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Lack of Genetic Association Between TREM2 and Alzheimer's Disease in East Asian Population: A Systematic Review and Meta-Analysis

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Abstract

Purpose: Large-scale genome-wide association studies have identified *TREM2* variants to be significantly associated with Alzheimer's disease (AD) in caucasian population. The goal of this systematic study and meta-analysis was to assess the association between Triggering receptor expressed on myeloid cells 2 (*TREM2*) variants and AD in East Asian population. **Methods:** In this study, literatures were searched in PubMed, MEDLINE, EMBASE, and the Cochrane library to screen citations from January 1990 to June 2014. Data analysis was done by using the Stata 12 software. **Results:** Twelve studies were considered for analysis. A total of 13 535 patients with AD and 22 976 healthy controls were studied. The results showed that rs75932628 variant was significantly associated with AD in caucasian population ($P < .001$, odds ratio = 3.17, 95% confidence interval 2.45-4.09). However, the association was not found in East Asian population. **Conclusion:** In our study, we found that *TREM2* variant is likely not associated with AD in East Asian population.

Keywords

Alzheimer's disease, East Asian, meta-analysis, rs75932628, TREM2

Introduction

Alzheimer's disease (AD), the most common form of dementia in the elderly patients, is a complex neurodegenerative disorder characterized by a slow but progressive loss of cognitive function. To date, genome-wide association studies have revealed several new genes associated with AD, including *APOE*, *CR1*, *CLU*, *PICALM*, *MS4A4*/*MS4A6E*, *CD2AP*, *CD33*, *EPHA1*, *TREM2*, and *ABCA7*.[1-3] Among these loci, the rare variants in *TREM2* were recently identified to be associated with AD in caucasian.[4]

TREM2 encodes a transmembrane glycoprotein consisting of 230 amino acid residues that is mainly expressed on osteoclasts and microglia, regulating inflammatory and phagocytic processes.[5] The rare missense variant p.R74H (rs75932628) of *TREM2* was found to be associated with risk of AD in Iceland, Dutch, German, and American populations.[6] With regard to Asian population, only 4 studies have investigated *TREM2* in patients with AD; however, none of them have found any association between AD and *TREM2* variants including p.R47H. Because it is a possibility that *TREM2* may be an ethnic-specific AD susceptibility variant, we carried out a meta-analysis to investigate the association between *TREM2* variants and AD in East Asian population.

Materials and Methods

Search Strategy and Inclusion Criteria

Four databases (PubMed, EMBASE, MEDLINE, and the Cochrane library) were screened to obtain citations from January 1990 to June 2014 for inclusion in this study. The key words *Alzheimer's disease* and *TREM2* were used to search relevant citations. We included those studies meeting the following 2 criteria: (1) studies evaluated the association

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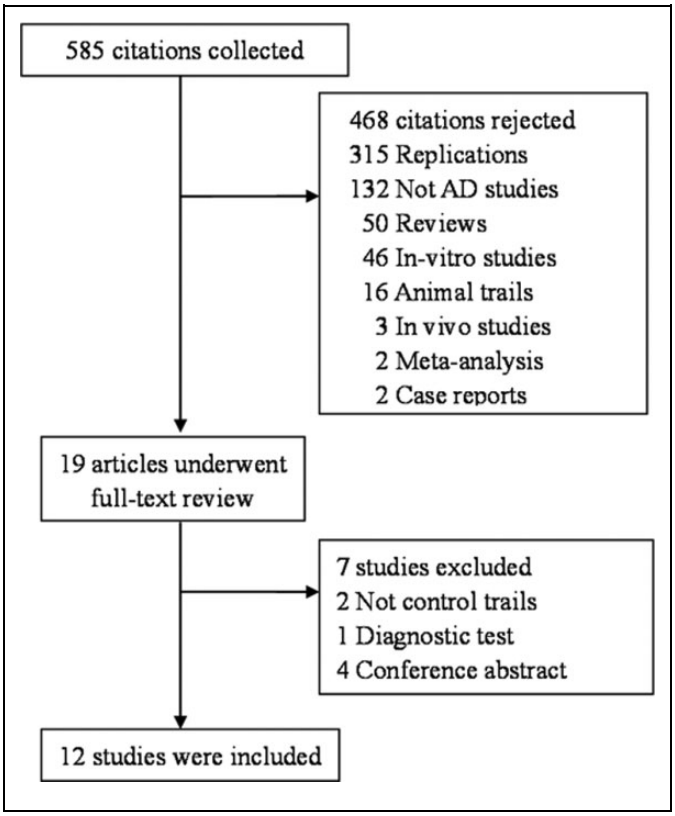

