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META-ANALYSIS

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Associations Between Genetic Variants in 19p13 and 19q13 Regions and Susceptibility to Alzheimer Disease: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Alzheimer disease (AD) has become an epidemic within the growing elderly population and effective therapies of AD have not been discovered. Genetic factors accounted for over 70% of the incidence of AD and the disease-related polymorphisms are located on chromosome 19, which is one of several prominent chromosomes related to the development of AD. Many inconsistent associations between polymorphisms in *ABCA7, CD33,* and *TOMM40* genes and the susceptibility to AD have been suggested by several independent studies.

Material/Methods: A comprehensive literature search for studies involving the association between gene polymorphisms and AD was performed, and we finally selected 3 genes (4 polymorphisms) for the meta-analysis: *ABCA7* (rs3764650), *CD33* (rs3865444), and *TOMM40* (rs157580, rs2075650).

Results: A total of 25 articles investigating 3 genes (4 polymorphisms) were included in the meta-analysis. The pooled results of 4 polymorphisms were all significantly associated with the susceptibility to AD. The pooled effect of *ABCA7* rs3764605 allele G was significantly associated with an increased the risk of AD (OR=1.20, 95% CI: 1.14–1.26, *P* value <0.001). Similarly, our evidence suggested that allele A of *TOMM40* rs2075650 polymorphism was a risk factor for AD (OR=2.87, 95% CI: 2.46–3.34, *P* value <0.001). Alleles A of *CD33* rs3865444 and A of *TOMM40* rs157580 were both protective factors for AD onset (OR=0.94, 95% CI: 0.90–0.98, *P* value=0.003; OR=0.62, 95% CI: 0.57–0.66, *P* value <0.001).

Conclusions: Results from the meta-analysis revealed that the pooled *ABCA7* rs376465, *CD33* rs3865444, *TOMM40* rs157580, and rs2075650 variants were significantly associated with the susceptibility to AD. However, the association differed significantly between Asian and Caucasian groups for SNPs of *CD33* rs3865444, *TOMM40* rs157580, and rs2075650.

MeSH Keywords: Alzheimer Disease • Chromosome Aberrations • Polymorphism, Single Nucleotide

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Background

Alzheimer disease (AD) is a complicated neurodegenerative disease common in elderly people [1] and it has become a major threat to the growing elderly population due to the lack of effective therapies [2]. Several strategies, including the prevention of amyloid buildup and the promotion of amyloid removal, have been tested in a range of clinical trials. However, none of these strategies showed significant efficacy [3–5]. More attention has been paid to those factors that affect the disease in its early stage and it is estimated that genetic risk factors contribute to approximately over 70% of the incidence of AD [6]. As a result of this, the identification of genetic risk factors enables us to understand the disease mechanism in a sensible way [7].

Until now, only apolipoprotein E ε4 (*APOE4*) allele has been confirmed to be associated with increased risk of AD development [8]. The *APOE4* gene is located in chromosome 19, which is one of several prominent chromosomes associated with the development of AD [8]. Recently, other genes in chromosome 19 associated with altered risks of AD, including *ABCA7* (ATP-Binding Cassette, sub-family A, member 7), *CD33* (Siglec-3), and *TOMM40* (Translocase of the Outer Mitochondrial Membrane 40) [9–11], have been identified by several large-scale genome-wide association studies focusing on disease-associated single-nucleotide polymorphisms (SNPs).

The important role of *ABCA7*rs3764650 polymorphism (location: 19p13) in AD pathogenesis has been investigated by several studies that suggested different associations between gene SNP and AD [12–15]. Apart from that, the *CD33* (location: 19q13) gene was observed to be associated with various immune functions, including cell adhesion, anti-inflammatory signaling, and endocytosis [16]. The protective allele A of rs3865444 in this gene has been revealed to be associated with a reduced risk of AD in genome-wide studies [9,10]. Furthermore, the *TOMM40* gene is also located in the 19q13 region, which is approximately 15 kb closer to *APOE*. Therefore, the *TOMM40* gene should be investigated carefully due to the linkage disequilibrium with the e4 allele [8]. Relevant research also indicated that a kind of a mitochondrial protein is coded by the *TOMM40* gene [17]. Moreover, the mitochondrial dysfunction is closely associated with aging, particularly for AD [18]. The genetic variants of rs157580 and rs2075650 in *TOMM40* have been revealed to be associated with altered risk of AD in independent genome-wide studies since 2008 [19,20].

