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Differential role of triggering receptors expressed on myeloid cells 2 R47H in 3 neurodegenerative diseases based on a systematic review and meta-analysis

Bin Zhang, MD[a], Rui Li, MD[a], Yufan Zhang, MD[a], Xia Gao, MD[b,*]

Abstract

Background: Recent studies have suggested that the potential functional polymorphism R47H in triggering receptors expressed on myeloid cells 2 (*TREM2*) is associated with several neurodegenerative diseases, however, the results remain inconclusive. This meta-analysis aimed to investigate the association between *TREM2* R47H and the risk for 3 typical neurodegenerative diseases: Alzheimer disease (AD), Parkinson disease (PD), and amyotrophic lateral sclerosis (ALS).

Methods: A literature review was carried out using PubMed, Medline, and Embase. Data analysis was conducted using Stata 15.0 software. The pooled odds ratio (ORs) and 95% confidence interval (CIs) were calculated.

Results: A total of 35 articles were identified as eligible: 22 on AD, 3 on ALS, 7 on PD, 2 on AD and ALS, and 1 on ALS and PD. The AD set included 23,092 cases and 30,920 controls, the ALS set included 7391 cases and 12,442 controls, and the PD set included 8498 patients and 9161 controls. We found that R47H was associated with an increased risk of AD in the total pooled population ($P < .001$, OR = 4.02, 95% CI = 3.15–5.13). However, this significant difference existed for Caucasian people (OR = 4.16, 95% CI = 3.24–5.33) but not for Asian or African people. Moreover, we did not find any significant differences in minor allele frequency distribution between the PD and control groups or between the ALS and control groups, not only for the total pooled population but also for the subgroups of different ethnicities.

Conclusion: Our study suggested that R47H in the *TREM2* gene leads to an increased risk for developing AD, but not for ALS and PD, which adds evidence to the notion that diverse pathogenesis may be involved in different neurogenerative diseases.

Abbreviations: AD = Alzheimer disease, ALS = amyotrophic lateral sclerosis, DLB = dementia with Lewy bodies, ET = essential tremor, FTD = frontotemporal dementia, MAF = minor allele frequency, MSA = multiple system atrophy, PD = Parkinson disease, *PGRN* = progranulin, TDP43 = TAR DNA-binding protein 43, *TREM2* = triggering receptors expressed on myeloid cells 2.

Keywords: Alzheimer disease, amyotrophic lateral sclerosis, association, Parkinson disease, R47H, triggering receptors expressed on myeloid cells 2

1. Introduction

Neurodegenerative diseases are characterized by a progressive loss of neuron cells in the particular regions of the brain that are correlated with each disease's symptoms. These diseases include Alzheimer disease (AD), frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), Parkinson disease (PD), and many others. In AD, this means a loss of neurons in the hippocampus and/or cortex; in ALS, motor neurons are lost, while in PD, there is a degeneration of dopaminergic neurons. These various types of damage lead to differing manifestations of motor and nonmotor symptoms.[1] However, the mechanisms that lead to neurodegeneration remain unclear.

Gene defects are prominent factors in both the etiology and pathogenesis of neurodegenerative diseases. In previous studies, gene mutations resulted in AD, ALS, and PD in only a small group of patients. In addition, hundreds of genetic variants located in dozens of genes have been associated with susceptibility to such diseases.[2] While the majority of these susceptible genes do not overlap across diseases, some mutations in certain genes, such as TAR DNA-binding protein 43 (*TDP43*), which was first reported in ALS,[3] or progranulin (*PGRN*), initially identified in FTD,[4] have been linked to other neurodegenerative diseases.[5] The rare missense variant p.R47H (rs75932628) of triggering receptors expressed on myeloid cells 2 (*TREM2*), which is a surface receptor expressed on myeloid cells, has been reported to be associated with a risk of sporadic late-onset AD for

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[a] *Department of Neurology, the First Hospital of Yulin, Yulin, Shaanxi,*
[b] *Department of Geriatrics, Dazhou Central Hospital, Dazhou, Sichuan, China.*