Figure 1. Flow diagram of the studies identified.

between *TREM2* variants and AD by a case–control design and (2) studies provided the numbers of *TREM2* genotype data. The search results were downloaded to a reference database and were further screened by 2 authors.

Data Extraction

For the case–control genetics studies, the following information was extracted from each study: (1) name of the first author, (2) year of publication, (3) ethnicity of the studied population, and (4) number of *TREM2* variants genotypes (rs75932628, rs2234255, and rs2234256) in cases and controls.

Data Analysis

Data analysis was performed by using the Stata 12 (Stata Corp, College Station, Texas). For each individual study, dichotomous data were reported as odds ratio (OR) with 95% confidence interval (CI). Meta-analysis was conducted using a fixed effect model. Heterogeneity between studies was evaluated by using Cochrane Q statistics and I^2 test. Subgroup meta-analysis was conducted by single-nucleotide polymorphism (SNP) and ethnicity.

In Silico Prediction

The effects of *TREM2* variants were predicted by Polymorphism Phenotyping v2 (Polyphen-2), Sorting Intolerant From Tolerant (SIFT), and SNPs&Go. The impacts of amino acid substitutions on structure and function were predicted using Polyophen-2 and SIFT. SNPs&Go was used to predict human disease-related mutations in functionally annotated proteins.

Table 1. Characteristics of the Trials Included in the Study.

Study	Population	Ethnicity	No. of Case	No. of Control	Method
rs75932628					
Yu et al[7]	Chinese	East Asian	1133	1159	PCR
Ma et al[8]	Chinese	East Asian	279	346	PCR
Jiao et al[9]	Chinese	East Asian	360	400	PCR
Miyashita et al[10]	Japanese	East Asian	2190	2498	Taqman
Gonzalez Murcia et al[11]	American	Caucasian	427	2540	Taqman
Cuyvers et al[12]	Belgian	Caucasian	1216	1094	PCR
Benitez et al[13]	Spanish	Caucasian	504	550	PCR
Ruiz et al[14]	Spanish	Caucasian	3172	2169	Taqman
Guerreiro et al[3]	European and North American	Caucasian	1091	1105	Taqman
Jonsson et al[6]	Icelandic	Caucasian	3759	11 050	Taqman
	Norwegian	Caucasian	117	2484	Taqman
	American	Caucasian	399	402	Taqman
	German	Caucasian	517	1891	Taqman
	Dutch	Caucasian	944	4950	Taqman
Pottier et al[15]	French	Caucasian	726	783	PCR
rs2234255					
Miyashita et al[10]	Japanese	East Asian	2190	2498	Taqman
Chung et al[16]	Korean	East Asian	400	605	Exome array
Cuyvers et al[12]	Belgian	Caucasian	1216	1094	PCR
Guerreiro et al[3]	European and North American	Caucasian	281	504	Taqman
rs2234256					
Miyashita et al[10]	Japanese	East Asian	2190	2498	Taqman
Chung et al[16]	Korean	East Asian	400	605	Exome array
Cuyvers et al[12]	Belgian	Caucasian	1216	1094	PCR
Guerreiro et al[3]	European and North American	Caucasian	281	503	Taqman

Abbreviation: PCR, polymerase chain reaction.

Results

Search Results and Characteristics

A total of 585 citations were obtained via database searches, among which 12 met the inclusion criteria for this study (Figure 1). Among the 12 studies identified, 5 studies were about Asian population and 7 studies were about caucasian population. A total of 8365 Asians have been involved, in which 3962 participants were patients with AD and 4403 participants were healthy controls. All 12 studies were published in full-text form. The information in these citations are summarized in Table 1.