Considering these inconsistent associations between polymorphisms in the above genes and the development of AD, it is critical to carry out a meta-analysis in order to produce a consistent result. Additionally, differences in sample sizes and heterogeneous populations may be considered as potential sources of heterogeneity among individual studies. Therefore, we performed the present meta-analysis with increased statistical power using a well-established method to assess the association between genetic mutation and disease [21] through incorporating all available published data. This meta-analysis on all eligible related studies was performed to evaluate the association between polymorphism of *ABCA7* rs3764650 or *CD33* rs3865444 or *TOMM40* rs157580/rs2075650 and the susceptibility to AD.

Material and Methods

Search Strategies

All of the potential eligible studies were screened based on the electronic databases PubMed, EMBASE, Medline, and China National Knowledge Internet (CNKI) up to 1 December 2014 using advanced searching strategies. Five MeSH terms, "Alzheimer Disease", "Single-nucleotide Polymorphism", "*ABCA7*", "*CD33*" and "*TOMM40*", were used to search for relevant articles. Systematic searching was performed using the combination of "Alzheimer Disease", "Single-nucleotide Polymorphism (SNP)" and each one of "*ABCA7*", "*CD33*" and "*TOMM40*" with other similar eligible terms. Additional studies were screened manually from the references contained in each eligible study.

Study selection and data extraction

The following 4 criteria were used to determine the inclusion of studies: (1) studies must assess the association between polymorphism of *ABCA7*rs3764650 or *CD33*rs3865444 or *TOMM40*rs157580/rs2075650 and the susceptibility to AD; (2) case-control studies must be based on humans; (3) sufficient information should be accessible (e.g., the study sample size for each research group, allele or genotype frequencies, effect sizes, and other useful information); (4) the diagnose of AD should meet the clinical criteria set by the World Health Organization.

A predesigned data collection form was used by 2 independent reviewers to collect the following data: first author name, year of publication, country of research, ethnicity of study population, type of AD, mean age of the case and control groups, sex ratio in the case and control groups, and frequency distributions of allele and numbers of different genotypes in the case and control groups. If several subpopulations were presented in the original articles, then they were considered as separate studies in this meta-analysis. Finally, relevant studies were selected and key data were collected by 2 independent reviewers.

Statistical analysis

The associations between *ABCA7* rs3764650 or *CD33* rs3865444 or *TOMM40* rs157580 or rs2075650 polymorphisms and the

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susceptibility to AD were quantified using odds ratios (ORs) with 95% confidence intervals (CIs). The final ORs and 95% CIs for each SNP were pooled from individual study ORs and 95% CIs. Pooled ORs and 95% CIs were estimated by allelic models. For each SNP, statistical heterogeneity among individual studies was inferred by Q test and I^2 statistic; these 2 heterogeneity tests were used to calculate the variability among individual studies and the combined I^2 metric was derived to assess the percentage of variation. Meta-analysis was first performed with the fixed-effects model. If the *P* value of the Q test was greater than 0.05 and the I^2 statistic result was less than 50% (P_h >0.05 and I^2 <50%), then there was no significant heterogeneity among individual studies and the fixed-effects model was suitable for analysis. On the other hand, if the *P* value of Q test was less than or equal to 0.05 or if the I^2 statistic result was greater than or equal to 50% (P_h ≤0.05 or I^2 ≥50%), then significant heterogeneity was presented in these studies [22] and the a random-effects model was appropriate for meta-analysis. Furthermore, subgroup analyses were performed by ethnic groups (Caucasian and Asian) to explore the effects of ethnicity on the association between gene polymorphisms and the susceptibility to AD. Publication bias was indicated by the funnel plot and plot asymmetry was confirmed by the rank correlation test. If the *P* value of the rank correlation test was greater than 0.05, then there is no significant evidence of publication bias, and a symmetrical inverted funnel was approximately presented in the plot; otherwise, there was significant publication bias. The robustness of these statistical results was evaluated by the sensitivity analysis. A 2-sided *P* value of 0.05 was selected as the significance level and all statistical analyses were performed using R software (Version 3.1.2, Copyright(C) 2014 The R Foundation for Statistical Computing).

Results

Study inclusion and characteristics

A total of 175 articles were initially identified based on the predefined searching strategies, including 71 articles for *ABCA7*, 60 articles for *TOMM40,* and 44 articles for *CD33*. Then 33 of the 175 articles were excluded because of duplication and 142 articles were screened manually for potential available information. After that, 119 of 142 articles were further excluded for several reasons. For example, some articles did not include essential information to evaluate the effect size and others did not have full-text available for review. Consequently, 23 case-control articles were included in

Supplementary Table 1. Characteristics of included studies for *ABCA7* gene.