[*] *Correspondence: Xia Gao, Department of Geriatrics, Dazhou Central Hospital, 635000, Dazhou, Sichuan, China (e-mail: 13778389992@139.com).*

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Spanish,[6] French,[7] British,[8] Portuguese, and American people.[7,9] However, no association between *TREM2* R47H and AD has been found in people from the UK,[10] Belgium,[11] or Iran[12] in different cohorts of replication studies. Moreover, various studies with Asian people, including 4 from China[13–16] and 1 from Korea,[17] have also failed to find the R47H variant in 5 cohorts of 2958 cases and 3358 controls. In Japan, while 3 subjects carrying R47H were reported, no significant association was found between this variant and AD.[18]

The R47H variant, which is located in exon 2 of *TREM2*, has been suggested to play a key role in neurodegenerative diseases due to its function in regulating cell numbers and phagocytosis, in controlling synaptic pruning, in monitoring synaptic function, and especially in modulating inflammatory responses.[19] As a result of these important functions, the variant has also been investigated in other neurodegenerative diseases, such as FTD,[20] ALS, PD, multiple system atrophy (MSA),[21] dementia with Lewy bodies (DLB),[22] and essential tremor (ET).[23] In MSA, DLB, or ET, only 1 or 2 studies have investigated the association between R47H in *TREM2* and each disease, and either no association or a marginally significant association was found.[21–23] In AD, FTD, ALS, and PD, at least 5 independent case–control studies have explored the association between the R47H variant in *TREM2* and susceptibility for each disease. However, inconsistent or indefinite correlations between this variant and disease risks were found for AD, ALS, and PD, although a recent meta-analysis found an increasing disease risk for developing FTD.[20]

As mentioned above, limited numbers of participants were included in each study. Additionally, the differing ethnicities of participants may contribute to this picture of inconsistent or conflicting results, especially for a variant in which risk allele is rare. We therefore carried out a meta-analysis and systematic review that aimed to investigate a more precise description of the relationship between the R47H variant of *TREM2* and the risk of developing AD, ALS, and MSA by pooling 47 case–control studies from a total of 35 published articles.

2. Methods

2.1. Literature search

To identify all articles that examined the association of *TREM2* polymorphisms with these 3 neurodegenerative diseases, 2 researchers independently conducted a literature search using the PubMed, Embase, and Medline databases (from January 2013 to November 15, 2019) using the keywords "*TREM2* or triggering receptor expressed on myeloid cells 2," "polymorphism or R47H or rs75932628" PLUS "Alzheimer disease or AD" OR "Parkinson disease or PD" OR "amyotrophic lateral sclerosis or ALS." Once the articles had been gathered, reference lists were examined manually to further identify potentially relevant studies.

The R47H polymorphism includes "T" and "C" alleles. T is minor and is taken as the high-risk allele, while C is the lower-risk allele. The following analyses are based on the allelic genetic model, which can be described as the T allele versus the C allele.

2.2. Inclusion and exclusion criteria

Studies had to meet the following criteria to be eligible: evaluate the association between the R47H variant of *TREM2* and 1 of the 3 neurodegenerative diseases involved in this study; follow an unrelated case–control study design, meaning that if studies had partly overlapping participants, only the study with a larger sample was selected; measure available genotype frequency in case and control groups plus sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI); and have genotype frequencies in the control group that were consistent with the Hardy–Weinberg equilibrium (HWE).

Studies were excluded if they had one or more of the following factors: the design was based on family, sibling pairs, or case only; the genotype/allele frequency of R47H of *TREM2* was neither reported nor available; there was insufficient information for the extraction of data; or the R47H variant of *TREM2* deviated from HWE in the control group.

2.3. Data extraction

All data were extracted independently by 2 authors (BZ and RL) following the criteria listed above. For each study, the following information was extracted: the name of the first author, publication year, the ethnicity (country) of the sample, sample collection area, genotyping methods, sample size (numbers of both cases and controls), types of neurodegenerative disease, genotype frequency, minor allele frequency, *P* value, OR (95% CI), age range, and sex ratio (see Table 1 and Supplementary Table 1, http://links.lww.com/MD/D679).

