Research article

Associations between CD33 rs3865444 and ABCA7 rs3764650 polymorphisms and susceptibility to Alzheimer's disease

Jing Wang[1], Xiangyi Kong[2], Lele Cong[1], Zhongxin Xu[1], Jianshi Du[2], Xianling Cong[3], Hongyan Sun[3], Yanan Xu[1], Qing Zhao[1,*]

[1] Department of Neurology, China-Japan Union Hospital of Jilin University, Chang Chun, 130033, Jilin Province, China
[2] Department of Vascular Surgery, China-Japan Union Hospital of Jilin University, Changchun, 130033, Jilin Province, China
[3] Department of Biobank, China-Japan Unoin Hospital, Jilin University, Changchun, 130033, Jilin Province, China

*Correspondence: zhaoqing@jlu.edu.cn (Qing Zhao)

Abstract

Several studies have evaluated the association of Siglec-3(CD33) rs3865444 polymorphism and ATP-binding cassette transporter A7(ABCA7) rs3764650 polymorphism with susceptibility to Alzheimer's disease. However, these studies have yielded contradictory results. Therefore, to resolve this issue, a meta-analysis was undertaken to examine 12 previously published studies. The pooled effect of CD33 rs3865444 showed no significant relationship with susceptibility to Alzheimer's disease under various genetic models. The pooled effect of ABCA7 rs3764650 also lacked association with susceptibility to Alzheimer's disease in the allele model ($p = 0.06$, OR = 1.06, 95% CI, 1.00–1.13), while significant associations were revealed for the dominant model ($p< 0.0001$ OR = 1.20, 95% CI, 1.10–1.31), recessive model ($p = 0.01$, OR = 1.59, 95% CI, 1.12–2.28), and additive model ($p = 0.003$, OR = 1.44, 95% CI, 1.13–1.83). A subsequent meta-analysis revealed significant association of these models for Caucasians (dominant: $p< 0.00001$, OR = 1.28, 95% CI, 1.16–1.41; recessive: $p = 0.002$, OR = 1.96, 95% CI, 1.27–3.04; additive: $p = 0.001$, OR = 1.96, 95% CI, 1.30–2.94), contrary to what was demonstrated for Asians. Results of the present meta-analysis indicate that ABCA7 rs3764650 might increase the risk of Alzheimer's disease, particularly for older Caucasians.

Keywords

Alzheimer's disease; single nucleotide polymorphisms; CD33 rs3865444; ABCA7 rs3764650; meta-analysis

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1. Introduction

Alzheimer's disease (AD) is a complex disease involving the interaction of genetic and environmental factors [1]. It has been shown that Aβ -amyloid (Aβ) deposition, related neuronal apoptosis, and neuroinflammation are important factors leading to cognitive deficits [2]. However, AD has a strong genetic component. Genome wide associated studies (GWAS) have identified polymorphisms in or near several genes that are associated with AD risk: ABCA7, CLU, CR1, CD33, CD2AP, EPHA1, BIN1, PICALM, MS4A [3, 4]. Genes such as Siglec-3(CD33) and ATP-binding cassette transporter A7 (ABCA7) are considered to play significant roles in AD progression. Siglec-3(CD33) is located on chromosome 19q13.3 [5]. It is a member of the sialic acid-binding Ig-like lectin family of receptors and is expressed on myeloid cells and microglia [6]. CD33 plays an important role in immunological regulation of Siglecs. Additionally, CD33 activates sialic acid binding, leading to monocyte inhibition via immunoreceptor tyrosine-based inhibitory motif domains [4]. Furthermore, CD33 rs3865444, which is proximal to CD33, was shown to reduce the risk of AD in GWAS [7]. The minor allele of CD33 rs3865444 is correlated with reduced CD33 mRNA expression and insoluble Aβ-amyloid(Aβ) in AD brains [8]. Moreover, CD33 positive immunoreactive microglia have a positive association with insoluble Aβ 42 and plaque burden in AD brains [9]. Thus, CD33

may play an important role in Aβ clearance and other neuroinflammatory pathways mediated by microglia in the brain. ATP-binding cassette transporter A7 (ABCA7) is a member of the ABC transporter superfamily and is encoded by a gene located on chromosome 19p13.3 [10], It assists both transport of substrate across the cell membrane and intracellular lipid into lipoprotein particles [11]. ABCA7 not only stimulates cholesterol efflux and inhibits Aβ secretion [12], but also regulates phagocytosis of apoptotic cells by macrophage through the C1q complement pathway [13]. It may have an effect on AD risk via cholesterol transfer to APOE or by clearance of Aβ aggregates [14, 15]. ABCA7 rs3764650 is associated with neuritic plaque burden in AD brains [16]. ABCA7 mRNA expression in autopsy brain tissue is also associated with advanced cognitive decline [17, 18]. It is expressed in hippocampal CA1 neurons but is 10-fold lower than that in microglia[19]. Thus, we considered that ABCA7 rs3764650 may play an important role in the risk of AD disease.

To date, a number of studies have been conducted to investigate the association between CD33 polymorphism and ABCA7 polymorphism and AD risk. But the number of studies concerned with AD is relatively small. The evidence for the role of single nucleotide polymorphisms in CD33 and ABCA7 as a genetic marker for AD risk is inconsistent. Relatively small sample size, weak effect, or weak penetrance in published studies may provide some of the rea-

sons for conflicting results. Thus, a meta-analysis examining all published data was conducted to determine the statistical evidence for an association between CD33 rs3865444 and ABCA7 rs3764650 polymorphisms and AD susceptibility.

2. Materials and methods

2.1. Data retrieval

Articles (to February 11, 2017) were electronically searched and screened a from databases including PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure database (CNKI), and Wanfang database (an affiliate of the Chinese Ministry of Science & Technology). Mesh terms with their corresponding synonyms were combined to form the search strategy: "Single nucleotide polymorphisms", "Alzheimer's disease", "CD33" and "ABCA7". Additional articles were also screened manually from the references in each eligible study.