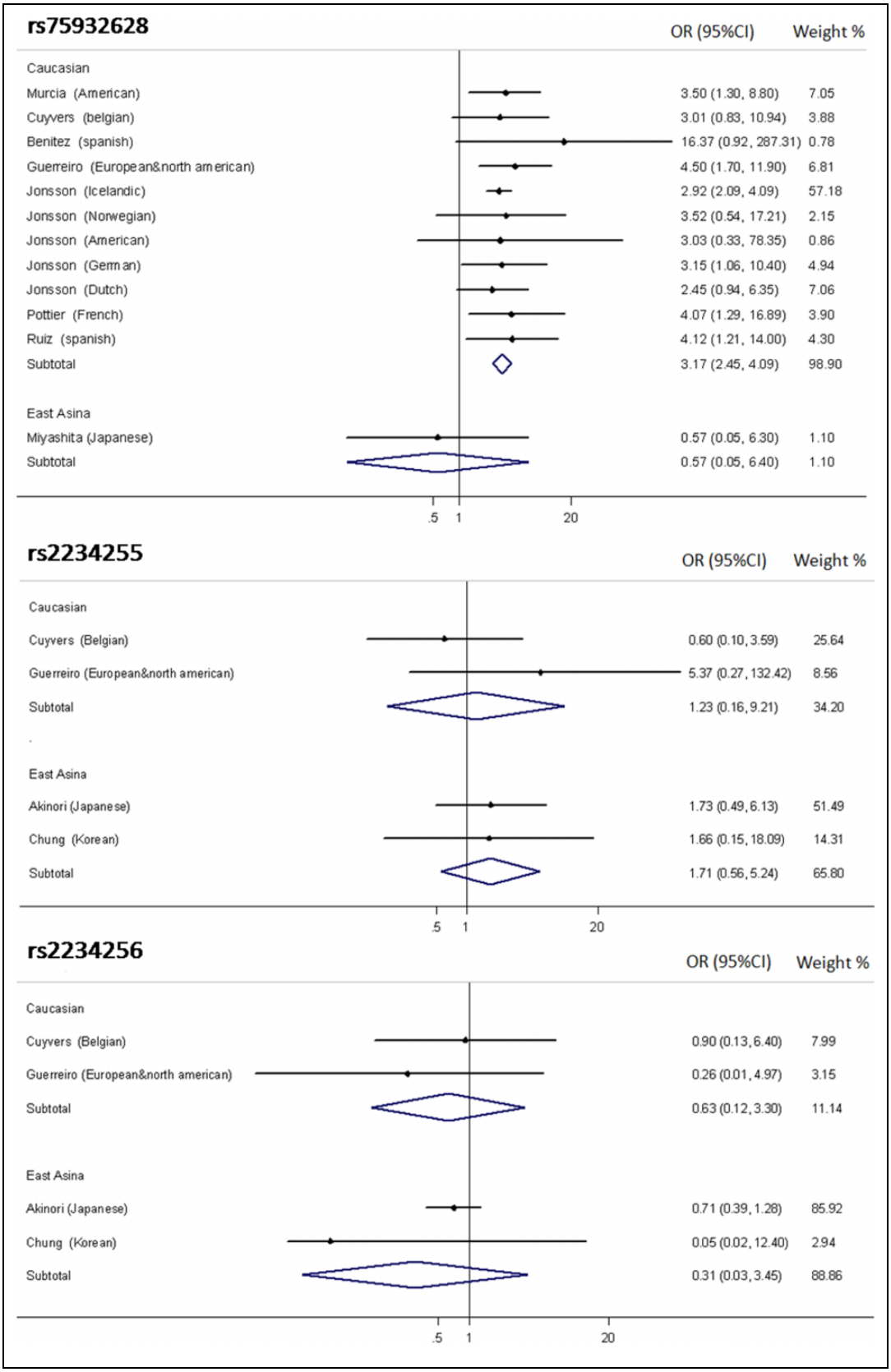

Figure 2. Forest plots for meta-analysis of the studies of *TREM2* missense mutations in Alzheimer's disease.

Table 2. The rs75932628 Variant in East Asian Population.