ABCA7	No.	First Author	Year	Country	Ethnicity	Case	Control	OR (95% CI)
rs3764650 T>G	01	Lambert	2009	France	Caucasians	2025	5328	1.29 (1.15–1.45)
	02	Harold	2009	UK/Ireland	Caucasians	2226	4704	1.29 (1.15–1.45)
	03	Harold	2009	Germany	Caucasians	555	824	0.98 (0.76–1.27)
	04	Harold	2009	USA	Caucasians	551	960	1.20 (0.94–1.54)
	06	Hollingworth (ADNI)	2011	USA	Caucasians	151	177	1.01 (0.58–1.76)
	07	Hollingworth (GERAD2)	2011	UK	Caucasians	3262	3320	1.32 (1.15–1.52)
	09	Hollingworth (deCODE)	2011	Iceland	Caucasians	925	612	1.23 (0.93–1.63)
	10	Hollingworth (AD-IG)	2011	USA	Caucasians	709	971	1.15 (0.83–1.59)
	11	Hollingworth (EADI1)	2011	France	Caucasians	2751	2620	1.31 (1.15–1.49)
	12	Hollingworth (CHARGE)	2011	Netherlands	Caucasians	1239	10813	1.09 (0.92–1.29)
	13	Hollingworth (MAYO2)	2011	USA	Caucasians	2490	4114	1.24 (1.10–1.40)
	14	Tan	2012	China	Asians	612	612	1.04 (0.88–1.24)
	15	Chung	2013	Korea	Asians	290	554	1.05 (0.85–1.29)
	16	Miyashita	2013	Japan	Asians	891	844	1.13 (1.01–1.26)
	17	Carrasquillo	2014	America	Caucasians	132	2486	1.08 (0.69–1.69)
	18	Liu	2014	China	Asians	350	283	1.10 (0.87–1.40)
	19	Omoumi	2014	Canada	Caucasians	580	524	1.32 (0.97–1.80)

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Supplementary Table 2. Characteristics of included studies for *CD33* gene.

CD33	No.	First Author	Year	Country	Ethnicity	Case	Control	OR (95% CI)
rs3965444 C>A	01	Logue(Logue)	2011	USA	Caucasians	513	496	0.95 (0.70–1.29)
	02	Hollingworth(GERAD1)	2011	Europe	Caucasians	3333	1225	0.91 (0.82–1.00)
	03	Hollingworth(EADI1)	2011	Europe	Caucasians	2025	5328	0.89 (0.82–0.99)
	04	Hollingworth(deCODE)	2011	Europe	Caucasians	925	612	0.85 (0.68–1.04)
	05	Naj(ADGC-GWAS)	2011	USA	Caucasians	8309	7366	0.88 (0.84–0.93)
	06	Naj(ADGC-REP)	2011	USA	Caucasians	3531	3565	0.92 (0.85–0.99)
	07	Carrasquillo(Jacksonville)	2011	USA	Caucasians	492	920	0.91 (0.77–1.08)
	08	Carrasquillo(Rochester)	2011	USA	Caucasians	312	1577	0.93 (0.77–1.12)
	09	Carrasquillo(Autopsy)	2011	USA	Caucasians	298	97	0.90 (0.64–1.27)
	10	Carrasquillo(Norway)	2011	Europe	Caucasians	327	541	0.98 (0.80–1.21)
	11	Carrasquillo(Poland)	2011	Europe	Caucasians	467	187	1.20 (0.92–1.57)
	12	Carrasquillo(ARUK)	2011	Europe	Caucasians	642	730	0.95 (0.81–1.11)
	13	Deng	2012	China	Asians	190	193	0.48 (0.35–0.66)
	14	Chung	2013	Korea	Asians	290	554	0.70 (0.53–0.92)
	15	Tan	2013	China	Asians	612	612	1.44 (1.18–1.76)
	16	Lambert(ADGC)	2013	Europe	Caucasians	10273	10892	0.89 (0.86–0.93)
	17	Lambert(CHARGE)	2013	Europe	Caucasians	1315	12968	1.00 (0.92–1.10)
	18	Lambert(EADI)	2013	Europe	Caucasians	2243	6017	0.90 (0.83–0.97)
	19	Lambert(GERAD)	2013	Europe	Caucasians	3177	7277	0.89 (0.77–1.02)
	20	Lambert	2013	Austria	Caucasians	210	829	1.08 (0.82–1.42)
	21	Lambert	2013	Belgium	Caucasians	878	661	0.95 (0.79–1.14)
	22	Lambert	2013	Finland	Caucasians	422	562	1.08 (0.89–1.30)
	23	Lambert	2013	Germany	Caucasians	972	2378	1.00 (0.89–1.13)
	24	Lambert	2013	Greece	Caucasians	256	229	0.79 (0.52–1.20)
	25	Lambert	2013	Hungary	Caucasians	125	100	0.94 (0.60–1.47)
	26	Lambert	2013	Italy	Caucasians	1729	720	1.12 (0.97–1.30)
	27	Lambert	2013	Spain	Caucasians	2121	1921	0.94 (0.85–1.04)
	28	Lambert	2013	Sweden	Caucasians	797	1506	0.99 (0.87–1.12)
	29	Lambert	2013	UK	Caucasians	490	1066	1.00 (0.84–1.19)
	30	Lambert	2013	USA	Caucasians	572	1340	0.93 (0.80–1.09)
	31	Miyashita	2013	Japan	Asians	891	844	1.04 (0.92–1.18)
	32	Omoumi	2014	Canada	Caucasians	580	524	0.76 (0.63–0.91)
	33	Walker	2014	USA	Caucasians	97	96	1.13 (0.74–1.70)