Inclusion criteria were defined as:

- Studies must assess the association between polymorphism of CD33 rs3865444 or ABCA7 rs3764650 and susceptibility to AD;
- Case-control studies must be based on humans;
- Studies containing sufficient information to obtain the odds ratio (OR) and 95% confidence intervals (CI);
- AD diagnosis should meet clinical criteria set by the NINCDS-ADRDA Alzheimer's Criteria (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association);
- Genotype distribution of controls conform to the Hardy–Weinberg equilibrium (HWE).

Exclusion criteria were defined as follows:

- Abstracts, reviews, meta-analysis, case reports, comments, and editorials;
- Duplications, grey literatures, unpublished articles;
- Studies without sufficient genotyping information.

2.2. Genetic Models

Allele, dominant, recessive, and additive models were employed for the meta-analysis. The CD33 rs3865444 polymorphism has two alleles, A and C, A is the minor allele. The ABCA7 rs3764650 polymorphism has two alleles, G and T, G is the minor allele. The four models were described as: CD33 rs3865444: allele model (A allele versus C allele), dominant model (AA + AC versus CC), recessive model (AA versus AC + CC), and additive model (AA versus CC); ABCA7 rs3764650: allele model (G allele versus T allele), dominant model (GG + GT versus TT), recessive model (GG versus GT + TT), and additive model (GG versus TT).

2.3. Heterogeneity Test

Cochran's Q-statistic and I^2 test were used to evaluate statistical heterogeneity. A p value of Cochran's Q test greater than 0.05 and I^2 statistic less than 50% ($p_h > 0.05$ and $I^2 < 50\%$), the fixed effect model was suitable for analysis due to lack of significant heterogeneity. When the p value of the Cochran's Q-test was less than or equal to 0.05 or I^2 statistic was greater than or equal to 50% ($p_h \leq 0.05$ or $I^2 \geq 50\%$), the random effects model was used for studies owing to the presence of significant heterogeneity [20]. Subgroup analysis by ethnicity (Asian, Caucasian) was performed for different heritability models that included allele, dominant, recessive, and additive models. Hardy-Weinberg equilibrium among the controls for each study was examined using Pearson's chi-square test ($p < 0.05$ was assumed to indicate deviation from Hardy-Weinberg equilibrium). Sensitivity analysis proceeded by individually omitting each study. Publication bias was assessed with Egger's test, Begg's test, and the inverted funnel plot [21]. All statistical analysis was performed with RevMan 5.3 and Stata 12.0 Software (StataCorp LP, College Station, Texas, USA).

3. Results

3.1. Literature search

The meta-analysis started with 173 articles. Initial review removed 46 duplicate articles to give 127 articles which were then subjected to abstract and keyword review. Of the 127 articles, 109 unrelated articles were discarded to give only 18 articles suited for full-text and data assessment, 6 articles lacked genotyping information, thus 12 eligible articles were finally available for data extraction [22–33]. The detailed information of each study is given in Table 1 and Table 2.

3.2. Heterogeneity Test and Meta-analysis

CD33 rs3865444. A total of 10 studies that included 22,262 patients with AD and 32,244 controls were suitable for the meta-analysis of CD33 rs3865444 polymorphism. Significant statistical heterogeneity was identified at the allelic level ($I^2 = 71\%$, $p_h < 0.00001$), the overall OR was then calculated with the random effect model and no significant association was found between CD33 rs3865444 polymorphism and AD ($p = 0.99$, OR = 1.00, 95% CI, 0.92–1.09, minor allele = A) (Fig. 1/Table 3). In addition to the allele model, dominant, recessive, and additive models were used to evaluate association between the CD33 rs3865444 polymorphism and AD. Only seven of ten articles were selected for further analysis as three models required the exact number of original genotypes. There was significant heterogeneity among the selected studies for the dominant model ($I^2 = 92\%$, $p_h < 0.00001$), the recessive model ($I^2 = 65\%$, $p_h = 0.001$) and the additive model ($I^2 = 69\%$, $p_h = 0.002$). Furthermore, the results of the meta-analysis revealed no significant associations using the dominant model ($p = 0.18$, OR = 1.25, 95% CI, 0.90–1.73), recessive model ($p = 0.15$, OR = 1.21, 95% CI, 0.93–1.58), or additive model ($p = 0.51$, OR = 1.10, 95% CI, 0.83–1.44) (Table 3).

