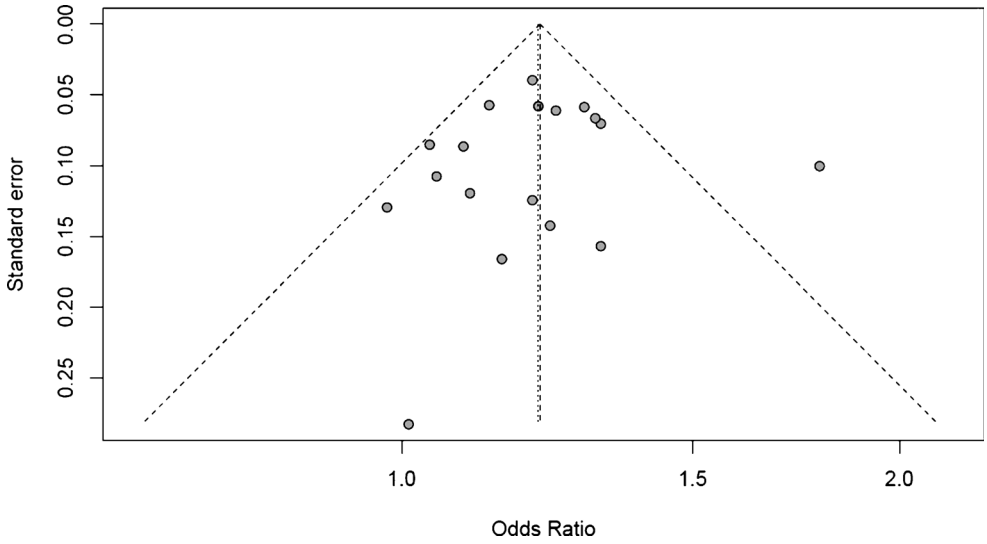

Fig. 3 Funnel plot for publication bias analysis of the rs3764650 polymorphism in AD using the allele model

a more significant association between rs3764650 and AD (P=1.76E−26) compared with a previous study (P=5.00E−21) [4]. Based on these findings, we consider that the weak and negligible associations between rs3764650 and AD may have been caused by relatively small sample sizes compared with the previous GWAS in populations of European ancestry [4].

In addition to the rs3764650 polymorphism (or its proxies, namely rs115550680, rs3752246, and rs4147929), common AD variants of another eight AD susceptibility genes (CR1, BIN1, PICALM, MS4A4/MS4A6E, CD2AP, CD33, EPHA1, and CLU) were also reported in the Caucasian population. Subsequent studies successfully corroborated the significance of these AD variants by analyzing a large-scale dataset of an Asian population (e.g., PICALM gene rs3851179 polymorphism, BIN1 gene rs744373 polymorphism, CR1 gene rs6656401 polymorphism, and CLU gene rs11136000 variant [23, 25–28]). These results indicated that analyzing relatively large-scale samples is effective in identifying significant associations between these common variants and AD.

Before our submission (January 27, 2014), we accessed the AlzGene database [29]. Among nine articles selected for our analysis, only two articles were included in AlzGene. Neither of the articles provided exact genotype numbers. Lambert et al. recently conducted a large, two-stage meta-analysis of AD GWAS in individuals of European ancestry [9]. In addition to the APOE locus, they identified 19 loci with genome-