2.4. Statistical analysis

Statistical analysis was carried out using STATA 15.0 (Stata Corp LP, College Station, TX). The association between *TREM2* R47H and the 3 neurodegenerative diseases was measured by calculating pooled ORs and 95% CIs. The significance of the pooled OR was measured using the *Z* test. The risk of R47H in neurodegenerative disease was evaluated through comparison with the reference wild allele C. Heterogeneity between individual studies was tested using Cochran (*Q*) chi-squared test, which is a weighted sum of the squares of the standard deviations of individual OR estimates from the overall estimation. The alpha level was set to 0.10. If the *Q* statistic was significant ($P_Q < .10$), a random-effects model was assumed; otherwise, a fixed-effects model was employed. We utilized a forest plot to graphically present the pooled ORs and 95% CIs. Each study was represented by a square in the plot, and the weight of each study was also shown. To evaluate ethnicity-specific effects, a subgroup analysis was performed according to the ethnicity of each study population. Publication bias was detected using Egger test. Additionally, Egger funnel plots were drawn. Sensitivity analysis was carried out to assess the potential influences of any single study on the pooled ORs. $P < .05$ was considered statistically significant.

2.5. Ethical review

Ethical or institutional review board approval was not required for this meta-analysis since data were extracted from previously published studies.

3. Results

3.1. Characteristics of studies

A total of 505 abstracts were retrieved by our search for "*TREM2* or triggering receptor expressed on myeloid cells 2,"

Table 1

Principal characteristics of studies included in the meta-analysis.