ABCA7 rs3764650. A total of eight studies including 52,214 patients with AD and 82,948 controls were included for the meta-analysis of ABCA7 rs3764650 polymorphism. There was no significant statistical heterogeneity among these studies using the allele model ($I^2 = 49\%$, $p_h = 0.001$), overall OR was then calculated with the random effect model and no significant association was found between the ABCA7 rs3764650 polymorphism and AD ($p = 0.06$, OR = 1.06, 95% CI, 1.00–1.13, minor allele = G) (Fig. 2/Table 4). Dominant, recessive, and additive models were used to evaluate the association between ABCA7 rs3764650 and AD. Only five of eight articles were suited for further analysis due to three models requiring the exact number of original genotypes. There was no significant heterogeneity among selected studies for the dominant model ($I^2 = 30\%$, $p_h = 0.20$), the recessive model ($I^2 = 44\%$, $p_h = 0.10$) or additive model ($I^2 = 36\%$, $p_h = 0.37$). Furthermore, results of the
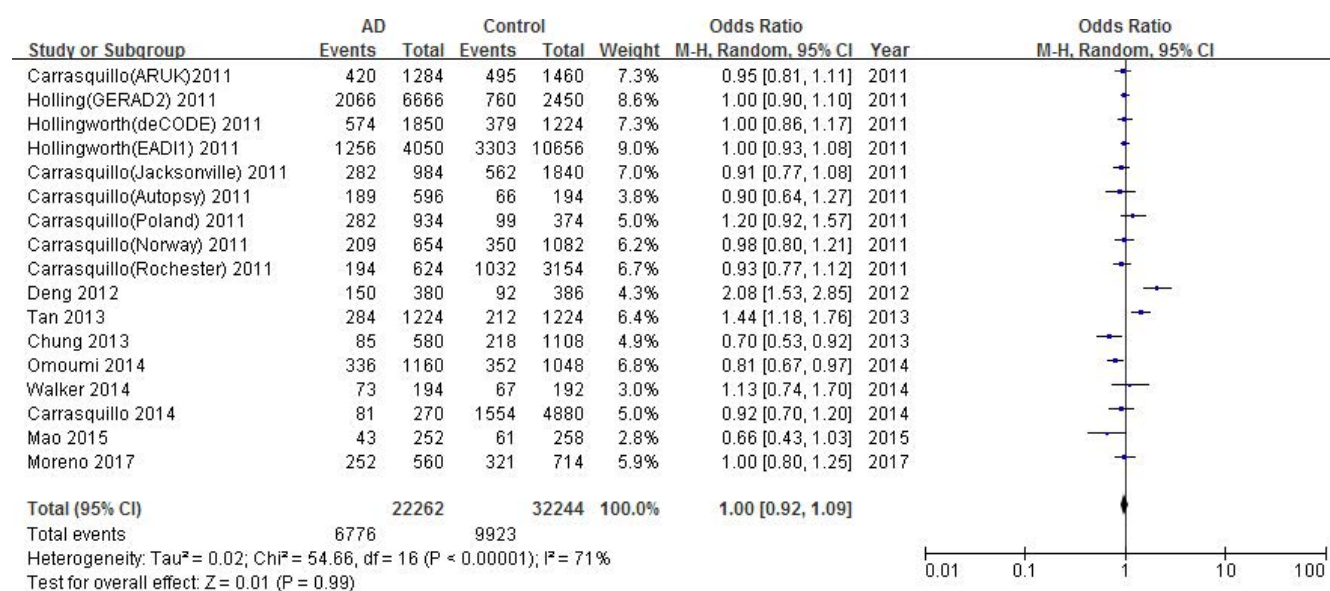
Fig. 1. Forest plot of CD33 rs3865444 polymorphism association with AD using the allele model. M-H, Mantel-Haenszel, random effect model, confidence interval (CI).
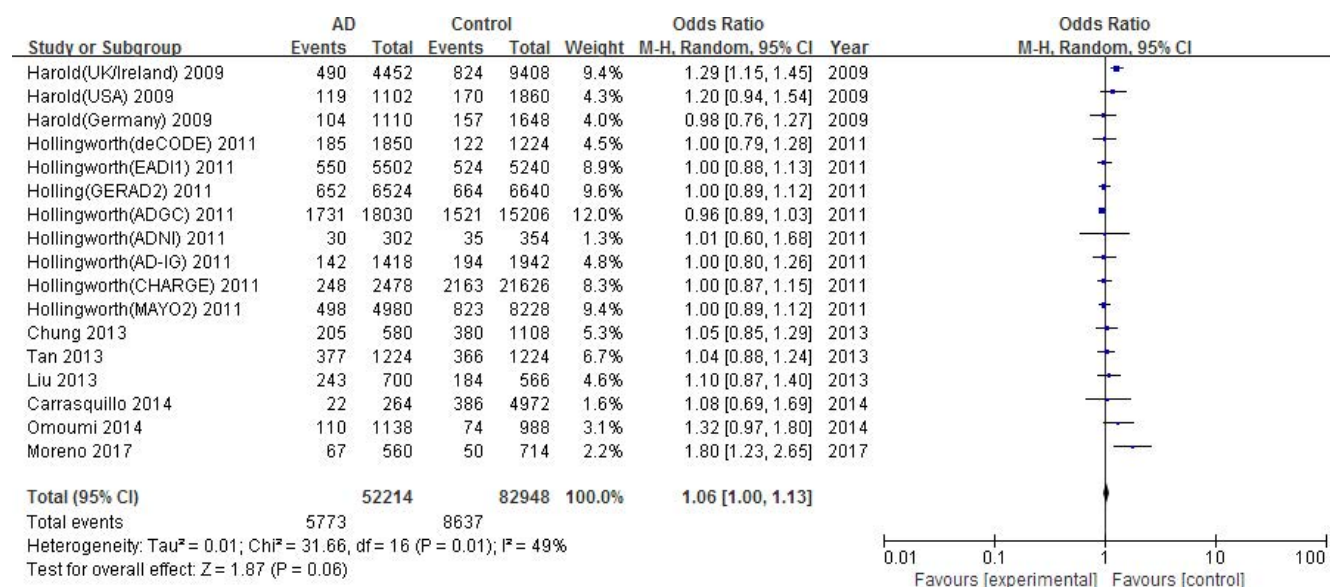

Fig. 2. Forest plot of ABCA7 rs3764650 polymorphism association with AD using the allele model. M-H, Mantel-Haenszel, random effect model, confidence interval (CI).

meta-analysis revealed significant associations using the dominant model ($p < 0.0001$ OR = 1.20, 95% CI, 1.10–1.31), recessive model ($p = 0.01$, OR = 1.59, 95% CI, 1.12–2.28), and additive model ($p = 0.003$, OR = 1.44, 95% CI, 1.13–1.83) (Table 4).

3.3. Subgroup analysis

CD33 rs3865444. The frequency of CD33 rs3865444 polymorphism was variable among two different subgroups (Asian and Caucasian). A total of 10 articles were suitable for further subgroup analysis of the allele model. There was a significant heterogeneity in Asians ($I^2 = 92\%$, $p_h < 0.00001$), but no significant heterogeneity in Caucasians ($I^2 = 0\%$, $p_h = 0.68$), the random effect model was then used for further subgroup analysis. Subsequent meta-analysis re-