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Supplementary Table 3. Characteristics of included studies for *TOMM40* gene.

TOMM40	No.	First Author	Year	Country	Ethnicity	Case	Control	OR (95% CI)
rs157580 T>G	01	Takei	2009	Japan	Asians	539	700	0.62 (0.53–0.73)
	02	Harold	2009	UK/Ireland	Caucasians	2227	4833	0.66 (0.61–0.71)
	03	Harold	2009	Germany	Caucasians	555	823	0.67 (0.57–0.80)
	04	Harold	2009	USA	Caucasians	1159	2187	0.57 (0.51–0.64)
	05	Carrasquillo(Stage I)	2009	USA	Caucasians	844	1255	0.51 (0.45–0.59)
	06	Carrasquillo(Stage II)	2009	USA	Caucasians	1547	1209	0.58 (0.52–0.65)
	07	Naj(Discovery)	2010	USA	Caucasians	931	1104	0.66 (0.57–0.75)
	08	Naj(Replication)	2010	USA	Caucasians	1242	1737	0.49 (0.36–0.68)
	09	Cervantes	2011	Spain	Caucasians	955	869	0.74 (0.63–0.88)
	10	Valant	2012	USA	Caucasians	308	215	0.48 (0.36–0.64)
	11	Ma	2013	China	Asians	787	791	0.72 (0.57–0.92)
	12	Bagnoli	2013	Italy	Caucasians	282	269	0.72 (0.57–0.92)
rs2075650 G>A	01	Harold	2009	UK/Ireland	Caucasians	2227	4832	2.48 (2.27–2.70)
	02	Harold	2009	Germany	Caucasians	555	824	2.31 (1.92–2.77)
	03	Harold	2009	USA	Caucasians	1159	2187	2.68 (2.37–3.02)
	04	Carrasquillo(Stage I)	2009	USA	Caucasians	844	1255	2.89 (2.49–3.36)
	05	Carrasquillo(Stage II)	2009	USA	Caucasians	1547	1209	3.93 (3.39–4.57)
	06	Naj(Discovery)	2010	USA	Caucasians	931	1104	2.96 (2.50–3.50)
	07	Naj(Replication)	2010	USA	Caucasians	1242	1737	5.72 (3.63–9.02)
	08	Cervantes	2011	Spain	Caucasians	955	869	2.94 (2.31–3.74)
	09	Valant	2012	USA	Caucasians	308	215	3.39 (2.40–4.80)
	10	Schott	2012	UK	Caucasians	114	102	4.30 (2.61–7.06)
	11	Ma	2013	China	Asians	787	791	1.52 (1.19–1.94)
	12	Chung	2013	Korea	Asians	290	554	3.57 (2.51–5.06)
	13	Bagnoli	2013	Italy	Caucasians	280	272	2.10 (1.46–3.01)
	14	Omoumi	2014	Canada	Caucasians	580	524	2.58 (2.04–3.25)

the analysis. [2,6,8–12,14,20,23–36]. Studies performed by Hollingworth [9], Naj [10], Harold [20], and Lambert [29] were considered as independent studies because they included different AD subgroup analyses by different countries. Similarly, studies by Naj [10] and Carrasquillo [23] were also treated as several independent studies because they were 2-stage studies including discovery and replication. Therefore, 25 published articles were included in this meta-analysis.