					Cases					Controls					
First author	Year	Ethnicity	Cohort	Genotyping	TT	CT	CC	Total	MAF (%)	TT	CT	CC	Total	MAF (%)	Control HWE
AD															
Ayer AH	2019	Caucasian	USA	TaqMan	0	18	719	737	1.22	0	16	2953	2969	0.26	0.883
Arboleda-Bustos CE	2018	Caucasian	Colombia	CASPar	1	5	352	358	0.98	0	0	329	329	0	na
Wang P	2018	Asian	China	sequencing	0	0	786	786	0	0	0	803	803	0	na
Landoulsi Z	2018	African	Tunisian	Sequencing	0	0	172	172	0	0	0	158	158	0	na
Peplonska B	2018	Caucasian	Polish	Sequencing	0	1	273	274	0.18	0	0	208	208	0	na
Jin SC	2015	African	USA	Sequencing	0	2	897	899	0.11	0	3	2468	2471	0.06	0.976
Mehrjoo Z	2015	Caucasian	Iranian	Sequencing	1	2	128	131	1.53	0	1	156	157	0.32	0.968
Rosenthal SL	2015	Caucasian	USA	Taqman	0	29	1584	1613	0.90	0	8	2919	2927	0.14	0.941
Roussos P	2015	Caucasian	USA	Sequencing	0	16	249	265	3.02	0	3	222	225	0.67	0.920
Jin SC	2014	Caucasian	European-American	Taqman	0	46	2004	2050	1.12	0	14	1602	1616	0.43	0.861
Miyashita A	2014	Asian	Japanese	Sequencing	0	1	2171	2172	0.02	0	2	2477	2479	0.04	0.984
Cuyvers E	2014	Caucasian	Belgium	Sequencing	0	10	1206	1216	0.41	0	3	1091	1094	0.14	0.964
Finelli D	2014	Caucasian	UK	CASPCR	5	7	462	474	1.79	0	2	606	608	0.16	0.968
Ma JF	2014	Asian	China	PCR-RLFP	0	0	279	279	0	0	0	346	346	0	na
Chung SJ	2014	Asian	Korea	Sequencing	0	0	400	400	0	0	0	650	650	0	na
Ruiz A	2014	Caucasian	Spanish	TaqMan, KASPar	0	18	3154	3172	0.28	0	3	2166	2169	0.07	0.974
Gonzalez Murcia J	2014	Caucasian	USA	Taqman	0	7	420	427	0.82	0	12	2528	2540	0.24	0.905
Slattery CF	2014	Caucasian	UK	MassARRAY, KASPar	1	13	957	971	0.77	0	5	529	534	0.47	0.913
Benitez BA	2013	Caucasian	Spanish	Sequencing	0	7	497	504	0.69	0	0	550	550	0	na
Pottier C	2013	Caucasian	French	CASPCR	0	15	711	726	1.03	0	4	779	783	0.26	0.943
Jiao B	2013	Asian	China	Sequencing	0	0	360	360	0	0	0	400	400	0	na
Giraldo M	2013	Caucasian	European–American	Array	0	5	990	995	0.25	0	1	578	579	0.09	0.983
Yu JT	2013	Asian	China	Array	0	0	1133	1133	0	0	0	1159	1159	0	na
Guerreiro R_1	2013	Caucasian	USA	Sequencing	1	31	1855	1887	0.87	0	15	4046	4061	0.18	0.906
Guerreiro R_2	2013	Caucasian	European-American	Taqman	0	22	1069	1091	1.01	0	5	1100	1105	0.23	0.940
ALS															
Ayer AH	2019	Caucasian	USA	TaqMan	0	1	19	20	2.5	0	16	2953	2969	0.26	0.883
Peplonska B	2018	Caucasian	Polish	Sequencing	0	0	194	194	0	0	0	208	208	0	na
Chen	2015	Asian	China	Sequenom Assay	0	0	868	868	0	0	0	869	869	0	na
Cady J	2015	Caucasian	USA	KASPar	0	10	910	920	0.54	0	3	1845	1848	0.08	0.972
Lill CM_1	2015	Caucasian	Netherlands-1	Taqman	0	2	430	432	0.23	0	3	417	420	0.36	0.941
Lill CM_2	2015	Caucasian	Netherlands-2	Taqman	0	8	1292	1300	0.31	0	10	1289	1299	0.38	0.889
Lill CM_3	2015	Caucasian	Italy (Chio)	Taqman	0	3	423	426	0.35	0	1	225	226	0.22	0.973
Lill CM_4	2015	Caucasian	Italy (SLAGEN)	Taqman	0	7	1832	1839	0.19	0	13	1684	1697	0.38	0.874
Lill CM_5	2015	Caucasian	UK	Taqman	0	7	620	627	0.56	0	15	1567	1582	0.47	0.850
Rayaprolu S	2013	Caucasian	USA	Taqman	0	5	760	765	0.33	0	6	1318	1324	0.23	0.934
PD															
Li Z	2018	Asian	China (Xiamen)	PCR	0	0	342	342	0	0	0	198	198	0	na
Tan T	2016	Asian	China (Changsha)	Sequenom Assay	0	0	512	512	0	0	0	512	512	0	na
Chen	2015	Asian	China (Chengdu)	Sequenom Assay	0	0	1216	1216	0	0	0	869	869	0	na
Feng SJ	2014	Asian	China (Guangzhou)	Sequence	0	1	475	476	0.11	0	0	432	432	0	na
Mengel D	2016	Caucasian	German	Sequencing	0	1	820	821	0.06	0	4	915	919	0.22	0.947
Lill CM_1	2015	Caucasian	Denmark	GWAS microarrays	0	5	1581	1586	0.16	0	7	1611	1618	0.22	0.931
Lill CM_2	2015	Caucasian	Norway	GWAS microarrays	0	1	597	598	0.08	0	3	663	666	0.23	0.954
Lill CM_3	2015	Caucasian	Sweden	GWAS microarrays	0	1	771	772	0.06	0	2	601	603	0.17	0.967
Rayaprolu S_1	2013	Caucasian	Irish	Taqman	0	5	362	367	0.68	0	2	368	370	0.27	0.958
Rayaprolu S_2	2013	Caucasian	Polish	Taqman	0	2	441	443	0.26	0	0	263	263	0	na
Rayaprolu S_3	2013	Caucasian	North American	Taqman	0	9	674	683	0.66	0	6	1318	1324	0.23	0.934
Benitez BA_1	2013	Caucasian	USA	NA	0	3	475	478	0.31	0	0	837	837	0	na
Benitez BA_2	2013	Caucasian	Spanish	NA	0	6	648	654	0.46	0	0	550	550	0	na

AD = Alzheimer disease, ALS = amyotrophic lateral sclerosis, HWE, Hardy–Weinberg equilibrium, MAF = minor allele frequency, PD = Parkinson disease.