vealed no significant association for either Asian ($p = 0.71$ OR = 1.10, 95% CI, 0.66–1.83) or Caucasian ($p = 0.26$, OR = 0.98, 95% CI, 0.93–1.02) populations (Fig. 3/Table 3). Furthermore, only eight of ten articles were selected for subgroup analysis using the dominant, recessive, and additive models. A subgroup analysis was then conducted for these models for Asians and Caucasians. There was significant heterogeneity in both Asians and Caucasians ($I^2 > 50\%$, $p_h < 0.05$) with the exception of the additive model (AA versus CC) for Caucasians ($I^2 = 0\%$, $p_h = 0.49$). The random effect model was ultimately selected for further subgroup analysis. There was no significant association with AD under these models for either Asians (dominant: $p = 0.33$, OR = 1.36, 95% CI, 0.74–2.51; recessive: $p = 0.80$, OR = 1.11, 95% CI, 0.49–2.50; additive $p = 0.27$, OR =
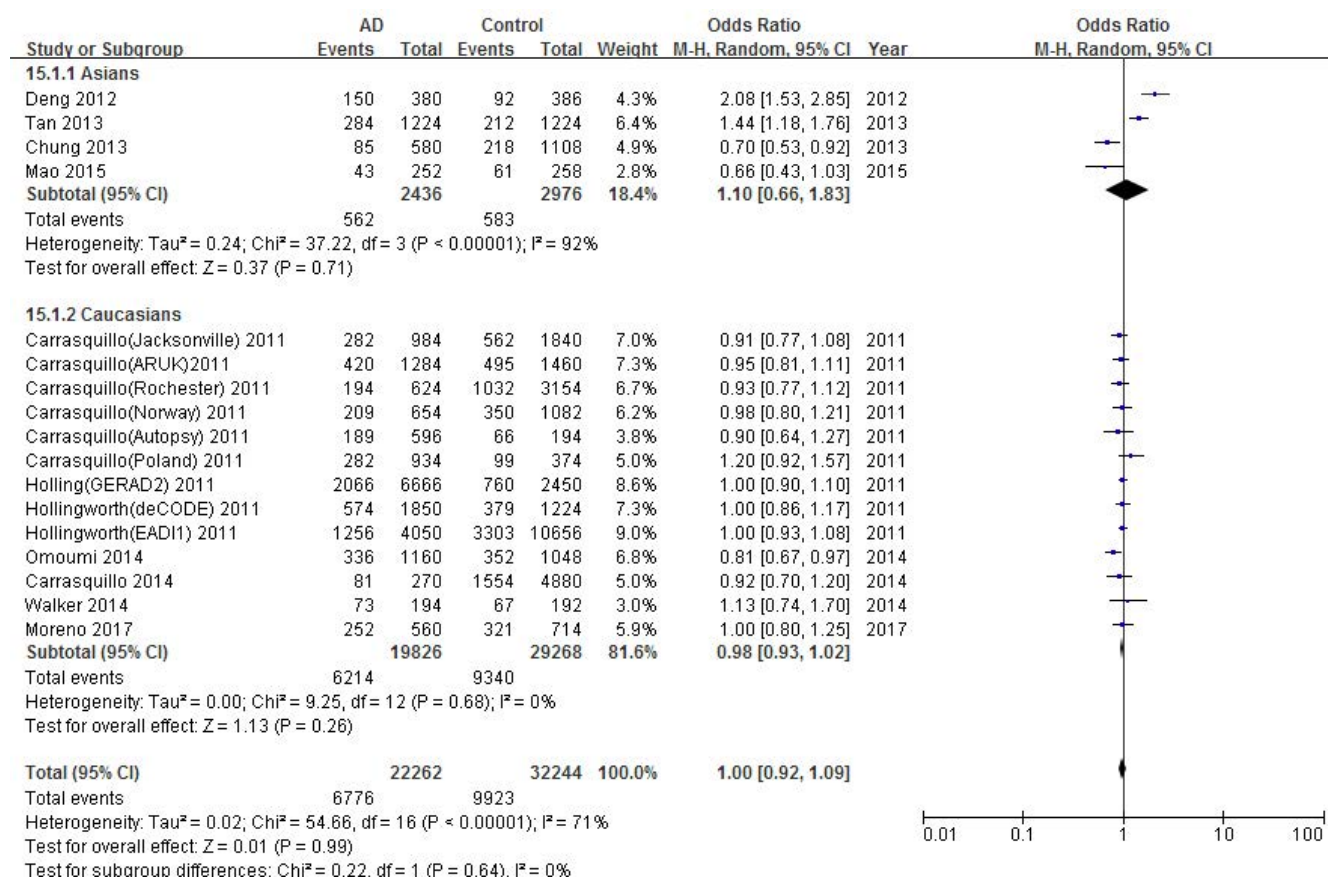
Study or Subgroup	AD Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
15.1.1 Asians							
Deng 2012	150	380	92	386	4.3%	2.08 [1.53, 2.85]	2012
Tan 2013	284	1224	212	1224	6.4%	1.44 [1.18, 1.76]	2013
Chung 2013	85	580	218	1108	4.9%	0.70 [0.53, 0.92]	2013
Mao 2015	43	252	61	258	2.8%	0.66 [0.43, 1.03]	2015
Subtotal (95% CI)		2436		2976	18.4%	1.10 [0.66, 1.83]	
Total events	562		583				

Heterogeneity: Tau² = 0.24; Chi² = 37.22, df = 3 (P < 0.00001); I² = 92%
Test for overall effect: Z = 0.37 (P = 0.71)

Study or Subgroup	AD Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
15.1.2 Caucasians							
Carrasquillo(Jacksonville) 2011	282	984	562	1840	7.0%	0.91 [0.77, 1.08]	2011
Carrasquillo(ARUK)2011	420	1284	495	1460	7.3%	0.95 [0.81, 1.11]	2011
Carrasquillo(Rochester) 2011	194	624	1032	3154	6.7%	0.93 [0.77, 1.12]	2011
Carrasquillo(Norway) 2011	209	654	350	1082	6.2%	0.98 [0.80, 1.21]	2011
Carrasquillo(Autopsy) 2011	189	596	66	194	3.8%	0.90 [0.64, 1.27]	2011
Carrasquillo(Poland) 2011	282	934	99	374	5.0%	1.20 [0.92, 1.57]	2011
Holling(GERAD2) 2011	2066	6666	760	2450	8.6%	1.00 [0.90, 1.10]	2011
Hollingworth(deCODE) 2011	574	1850	379	1224	7.3%	1.00 [0.86, 1.17]	2011
Hollingworth(EADI1) 2011	1256	4050	3303	10656	9.0%	1.00 [0.93, 1.08]	2011
Omoumi 2014	336	1160	352	1048	6.8%	0.81 [0.67, 0.97]	2014
Carrasquillo 2014	81	270	1554	4880	5.0%	0.92 [0.70, 1.20]	2014
Walker 2014	73	194	67	192	3.0%	1.13 [0.74, 1.70]	2014
Moreno 2017	252	560	321	714	5.9%	1.00 [0.80, 1.25]	2017
Subtotal (95% CI)		19826		29268	81.6%	0.98 [0.93, 1.02]	
Total events	6214		9340				