		Patients With Alzheimer's disease		Controls			
Study	Population	No. of Alleles	No. of Case	No. of Alleles	No. of Controls	*P* Value	OR (95% CI)
Yu et al[7]	Chinese	0	1133	0	1159	NA	NA
Ma et al[8]	Chinese	0	279	0	346	NA	NA
Jiao et al[9]	Chinese	0	360	0	400	NA	NA
Miyashita et al[10]	Japanese	1	2190	2	2498	1	0.57 (0.05-6.30)
Chung et al[16]	Korean	0	400	0	605		
Total		1	4362	2	5008		

Abbreviations: CI, confidence interval; OR, odds ratio; NA, not applicable.

The Meta-Analysis of TREM2 *Polymorphism in East Asian and Caucasian Populations*

We performed a meta-analysis of the *TREM2* polymorphism in both East Asian and caucasian populations with 3 SNPs, namely, rs75932628, rs2234255, and rs2234256 (Figure 2). There was a significant association between rs75932628 and AD with $P < .001$ (OR = 3.17, 95% CI 2.45-4.09) in caucasian population. We did not observe either rs2234255 or rs2234256 associated with AD in both East Asian and caucasian populations.

The Analysis of rs75932628 Polymorphism in East Asian Population

According to the meta-analysis results, the rs75932628 variant showed a strong association with AD in caucasian population. By pooling the data from Asian studies together, it was found that rs75932628 variant was rarer in East Asian population than in caucasian population. However, none of the studies has found the association between rs75932628 and AD (Table 2).

The Variants in TREM2 Protein

In total, 9 nonsynonymous mutations have been identified in TREM2 protein (NP_061838.1) by Asian studies (Figure 3). According to Polyphen-2 results, 6 variants (p.R47H, p.D87N, p.A105V, p.G115S, p.H157Y, and p.A192T) were considered probably damaging or possibly damaging the structure or function of the TREM2 protein (Table 3).

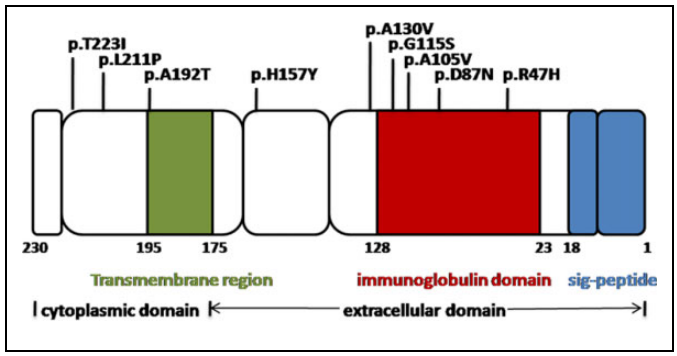

Figure 3. Schematic position of variants in TREM2 protein.

Discussion and Conclusion

TREM2 is a transmembrane glycoprotein regulating immune system. The exact function of TREM2 remained unknown. Recently, *TREM2* was identified as a novel susceptibility gene for AD in caucasian population, while there was absence of studies reporting association between *TREM2* and AD in East Asian population. Consistent with previous studies, the results of our meta-analysis showed rs75932628 variant was significantly associated with AD in caucasian population, while rs2234255 and rs2234256 were not associated with AD. A total of 9370 Asians were tested for rs75932628 variant, of which only 3 cases were detected. The mutation frequency of rs75932628 in humans was lower in East Asian than in caucasian population.

To date, 5 studies have investigated *TREM2* variants in East Asian population, including 3 Chinese studies, 1 Japanese study, and 1 Korean study. Yu et al's[7] study, which consisted of 1133 AD cases and 1159 healthy controls, examined *TREM2* variants in Han Chinese population. They discovered a nonsynonymous mutation located on exon2 of *TREM2* that leads to amino acid substitution (p.Gly115Ser) in patients with AD. However, it was not associated with increasing AD risk. Jiao et al[9] found 2 patients with AD having missense variant rs201280312 in *TREM2* with $P = .13$. None of the 3 studies from China have detected the rs75932628 variant. Chung et al[16] used Axiom Exome Genotyping Array to identify novel genetic variants in Korean patients with AD. Six *TREM2* variants were found but none of them showed a significant association with AD. Only 3 cases of rs75932628 variant (1 AD case and 2 healthy controls) were detected in Japanese population. Unfortunately, the variant did not associate with AD. So far, there is still not enough evidence to prove that *TREM2* variants increase risk of AD in East Asian population. Consistent with our study, a recent study on caucasians reported that due to the low frequency of R47H and overall modest effects on risk of AD, TREM2 variant would not possess clinical utility as a predictor or diagnostic marker for AD.[17]