The detailed characteristics of these studies are presented in the Supplementary Tables 1–3. All the research subjects came from Europe, Asia, and North America. A total of 19 739 cases and 39 746 controls were included for *ABCA7* polymorphism studies. Studies for *CD33* comprised 49 414 cases and 73 933 controls, whereas studies for *TOMM40* comprised 11 490 cases and 16 094 controls. The study populations and structures varied among all studies and only a few studies stated that the study populations were matched by race and environmental

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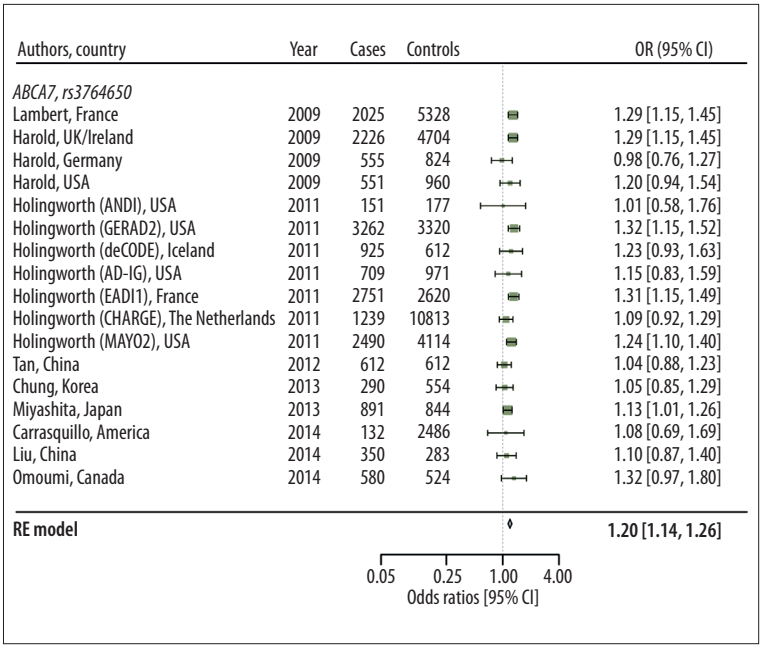

Figure 1. The forest plot of *ABCA7* genetic variation with AD.

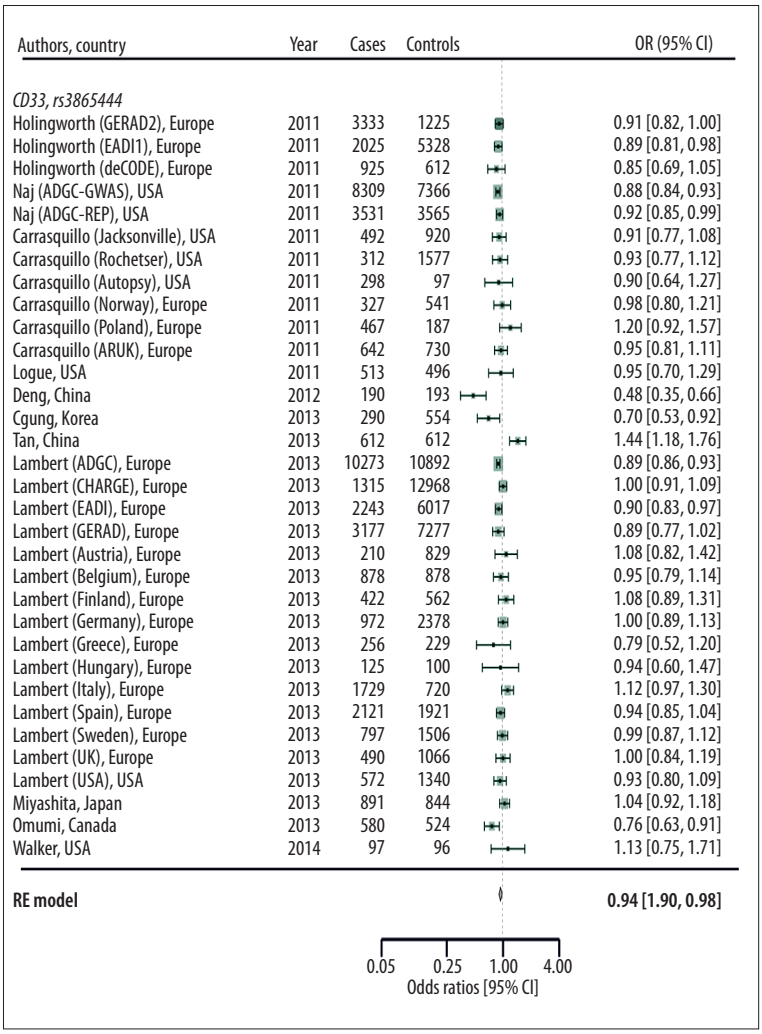

Figure 2. The forest plot of *CD33* genetic variation with AD.