Heterogeneity: Tau² = 0.00; Chi² = 9.25, df = 12 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)

Total (95% CI)		22262		32244	100.0%	1.00 [0.92, 1.09]	
Total events	6776		9923				

Heterogeneity: Tau² = 0.02; Chi² = 54.66, df = 16 (P < 0.00001); I² = 71%
Test for overall effect: Z = 0.01 (P = 0.99)
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%

Fig. 3. Forest plot of CD33 rs3865444 polymorphism association with AD using the allele model for different ethnicities. M-H, Mantel-Haenszel, rondom effct model, confidence interval (CI).
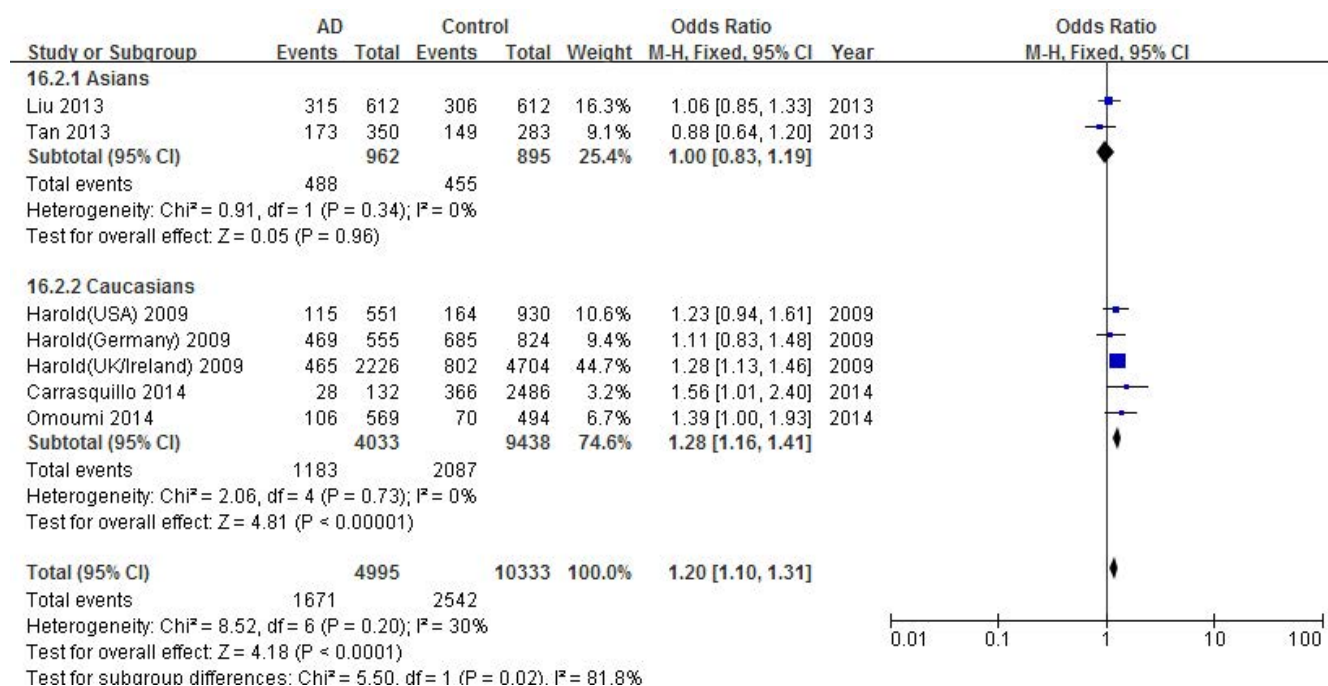
Study or Subgroup	AD Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
16.2.1 Asians							
Liu 2013	315	612	306	612	16.3%	1.06 [0.85, 1.33]	2013
Tan 2013	173	350	149	283	9.1%	0.88 [0.64, 1.20]	2013
Subtotal (95% CI)		962		895	25.4%	1.00 [0.83, 1.19]	
Total events	488		455				

Heterogeneity: Chi² = 0.91, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)

Study or Subgroup	AD Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
16.2.2 Caucasians							
Harold(USA) 2009	115	551	164	930	10.6%	1.23 [0.94, 1.61]	2009
Harold(Germany) 2009	469	555	685	824	9.4%	1.11 [0.83, 1.48]	2009
Harold(UK/Ireland) 2009	465	2226	802	4704	44.7%	1.28 [1.13, 1.46]	2009
Carrasquillo 2014	28	132	366	2486	3.2%	1.56 [1.01, 2.40]	2014
Omoumi 2014	106	569	70	494	6.7%	1.39 [1.00, 1.93]	2014
Subtotal (95% CI)		4033		9438	74.6%	1.28 [1.16, 1.41]	
Total events	1183		2087				

Heterogeneity: Chi² = 2.06, df = 4 (P = 0.73); I² = 0%
Test for overall effect: Z = 4.81 (P < 0.00001)

Total (95% CI)		4995		10333	100.0%	1.20 [1.10, 1.31]	
Total events	1671		2542				

Heterogeneity: Chi² = 8.52, df = 6 (P = 0.20); I² = 30%
Test for overall effect: Z = 4.18 (P < 0.0001)
Test for subgroup differences: Chi² = 5.50, df = 1 (P = 0.02), I² = 81.8%