"polymorphism or R47H or rs75932628" PLUS "Alzheimer disease or AD" OR "Parkinson disease or PD" OR "Amyotrophic Lateral Sclerosis or ALS." From these, 35 articles that met the inclusion criteria were found. A flow chart for the selection of studies and reasons for exclusion is shown in Fig. 1.

Aside from 2 articles[24,25] that included participants living with AD and ALS and another[26] that included those with ALS and PD, the remaining 32 articles investigated just 1 disease. Twenty-four articles,[6–18,24,25,27–35] comprising 25 studies about AD, were included in our meta-analysis (23,092 cases and 30,920

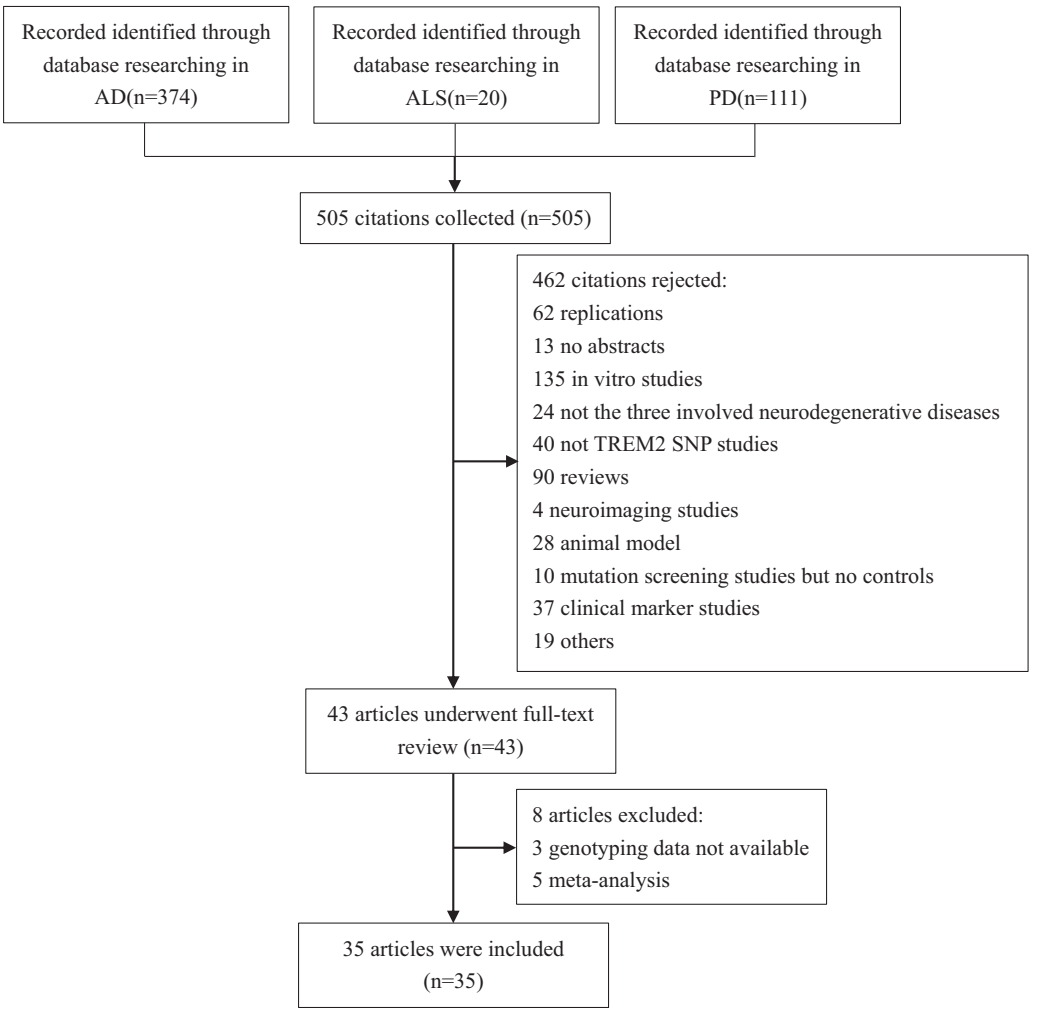

Figure 1. Flow chart of the electronic search strategy for meta-analysis.