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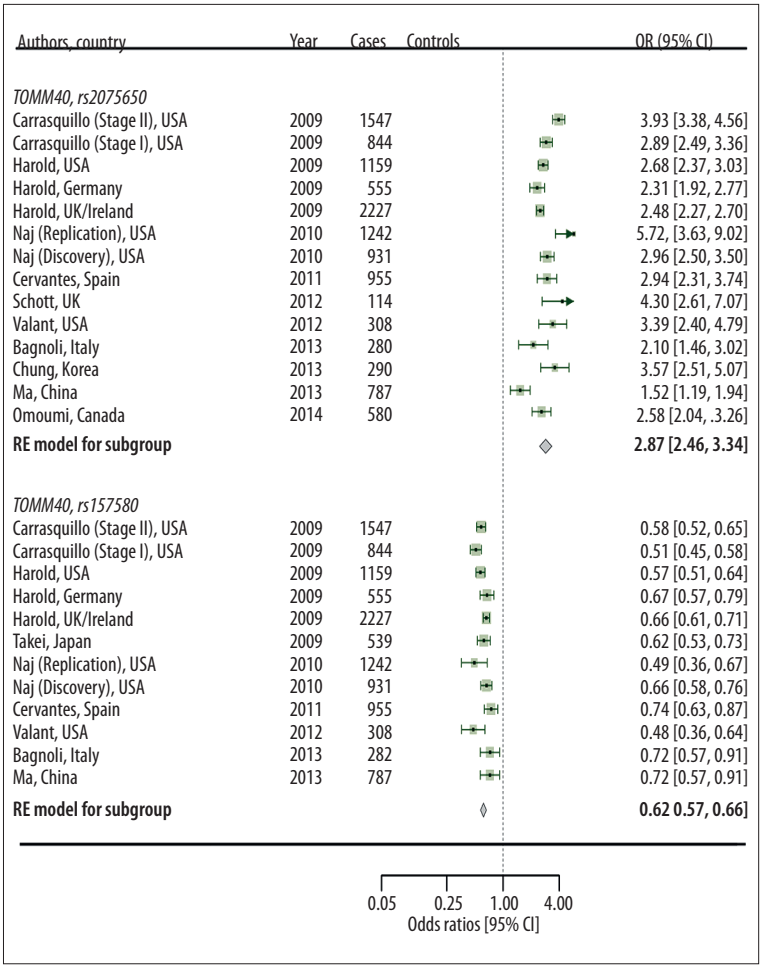

Figure 3. The forest plot of *TOMM40* genetic variation with AD.

factors. Several genotype methods were mentioned in the included research.

Meta-analyses results

The results of meta-analysis for *ABCA7* rs3764605 polymorphism are presented in Figure 1. The pooled OR was 1.20 (95% CI: 1.14–1.26, *P* value < 0.001), which suggested that *ABCA7* rs3764605 allele G was significantly associated with an increased risk of AD. As indicated by Figure 1, only 6 of 17 the studies showed significant association between *ABCA7* rs3764605 polymorphism and AD. Similarly, meta-analysis of *CD33* polymorphism rs3865444 is displayed in Figure 2, which revealed that the allele A of rs3865444 was a protective factor for AD onsets (OR=0.94, 95% CI: 0.90-0.98, *P* value=0.003). Furthermore, evidence indicated that the 2 polymorphisms of *TOMM40* had opposite associations (Figure 3); genetic variant A of rs157580 was significantly associated with a reduced susceptibility to AD (OR=0.62, 95% CI: 0.57–0.66, *P* value <0.001), while allele A of rs2075650 polymorphism was a risk factor for AD (OR=2.87, 95% CI: 2.46–3.34, *P* value <0.001).

Subgroup analysis

Table 1 shows that all polymorphisms except rs3764650 in *ABCA7* (P_h=0.362, I^2=20.42%) had significant heterogeneity among individual studies. Therefore, subgroup analyses by ethnicity (Asian and Caucasian) indicated significantly different ORs and 95% CIs for polymorphisms of rs157580, rs2075650, and rs3865444. For instance, *CD33* rs3865444 and *TOMM40* rs2075650 polymorphisms in the Asian group did not have significant association with the susceptibility to AD (OR=0.86, 95% CI=0.58–1.27; OR=2.45, 95% CI=0.45–4.45).

Publication bias and sensitivity analysis

Funnel plots were constructed to assess publication bias for each genetic variants group (Figure 4A: *ABCA7*rs3764650, Figure 4B: *CD33*rs3865444, Figure 4C: *TOMM40*rs2075650, Figure 4D: *TOMM40*rs157580). *P* value of the rank correlation test for each polymorphism was greater than 0.05 (Table 1: *ABCA7*rs3764650, *P* value=0.433; *CD33*rs3865444, *P* value=0.794; *TOMM40*-rs157580, *P* value=0.945; *TOMM40*rs2075650, *P* value=0.233), which suggested that there was no significant publication bias

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Table 1. Meta-analysis of four polymorphisms and AD susceptibility.