Fig. 4. Forest plot of ABCA7 rs3764650 polymorphism association with AD using the dominant model for different ethnicities. M-H, Mantel-Haenszel, random effect model, confidence interval (CI).
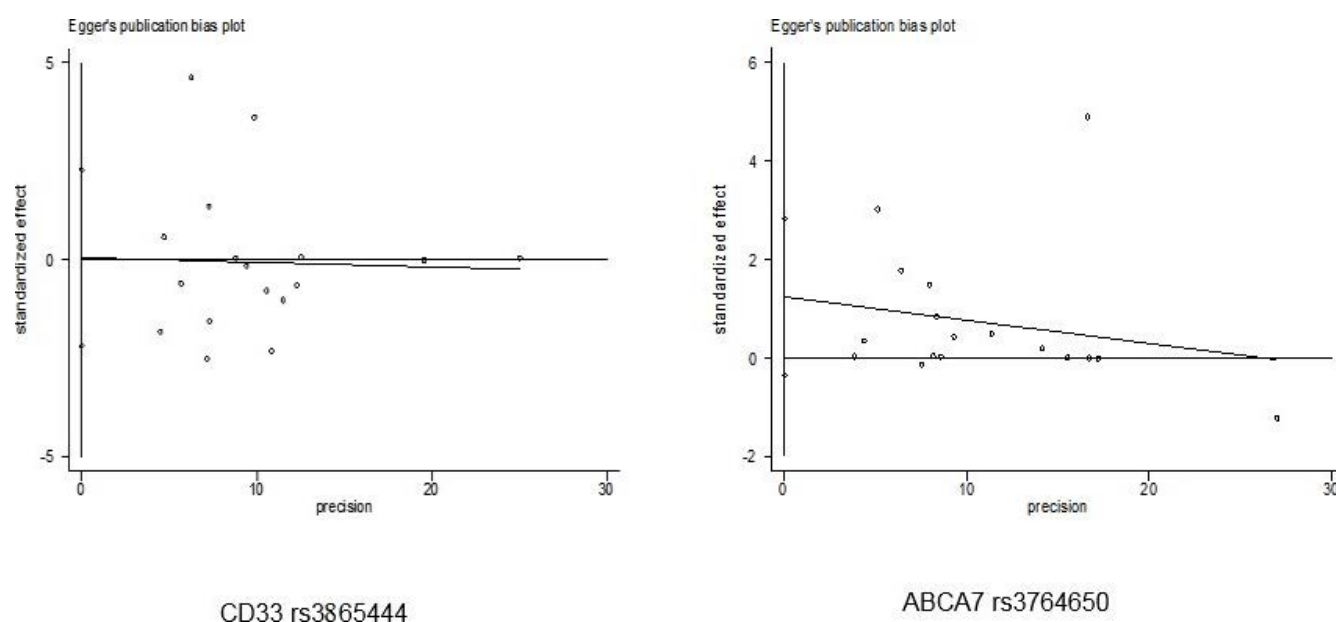
Fig. 5. Publication bias for CD33 rs3865444 and ABCA7 rs3764650 under the allele model detected by Egger's publication bias plot analysis. SE:Standard error of mean.

Table 1. Characteristics of case-control studies for CD33 gene included in meta-analysis

First author	Year	Country	Ethnicity	Case	Control	HWE
CD33 rs3865444						
Hollingworth(GERAD1) [22]	2011	Europe	Caucasian	3333	1225	yes
Hollingworth(EADI1) [22]	2011	Europe	Caucasian	2025	5328	yes
Hollingworth(deCODE) [22]	2011	Europe	Caucasian	925	612	yes
Carrasquillo(Jacksonville) [29]	2011	USA	Caucasian	492	920	yes
Carrasquillo(Rochester) [29]	2011	USA	Caucasian	312	1577	yes
Carrasquillo(Autopsy) [29]	2011	USA	Caucasian	298	97	yes
Carrasquillo(Norway) [29]	2011	Europe	Caucasian	327	541	yes
Carrasquillo(Poland) [29]	2011	Europe	Caucasian	467	187	yes
Carrasquillo(ARUK) [29]	2011	Europe	Caucasian	642	730	yes
Deng [28]	2012	China	Asian	190	193	yes
Chung [27]	2013	Korea	Asian	290	554	yes
Tan [25]	2013	China	Asian	612	612	yes
Omoumi [23]	2014	Canada	Caucasian	580	524	yes
Walker [31]	2014	USA	Caucasian	97	96	yes
Carrasquillo [33]	2014	USA	Caucasian	135	2440	yes
Mao [30]	2015	China	Asian	126	129	yes
Moreno [24]	2017	Colombia	Caucasian	280	357	yes

HWE: Hardy-Weinberg equilibrium

1.76, 95% CI, 0.65–4.81) or Caucasians (dominant: $p = 0.32$, OR = 1.22, 95% CI, 0.82–1.81; recessive: $p = 0.45$, OR = 1.09, 95% CI, 0.87–1.38; additive: $p = 1.31$, OR = 0.90, 95% CI, 0.78–1.03) (Table 3).

ABCA7 rs3764650. The frequency of ABCA7 rs3764650 polymorphism was variable among different subgroups (Asian and Caucasian). A total of eight articles were suited for further subgroup analysis for the allele model. There was no significant heterogeneity for Asians ($I^2 = 0\%$, $p_h = 0.92$) but there was significant heterogeneity for Caucasians ($I^2 = 59\%$, $p_h = 0.003$). The random effect model was selected to conduct a further subgroup analysis. The subsequent meta-analysis revealed no significant association for Asian ($p = 0.33$,

OR = 1.06, 95% CI, 0.94–1.19) or Caucasian ($p = 0.1$, OR = 1.06, 95% CI, 0.99–1.14) populations (Table 4). Furthermore, only five of eight articles were selected for analysis using the dominant, recessive, or additive models. A subgroup analysis was then conducted for these models for Asians and Caucasians. There was no significant heterogeneity in Caucasians or Asians ($p > 0.05$ and $I^2 < 50\%$) under the dominant and additive models, thus the fixed effect model was selected for subgroup analysis under these two genetic models in Caucasians and Asians. A significant association was found under these models in Caucasians (dominant: $p < 0.00001$, OR = 1.28, 95% CI, 1.16–1.41) (Fig. 4/Table 4); (additive: $p = 0.001$, OR = 1.96, 95% CI, 1.30–2.94) (Table 4). However, a significant heterogeneity