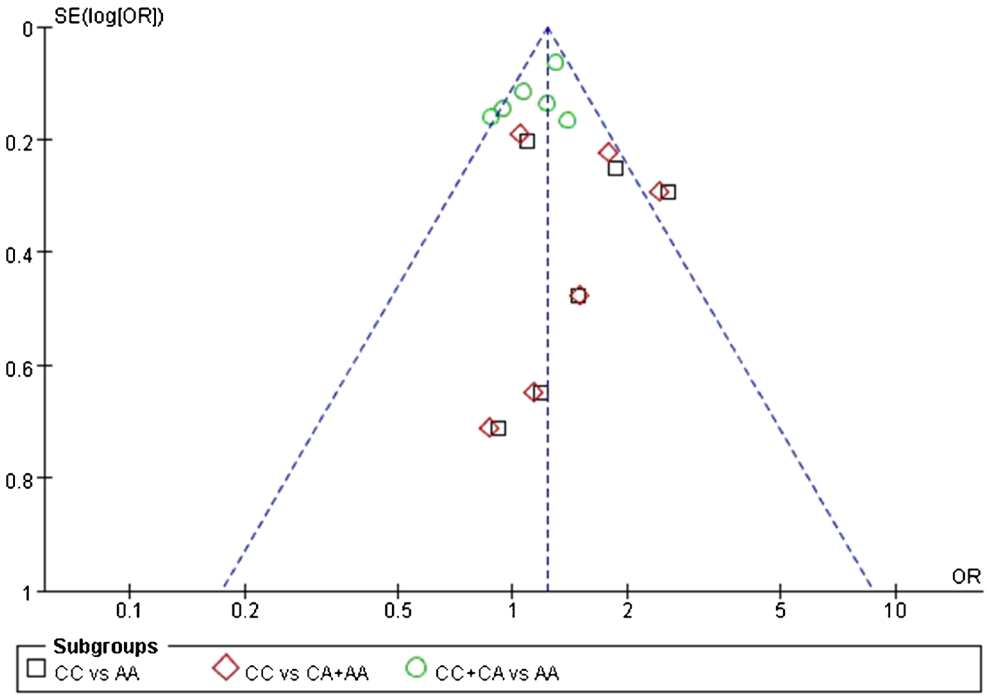

Fig. 4 Funnel plot for publication bias analysis of rs3764650 polymorphism in AD using the recessive, dominant, and additive models

wide significance ($P<5.00E-08$), of which 11 were newly associated with AD. However, the rs3764650 polymorphism was not included in the 19 loci.

Despite these interesting results, our study has a limitation. Here, we investigated the association between rs3764650 (or its proxies, namely rs115550680, rs3752246, and rs4147929) and AD using allele, dominant, recessive, and additive models. The dominant, recessive, and additive models required exact genotype numbers of all studies used in our analysis. We attempted to obtain these genotype numbers but were not successful. The Alzheimer's Disease Genetic Consortium (ADGC) study from Naj et al. contained 15 discrete datasets and had a total sample number that was much greater than all of the other included studies combined (after removing datasets that were counted twice). However, the ADGC study could not provide exact genotype numbers for all of the studies. Thus, we divided the selected studies into two classifications: those that could provide exact genotype numbers and those that could not, as described in Table 1. Six of the 18 studies with exact genotype numbers were selected for meta-analyses using dominant, recessive, and additive models. It was important to analyze the dominant, recessive, and additive models; however, the results from these models cannot be compared with those from the allelic model due to discrepancies between the numbers of studies included. Future studies using genotype data are required to corroborate our findings.

To our knowledge, this is the first meta-analysis to investigate the association between the rs3764650 polymorphism (or its proxies, namely rs115550680, rs3752246, and rs4147929) and AD in East Asian, African American, Canadian, and Caucasian populations. Our analysis supports previous findings that the ABCA7 rs3764650 polymorphism contributes to AD susceptibility. We believe that our findings will be very useful for future genetic studies on AD. The more detailed Supplementary Data can also be found from the website http://www.bioapp.org/research/ADrs3764650/.

Acknowledgments This work was supported by funding from the National Nature Science Foundation of China (grant numbers 81300945, 31200934, 31301938, 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 None.