Gene	SNP	OR (95% CI)*	*P-value*	TAU²	I²	$P_{heterogeneity}$	$P_{funnel\ plot\ asymmetry}$	Ethnicity	
								Caucasians	Asians
ABCA7	rs3764650	1.20 (1.14–1.26)	<0.001	0.002	20.42%	0.3615	0.433	1.24 (1.19–1.31)	1.10 (1.01–1.19)
CD33	rs3865444	0.94 (0.90–0.98)	0.003	0.007	63.91%	<0.0001	0.794	0.93 (0.90–0.95)	0.86 (0.58–1.27)
TOMM40	rs157580	0.62 (0.57–0.66)	<0.001	0.009	61.97%	0.0031	0.945	0.61 (0.56–0.66)	0.65 (0.56–0.73)
	rs2075650	2.87 (2.46–3.34)	<0.001	0.067	88.05%	<0.0001	0.233	2.84 (2.54–3.13)	2.45 (0.45–4.45)

* Pooled odds ratios and 95% confidence intervals

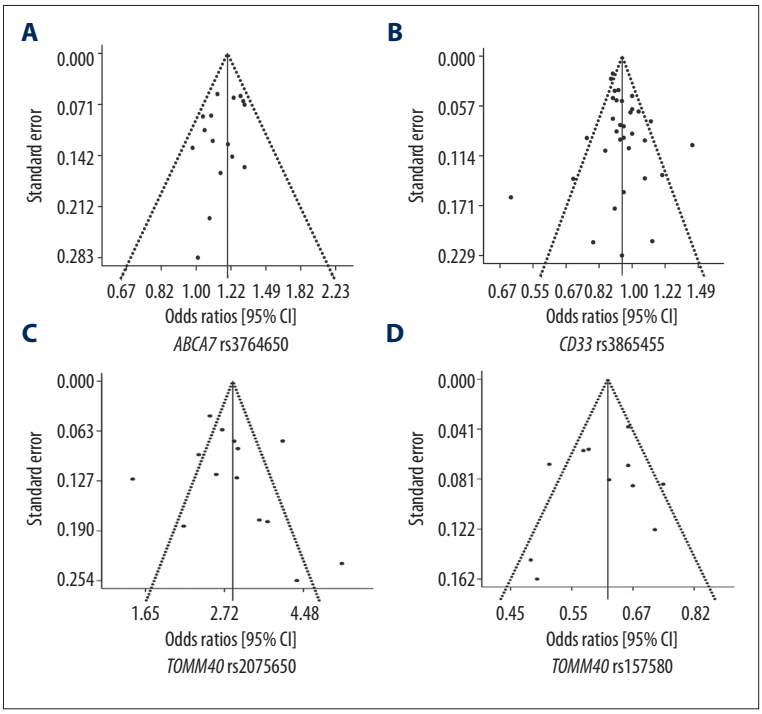

Figure 4. Funnel plot for publication bias of all included studies by genetic mutations.

in each polymorphism study. The sensitivity analyses results revealed that no individual study significantly affected the overall value of ORs and 95% CIs.

Discussion

In this meta-analysis, a systematic overview of case-control studies for assessing the association between genetic variants and the susceptibility to AD was performed. All the eligible databases were searched electronically and the potential articles were screened to be included in this meta-analysis. Eventually, 25 articles investigating 4 SNPs of 3 AD candidate genes were included in this meta-analysis. The pooled results showed significant association between the 4 SNPs (rs3764650, rs157580, rs2075650, and rs3865444) and the susceptibility to AD. Two SNPs (rs3764650 and rs2075650) were found to be significantly associated with increased risk of AD, whereas the other 2 SNPs (rs3865444 and rs157580) were significantly associated with a decreased risk of AD. In addition, subgroup analyses suggested that the association between SNPs and the susceptibility to AD was significantly different between the Asian and Caucasian groups for SNP of rs157580, rs2075650, and rs3865444.