Table 2. Characteristics of the case-control studies for ABCA7 gene included in meta-analysis

First author	Year	Country	Ethnicity	Case	Control	HWE
ABCA7 rs3764650						
Harold [32]	2009	UK/Ireland	Caucasian	2226	4704	no
Harold [32]	2009	Germany	Caucasian	555	824	no
Harold [32]	2009	USA	Caucasian	551	930	yes
Hollingworth(ADNI) [22]	2011	USA	Caucasian	151	177	yes
Hollingworth(GERAD2) [22]	2011	UK	Caucasian	3262	3320	yes
Hollingworth(deCODE) [22]	2011	Iceland	Caucasian	925	612	yes
Hollingworth(AD-IG) [22]	2011	USA	Caucasian	709	971	yes
Hollingworth(CHARGE) [22]	2011	Netherlands	Caucasian	1239	10813	yes
Hollingworth(MAYO2) [22]	2011	USA	Caucasian	2490	4114	yes
Hollingworth(EADI1) [22]	2011	France	Caucasian	2751	2620	yes
Tan [25]	2013	China	Asian	612	612	yes
Chung [27]	2013	Korea	Asian	290	554	yes
Carrasqillo [33]	2014	America	Caucasian	132	2486	yes
Liu [26]	2014	China	Asian	350	283	yes
Omoumi [23]	2014	Canada	Caucasian	580	524	yes
Moreno [24]	2017	Colombia	Caucasian	280	357	yes

HWE: Hardy-Weinberg equilibrium

Table 3. Meta-analysis of the CD33 rs3865444 polymorphisms with Alzheimer's disease

CD33 rs3865444 polymorphism						
Genetic model	Cases/controls(n/n)	Ethnicity	No. of studies	OR (95% CI)	*p*-value	I^2 (%)
allele (A vs. C)	22262/32244	Overall	10	1.00[0.92, 1.09]	0.99	71
	2436/2976	Asian	4	1.10[0.66, 1.83]	0.71	92
	19826/29268	Caucasian	6	0.98[0.93, 1.02]	0.26	0
Dominant(AA + AC vs. CC)	4052/8237	Overall	7	1.25[0.90, 1.73]	0.18	92
	928/934	Asian	3	1.36[0.74, 2.51]	0.33	87
	3124/7303	Caucasian	4	1.22[0.82, 1.81]	0.32	93
Recessive(AA vs. AC + CC)	4052/8293	Overall	7	1.21[0.93, 1.58]	0.15	65
	928/934	Asian	3	1.11[0.49, 2.50]	0.8	73
	3124/7359	Caucasian	4	1.09[0.87, 1.38]	0.45	50
Additive(AA vs. CC)	2686/4964	Overall	7	1.10[0.83, 1.44]	0.51	69
	601/649	Asian	3	1.76[0.65, 4.81]	0.27	78
	2085/4315	Caucasian	4	0.90[0.78, 1.03]	0.13	0

for Asians was found ($I^2 = 70\%$, $p_h = 0.07$) for the recessive model, thus, the random effect model was ultimately selected. A significant association was found under the recessive model in Caucasians ($p = 0.002$, OR = 1.96, 95% CI, 1.27-3.04), while there was no association between ABCA7 rs3764650 polymorphism and Alzheimer's disease in Asians subgroups ($p = 0.28$, OR = 1.34, 95% CI, 0.79-2.26) (Table 4).

3.4. Sensitivity Analysis and Publication Bias Analysis

Sensitivity analysis was conducted by excluding one study at a time to assess whether any single study had a strong influence on the pooled OR. For CD33 rs3865444, sensitivity analysis indicate that no single study significantly influenced the pooled OR (data not shown). However, for ABCA7 rs3764650, by excluding the study from Harold *et al.* [32]. (UK/Ireland) using the additive model, G versus T with OR = 1.44, 95% CI, 1.13–1.83, $p = 0.003$ changed to OR = 1.29, 95% CI, 0.99–1.68, $p = 0.06$. Furthermore, Begg's funnel plot and Egger's linear regression test were performed to

assess publication bias. For CD33 rs3865444, the shapes of the funnel plots show no evidence of publication bias under either the allele model (Begg's test, $p = 0.972$; Egger's test, t = 0.04, $p = 0.972$) (Fig. 5), dominant model (Begg's test, $p = 0.828$; Egger's test, t = -0.22, $p = 0.828$), recessive model (Begg's test, $p = 0.862$; Egger's test, t = 0.18, $p = 0.862$), or additive model (Begg's test, $p = 0.333$; Egger's test, t = 1.02, $p = 0.333$). For ABCA7 rs3764650, there was also no significant publication bias for the allele model (Begg's test, $p = 0.118$; Egger's test, t = 1.66, $p = 0.118$) (Fig. 5), dominant model (Begg's test, $p = 0.674$; Egger's test, t = -0.46, $p = 0.674$), recessive model (Begg's test, $p = 0.606$; Egger's test, t = 0.55, $p = 0.606$), or additive model (Begg's test, $p = 0.459$; Egger's test, t = 0.80, $p = 0.459$).