controls), as well as 6 articles that comprised 9 studies on ALS (7391 cases, 12,442 controls)[24–26,36–38] and 8 articles that comprised 13 studies on PD (8498 cases, 9161 controls).[26,37,39–44] There were 35 studies with Caucasian people, 11 studies with Asian people, and 2 with African people. Detailed characteristics for each study in the meta-analysis can be seen in supplementary Table 1, http://links.lww.com/MD/D679 and Table 1.

3.2. Quantitative synthesis

The Q test and I^2 statistics were used to examine heterogeneity. Fixed-effects models were used for AD and PD ($P_Q > .10$), while random-effects models were used for ALS ($P_Q < .10$). The results of the meta-analysis on the association between R47H and the risk of developing neurodegenerative diseases are shown in Table 2. Pooled results showed that the T allele was associated with an increased risk of AD (OR, 4.02; 95% CI, 3.15–5.13; $P < .001$). When studies were divided according to genetic background, the results indicated that significant associations were observed in Caucasian people (OR, 4.16; 95% CI, 3.24–5.33; $P < .001$) but not in Asian or African people (Fig. 2A). Moreover, marginally significant differences in the minor allele frequency distribution between *TREM2* R47H and PD in the pooled and European subgroups were found ($P = .063$, $P = .073$, respectively) but were not found in the Asian subgroup (Fig. 2C). However, there was no significant difference found between the R47H variant and ALS, not only in the pooled but also in the ethnicity-based analysis (Fig. 2B).

3.3. Assessment of potential publication bias

Both funnel plots and Egger test were performed to assess the publication bias of the included studies. All values of Egger test were >0.10, indicating that there was no statistical evidence for publication bias among these studies. Funnel plots for the meta-analysis of the *TREM2* R47H variant in the studies under the allelic genetic model appeared symmetrical in all diseases and can be seen in Fig. 3.

3.4. Sensitivity analysis

A sensitivity analysis was conducted to evaluate the stability of the results. The omission of any study made no significant difference in the association between the R47H variant in *TREM2* and the 3 neurodegenerative diseases (supplementary

Table 2

Summary risk estimates for association between R47H of *TREM2* and 3 neurodegenerative diseases.

Stratifications	Studies	Model	Pooled estimate		Heterogeneity	
			OR (95% CI)	Pz	I^2 (%)	P_Q
AD						
Pooled	25	Fixed	4.02 (3.15–5.13)	<0.001	0.0	.708
Caucasian	17	Fixed	4.16 (3.24–5.33)	<0.001	0.0	.804
Asian	6	Fixed	0.57 (0.05–6.29)	0.647	-	-
African	2	Fixed	1.83 (0.31–10.98)	0.507	-	-
ALS						
Pooled	10	Random	1.39 (0.71–2.72)	0.618	55.4	.028
Caucasian	9	Random	1.39 (0.71–2.72)	0.618	55.4	.028
Asian	1	Random	-	-	-	-
PD						
Pooled	13	Fixed	1.62 (0.97–2.68)	0.063	28.5	.182
Caucasian	9	Fixed	1.59 (0.95–2.66)	0.076	35.8	.132
Asian	4	Fixed	2.73 (0.11–67.00)	0.539	-	-

AD = Alzheimer disease, ALS = amyotrophic lateral sclerosis, CI = confidence interval, OR = odds ratio, PD = Parkinson disease, *TREM2* = triggering receptors expressed on myeloid cells 2.