ABCA7 is a new member of the A-subfamily, which is also an integral transmembrane adenosine triphosphates-binding cassette transporter [37]. The biogenesis of high-density lipoprotein was mediated by its protein and combined with helical apolipoproteins and cellular lipid [37]. Moreover, cholinergic dysfunction, amyloid precursor protein processing, and Aβ production of deposition, which are the neuropathologic landmarks of AD, are all regulated by local lipid homeostasis integrity [38]. Using reverse transcription-PCR analysis and Northern blot, previous studies concluded that the *ABCA7* gene is expressed in human brain, particularly on the CA1 hippocampal neurons [39–41]. Therefore, functions of the *ABCA7* gene were considered to have important

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associations with the susceptibility to AD. Furthermore, the results of our meta-analysis confirmed that rs3764650 allele G of *ABCA7* was associated with a 20% increase in the risk of AD development. In addition, the evidence suggested that the association between SNP (rs157580, rs2075650, and rs3865444) and the susceptibility to AD differed significantly between the Asian and Caucasian groups. Unfortunately, there was no available data investigating how genetic variants in Africans affect the susceptibility to AD, whereas another SNP, rs115550680 in *ABCA7,* has been discovered to be significantly associated with AD in African-Americans [42]. Based on Haploview, polymorphism of rs115550680 is in linkage disequilibrium with rs3764650. Among these 19 studies selected for our analysis, only 7 provided exact genotype numbers; therefore, meta-analysis was carried out using the allelic model only.

As a member of the sialic acid-binding immunoglobulin-like lectins (Siglec) family, the *CD33* gene is located on chromosome 19q13.3 region [43]. Previous research suggested that the main function of *CD33* related to Siglecs is immunological regulation, which is involved in the microglial cleansing process. Studies also suggested that the amyloid plaques in AD can be prevented [44,45]. *CD33* rs3865444 polymorphism was first suggested by GWAS studies as a risk factor for AD [9,10]. Moreover, Griciuc et al. reported that the increased expressions of CD33 in microglial cells were observed in AD patients [46]. However, inconsistent associations between rs3865444 polymorphism and the susceptibility to AD were suggested by several independent case-control studies. On the other hand, our meta-analysis results revealed that rs3865444 allele A contributed significantly to reduced risk of AD. However, the effect of rs3865444 allele A on the susceptibility to AD differed significantly between the Asian and Caucasian groups, as indicated by the subgroup analyses. Although the rs3865444 risk allele (C) was found to have greater cell surface expression of *CD33* in African-Americans, the complete data were not available [47]. Among included studies on rs3865444, only 4 were based on Asians. Therefore, we strongly recommend that further studies should be carried out on Africans and South Asians to confirm the association between rs3865444 SNP and the susceptibility to AD in other ethnic groups.

Tom40 is a subunit of the translocase of the outer membrane (TOM), which is encoded by the *TOMM40* gene. *Tom40* is located in the mitochondria and is involved in transporting cytoplasmic peptides and proteins during mitochondrial biogenesis [48]. The role of *Tom40* in regulating protein traffic across the outer mitochondrial membrane appears to be important in the development of AD, perhaps because of the unique bioenergetic requirements of neurons [49,50]. Mitochondrial dysfunction and oxidative imbalance have been linked to neuronal cell death and AD [48]. Two polymorphisms of *TOMM40* were first found to be significantly associated with AD in genome-wide studies. However, inconsistent associations were reported by basic case-control studies due to different study methods and target populations. To identify the genetic association between SNPs and susceptibility to AD, genome-wide analysis is a viable method with great statistical power. However, genotype data were only available in Asians and Caucasians and further studies need to be performed in other ethnic groups to assess the effect of ethnicity on the overall association between gene SNP and the development of AD.

To the best of our knowledge, this is the first study to investigate 4 SNPs of 3 different genes located on the same chromosome – chromosome 19. The present meta-analysis has several limitations. First, some articles without sufficient genotype information were excluded and this may have introduced selection bias and reduced the statistical power. Second, the meta-analysis method is not able to cope with different study designs and population structures, which might contribute to the heterogeneity among individual studies.

Conclusions

Significant associations between the 4 SNPs (rs3764650, rs157580, rs2075650, and rs3865444) and susceptibility to AD were suggested by our study. Meta-analysis based on 19 739 cases and 39 746 controls confirmed that *ABCA7* rs3764650 allele G is a risk factor of AD in both Caucasians and Asians. Furthermore, meta-analysis including 49 414 cases and 73 933 controls suggest that *CD33* rs3865444 allele A is a protective factor of AD in Caucasians but this association was not significant in Asians. In addition, meta-analyses of 2 polymorphisms in *TOMM40* (rs157580 and rs2075650) gene yielded contrary results; SNP of rs157580 was significantly associated with a reduced risk of AD, whereas SNP of rs2075650 was significantly associated with an increased risk of AD, but the association between the Asian and Caucasian groups was significantly different, as indicated by the heterogeneity test. Subgroup analysis by ethnicity was limited by the small sample size in Asians. Therefore, we recommend that well-designed studies with larger sample sizes should be performed. Genetic variants and other factors, such as individual biological characteristics and environmental factors, particularly in African and Asian populations, should be investigated together to assess the interaction between different factors that may significantly affect development of AD.

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Conflict of interest

The authors have declared that no competing interests exist.

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