References

1. Saloni T (2013) Priority medicines for Europe and the world. "A public health approach to innovation". World Health Organization: 11
2. Lambert JC, Grenier-Boley B, Chouraki V, Heath S, Zelenika D et al (2010) Implication of the immune system in Alzheimer's disease: evidence from genome-wide pathway analysis. J Alzheimers Dis 20: 1107–1118
3. Seshadri S, Fitzpatrick AL, Ikram MA, DeStefano AL, Gudnason V et al (2010) Genome-wide analysis of genetic loci associated with Alzheimer disease. JAMA 303:1832–1840
4. Hollingworth P, Harold D, Sims R, Gerrish A, Lambert JC et al (2011) Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. Nat Genet 43:429–435
5. Lambert JC, Heath S, Even G, Campion D, Sleegers K et al (2009) Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet 41:1094–1099
6. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A et al (2009) Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet 41: 1088–1093
7. Naj AC, Jun G, Beecham GW, Wang LS, Vardarajan BN et al (2011) Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. Nat Genet 43: 436–441
8. Reitz C, Jun G, Naj A, Rajbhandary R, Vardarajan BN et al (2013) Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E 4, and the risk of late-onset Alzheimer disease in African Americans. JAMA 309:1483–1492
9. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R et al (2013) Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet 45:1452–1458
10. Johnson AD, Handsaker RE, Pulit SL, Nizzari MM, O'Donnell CJ et al (2008) SNAP: a web-based tool for identification and annotation of proxy SNPs using HapMap. Bioinformatics 24:2938–2939
11. Vasquez JB, Fardo DW, Estus S (2013) ABCA7 expression is associated with Alzheimer's disease polymorphism and disease status. Neurosci Lett 556:58–62
12. Shulman JM, Chen K, Keenan BT, Chibnik LB, Fleisher A et al (2013) Genetic susceptibility for Alzheimer disease neuritic plaque pathology. JAMA Neurol 70:1150–1157
13. Karch CM, Jeng AT, Nowotny P, Cady J, Cruchaga C et al (2012) Expression of novel Alzheimer's disease risk genes in control and Alzheimer's disease brains. PLoS One 7:e50976
14. Tan L, Yu JT, Zhang W, Wu ZC, Zhang Q et al (2013) Association of GWAS-linked loci with late-onset Alzheimer's disease in a northern Han Chinese population. Alzheimers Dement 9:546–553
15. Liu LH, Xu J, Deng YL, Tang HD, Wang Y, et al. (2013) A complex association of ABCA7 genotypes with sporadic Alzheimer disease in Chinese Han population. Alzheimer Disease and Associated Disorders
16. Chung SJ, Lee JH, Kim SY, You S, Kim MJ et al (2013) Association of GWAS top hits with late-onset Alzheimer disease in Korean population. Alzheimer Dis Assoc Disord 27:250–257
17. Miyashita A, Koike A, Jun G, Wang LS, Takahashi S et al (2013) SORL1 is genetically associated with late-onset Alzheimer's disease in Japanese, Koreans and Caucasians. PLoS One 8:e58618
18. Omoumi A, Fok A, Greenwood T, Sadovnick AD, Feldman HH et al (2014) Evaluation of late-onset Alzheimer disease genetic susceptibility risks in a Canadian population. Neurobiol Aging 35(4):936.e5–936.e12
19. Logue MW, Schu M, Vardarajan BN, Buros J, Green RC et al (2011) A comprehensive genetic association study of Alzheimer disease in African Americans. Arch Neurol 68:1569–1579
20. Clark MF, Baudouin SV (2006) A systematic review of the quality of genetic association studies in human sepsis. Intensive Care Med 32: 1706–1712
21. Lv H, Jiang Y, Li J, Zhang M, Shang Z et al (2014) Association between polymorphisms in the promoter region of interleukin-10 and susceptibility to inflammatory bowel disease. Mol Biol Rep 41(3): 1299–1310

22. Lewis CM, Knight J (2012) Introduction to genetic association studies. Cold Spring Harb Protocol 2012:297–306
23. Liu G, Zhang S, Cai Z, Ma G, Zhang L et al (2013) PICALM gene rs3851179 polymorphism contributes to Alzheimer's disease in an Asian population. Neuromol Med 15:384–388
24. Jiang Y, Zhang R, Zheng J, Liu P, Tang G et al (2012) Meta-analysis of 125 rheumatoid arthritis-related single nucleotide polymorphisms studied in the past two decades. PLoS One 7:e51571
25. Liu G, Zhang S, Cai Z, Li Y, Cui L et al (2013) BIN1 gene rs744373 polymorphism contributes to Alzheimer's disease in East Asian population. Neurosci Lett 544:47–51
26. Liu G, Zhang L, Feng R, Liao M, Jiang Y et al (2013) Lack of association between PICALM rs3851179 polymorphism and Alzheimer's disease in Chinese population and APOEepsilon4-negative subgroup. Neurobiol Aging 34(1310):e1319–1310
27. Jin C, Li W, Yuan J, Xu W, Cheng Z (2012) Association of the CR1 polymorphism with late-onset Alzheimer's disease in Chinese Han populations: a meta-analysis. Neurosci Lett 527: 46–49
28. Liu G, Wang H, Liu J, Li J, Li H et al (2014) The CLU gene rs11136000 variant is significantly associated with Alzheimer's disease in Caucasian and Asian populations. Neuromol Med 16: 52–60
29. Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE (2007) Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. Nat Genet 39:17–23