Totally, 9 variants of TREM2 protein have been identified in East Asian population by current studies with minor allele frequency (MAF, < 1%).[7] To evaluate the impact of these

Table 3. In Silico Prediction of *TREM2* Variants in East Asian Population.

	Genomic Position	Protein Position	SNP Number	Polyphen-2	SIFT	SNP&Go Predicion	Reliability Index	Probability
Exon 2	41129252C>T	p.Arg47His	rs75932628	Probably damaging(1)	Tolerated(0.11)	Neutral	6	.187
	41129133C>T	p.Asp87Asn	rs142232675	Probably damaging(1)	Tolerated(0.059)	Neutral	9	.054
	41129078G>A	p.Ala105Val	rs14508091	Probably damaging(1)	Damaging(0.005)	Neutral	8	.089
	41129049G>A	p.gly115Ser	—	Probably damaging(1)	Tolerated(0.15)	Neutral	8	.108
	41129003C>T	p.Ala130Val	rs201280312	Benign(0.1)	Tolerated(1)	Neutral	7	.28
Exon 3	41127543G>A	p.His157Tyr	rs2234255	Possibly damaging(0.73)	Tolerated(0.11)	Neutral	8	.114
Exon 4	41126713C>T	p.Ala192Thr	rs150277350	Possibly damaging(0.65)	Tolerated(0.14)	Neutral	8	.121
	41126655A>G	p.Leu211Pro	rs2234256	Benign(0.001)	Tolerated(0.3)	Neutral	10	.016
	41126619G>A	p.Thr223Ile	rs138355759	Benign(0.005)	Tolerated(0.52)	Neutral	9	.028

Abbreviations: CI, confidence interval; OR, odds ratio; SIFT, Sorting Intolerant From Tolerant; SNP, single-nucleotide polymorphism.

variants, we used the online prediction softwares. The results showed that 6 variants were considered to damage the structure of TREM2 protein, of which 4 variants in immunoglobulin domain involved in a wide variety of functions usually require an interaction of the intact domain with another protein or molecule.[5] The variants located in TREM2 immunoglobulin domain were detected in 2 patients with AD and 6 healthy controls. The results indicated that *TREM2* was more rare variant in East Asia population compared to caucasian population. Possible explanations for this discrepancy may be that (1) variant frequency may be affected by the ethnic differences in genetic and epigenetic backgrounds. (2) Studies included in our meta-analysis were conducted in 3 major East Asian countries, thus the results seemed to be insufficient to reflect the real association in general East Asian population. (3) Lacking relevant unpublished results may lead to unexpected bias.

It was also noted that there were some limitations in our study. First, a potential weakness of this meta-analysis was caused by the fact that the included trials from Asian were different in study design. For example, Yu et al[7] screened variants on exon 2 of TREM2, while Miyashita et al[10] just chose 10 variants to investigate. This may result in some potential variants not to be detected. Second, considering the very low MAF of variants, the small sample size of our study had limited power to identify the association between TREM2 and AD. Third, the other races (eg, Latin American and African American) in the studies we included for analysis of caucasian may influence the results, as not all of these studies described the population composition. However, we think the influence is limited because the main population of the United States and European countries is caucasian.

In conclusion, we were not able to find association between *TREM2* variants and AD in East Asian population. Considering the studies about caucasian, *TREM2* may contribute to susceptibility of AD only in caucasians, while the association seems much weaker in East Asians. *TREM2* may not be one of the risk genes for Chinese patients with AD. Large-scale studies about Asian population and other ethnicities are needed to evaluate whether *TREM2* is associated with AD in Asian or only in caucasian population.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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