4. Discussion

In this meta-analysis, a systematic overview of case-control studies for assessing the association between genetic variants and susceptibility to AD was performed. This meta-analysis, including data

Table 4. Meta-analysis of the ABCA7 rs3764650 polymorphisms with Alzheimer's disease

ABCA7 rs3764650 polymorphism

Genetic model	Cases/controls(n/n)	Ethnicity	No. of studies	OR (95% CI)	p-value	I^2 (%)
allele(G vs. T)	52214/82948	Overall	8	1.06[1.00, 1.13]	0.06	49
	2504/2898	Asian	3	1.06[0.94, 1.19]	0.33	0
	49710/80050	Caucasian	5	1.06[0.99, 1.14]	0.1	59
Dominant(GG + GT vs. TT)	4995/10333	Overall	8	1.20[1.10, 1.31]	< 0.0001	30
	962/895	Asian	3	1.00[0.83, 1.19]	0.96	0
	4033/9438	Caucasian	5	1.28[1.16, 1.41]	< 0.00001	0
Recessive(GG vs. GT + TT)	4995/10333	Overall	8	1.59[1.12, 2.28]	0.01	44
	962/895	Asian	3	1.34[0.79, 2.26]	0.28	70
	4033/9438	Caucasian	5	1.96[1.27, 3.04]	0.002	9
Additive(GG vs. TT)	3886/8484	Overall	8	1.44[1.13, 1.83]	0.003	36
	606/535	Asian	3	1.23[0.92, 1.66]	0.16	23
	3280/7949	Caucasian	5	1.96[1.30, 2.94]	0.001	5

CD33: siglec-3; ABCA7: ATP-Bing Cassette, sub-family A; OR, odds ratio; CI, confidence interval

from different ethnic groups, may provide a more holistic view of associations. However, the current meta-analysis is somewhat limited. Significant heterogeneity between studies was observed for some comparisons, primarily due to limited sample size, variability among populations, and variations in genotyping and experimental design. Additionally, only data published in selected databases were included. Possibly relevant unpublished studies reporting invalid results were missed, leading to the reported results containing inaccuracies. Despite such limitations, the random or fixed effect model was selected according to the heterogeneity. Hardy-Weinberg equilibrium, sensitivity, and publication bias were also tested. Allele model genotype data were provided in only three of ten studies of CD33. Thus, it is unclear how each study might affect the results of the meta-analysis. ABCA7 likely generates relatively little impact due to the inclusion of specific genetic information.

Many independent studies are concerned with and report the relationship between rs3865444 and AD susceptibility. For example, Omoumi et al. [23] and Chung et al. [27] suggested that rs3865444 can reduce susceptibility to AD, while Deng et al. [28] and Tan et al. [25] demonstrated rs3865444 as a risk factor for AD. Several meta-analyses have also been reported. For example, in a meta-analysis based on 11 studies, Bao et al. [34] showed that rs3865444 is associated with a decreased risk of AD susceptibility (OR = 0.94, 95% CI, 0.90–0.98, p = 0.003), which is consistent with a meta-analysis based on eight studies reported by Li et al. [35](OR = 0.94, 95% CI, 0.91–0.97, p = 1.22E-11). However, no significant association was observed between rs3865444 and AD susceptibility in the current meta-analysis. There are many reasons for different results. Firstly, meta-analyses reported by Bao et al. [34] and Li et al. [35] provide only allelic patterns Although subgroup analyses were also reported, no dominant, additive, or recessive genetic models were investigated. These latter three model types are very important for meta-analysis. Secondly, recently published data have been included here and will have an impact on the results of this meta-analysis. Finally, racial differences also impact meta-analyses. The association between rs3865444 and AD under various specific genetic models have first been reported here. Sensitivity analysis and publication bias analysis indicates these results are robustand exhibit no publi-

cation bias. As only four Asian-based studies were included in this meta-analysis [25, 27, 28, 30], the was a relatively small number of Asians when compared to the Caucasian sample size. Further studies are strongly advised for Asian, African, and Caucasian populations to further confirm any association between the rs3865444 SNP and AD susceptibility in other ethnic groups.

The current meta-analysis is based on eight case-controlled studies, including 52,214 patients with AD and 82,948 controls from Asian and Caucasian populations, for comprehensive analysis of the association between rs3764650 SNP and AD susceptibility. Bamji-Mirza et al. [36] suggested that the rs3764650 SNP is significantly associated with AD risk. However, articles have reported that the rs3764650 SNP lacks any association with AD [23, 25–27, 32]. A meta-analysis by Liu et al. [37] based on nine studies suggested that rs3865444 indicates increased risk for AD susceptibility (OR = 1.21, 95% CI, 1.17–1.26, p< 0.001), which is inconsistent with a meta-analysis reported by Bao et al. [34] based on 11 studies (OR = 0.94, 95% CI, 0.91–0.97, p< 0.001). A more significant association is reported between rs3764650 and AD susceptibility in this meta-analysis (OR = 1.28, 95% CI, 1.16–1.41, p< 0.00001) under the dominant model. The reason for the difference is likely that criteria for article selection was different. This meta-analyses has a larger sample size and more comprehensive analysis that includes dominant, additive, and recessive genetic models.

It is well known that CD33 and ABCA7 play significant roles in AD pathogenesis. Cao & Crocker [38] have previously suggested that increased CD33 expression of microglia may result in significantly reduced amyloid beta (Aβ) peptide phagocytosis, which reduces the risk of developing AD. Griciuc et al. [4] also recognized that the minor allele A of CD33 rs3865444 was associated with reductions in both CD33 expression and insoluble amyloid beta 42 (Aβ 42) levels in AD brain. Pahnke et al. [39] have indicated that the ABCA7 protein is involved in the processing of amyloid precursor protein. Mao et al. [30] have suggested from in vivo imaging that ABCA7 genotypes contribute to AD risk through involvement in amyloid deposition, but not tau pathology. A single nucleotide polymorphism (SNP), rs3764650 in ABCA7, is reportedly associated with neuritic plaque burden in AD brains, Chan et al. [18]. Although no significant

association was observed between rs3865444 and AD susceptibility in this meta-analysis, CD33 and ABCA7 play significant roles in AD pathogenesis. Better-designed studies with larger sample sizes are needed to more comprehensively analyze the associations, which may further reveal the relationship between Alzheimer's disease and genetic polymorphism.

5. Conclusion

The pooled effect of CD33 rs3865444 showed no significant relationship with susceptibility to AD under the various genetic models investigated in this meta-analysis. ABCA7 rs3764650 was associated with an increased risk in AD for the dominant model, recessive model, and additive model, while no significant association was revealed by the allele model. The results of this meta-analysis indicate that ABCA7 rs3764650 might increase the risk of AD, especially among Caucasian populations, contrary to what found for an Asian population.

Acknowledgments

Conflict of Interest

All authors declare no conflict of interest.

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