Figure 1, http://links.lww.com/MD/D680), suggesting that our results are statistically robust.

4. Discussion

This meta-analysis provides a systematic evaluation of the roles of *TREM2* R47H in susceptibility to the 3 representative neurodegenerative diseases under investigation. We found that R47H in *TREM2* increased the risk for AD in Caucasian people but not Asian or African people. However, this variant was not associated with a risk of developing ALS or PD.

TREM2 is expressed on many cells of the myeloid lineage, such as dendritic cells and osteoclasts, as well as bone marrow- and monocyte-derived macrophages. The majority of evidence suggests that TREM2 is expressed within the brain exclusively by microglia.[19] However, TREM2 expression in the central nervous system can also be seen to be regulated throughout development and displays a different expression pattern across different brain regions, such as early elevated expression in specific brain regions, and more expression in the white matter, hippocampus, and spinal cord than in other brain regions[19]; a high density of microglia is also suggested in these regions.

TREM2 regulates myeloid cell numbers, meaning that TREM2 deficiency was shown to prevent increases in brain myeloid cell populations in response to injury and disease. In addition, TREM2 improves myeloid cell survival, proliferation, and differentiation; regulates phagocytic function; and modulates inflammatory responses.[19] All of this suggests a crucial role of TREM2 in neuroimmunology and neuroinflammation. Additionally, other studies have suggested additional roles for TREM2, such as the regulation of synaptic pruning and the monitoring of synaptic function.[45] However, whether TREM2 was the cause of the pathological hallmark of neurodegenerative diseases or was activated by the pathological alterations remains unknown.

Variants in *TREM2*, such as R47H, R62H, D87N, and L211P, have been extensively found to be associated with neurodegenerative diseases.[19] Among them, R47H, a nonsynonymous substitution, was reported in many neurodegenerative diseases, such as AD, FTD, PD, ALS, MSA, DLB, and ET. Functionally, a recent study found that TREM2 carrying R47 could function to position elements of the ligand-binding surface. However, a disruption of receptor oligomerization by the R47H mutation led to ligand-induced clustering in receptor signaling as well as a reduction in soluble TREM2 levels.[46] More directly, TREM2 has an immune-mediated link to clean up Aβ aggregates by appearing to be capable of mediating Aβ internalization, while Aβ oligomers induce nuclear factor of activated T-cell (NFAT) signaling. However, R47H has been shown to reduce both Aβ internalization and downstream NFAT signaling activity in response to Aβ42.[47] Additionally, the impaired splicing and reduced *TREM2* mRNA and protein by R47H confers a loss-of-function-like phenotype in AD, including a reduced density of TREM2 around plaques and increased plaque-associated neuritic dystrophy in mice.[48] Evidence therefore suggests that the R47H polymorphism is a functional variant associated with AD.

In this review, a meta-analysis of 24 articles comprising 25 studies on the association between R47H and AD led to a large sample size. Consistent with previous functional studies, we found that the R47H variant of *TREM2* increased the risk of AD in Caucasian people but not in Asian or African people. Undeniably, the minor allele frequency (MAF) of the R47H *TREM2* variant is very low, at approximately 0.26% (172/66274) in European people and 0.09% (9/10216) in African people, and is almost absent (0/8614) in Asian people (Exome Aggregation Consortium database). Therefore, studies with large sample sizes are crucial. In 11 of 17 studies with Caucasian people, the total sample sizes for each study were >2000. In contrast, with 2 studies,[11,29] 9 studies consistently found that this variant increased the risk for AD,[6–9,30–32] which was also seen in the heterogeneity tests (Fig. 2, $I^2 = 0.0\%$, $P = .804$). For Caucasian people, the MAF is approximately 0.80% (270/33,782) in AD patients but is 0.20% (92/44,908) in control groups.

Our analyses represent the most comprehensive assessment of this issue and provide strong statistical evidence that the presence of the rare nonsynonymous variant R47H in *TREM2* increases the risk for AD by approximately 4.16-fold in Caucasians. This OR is larger than that estimated in earlier analyses (OR ~3.17),[37,49,50] which were based on smaller

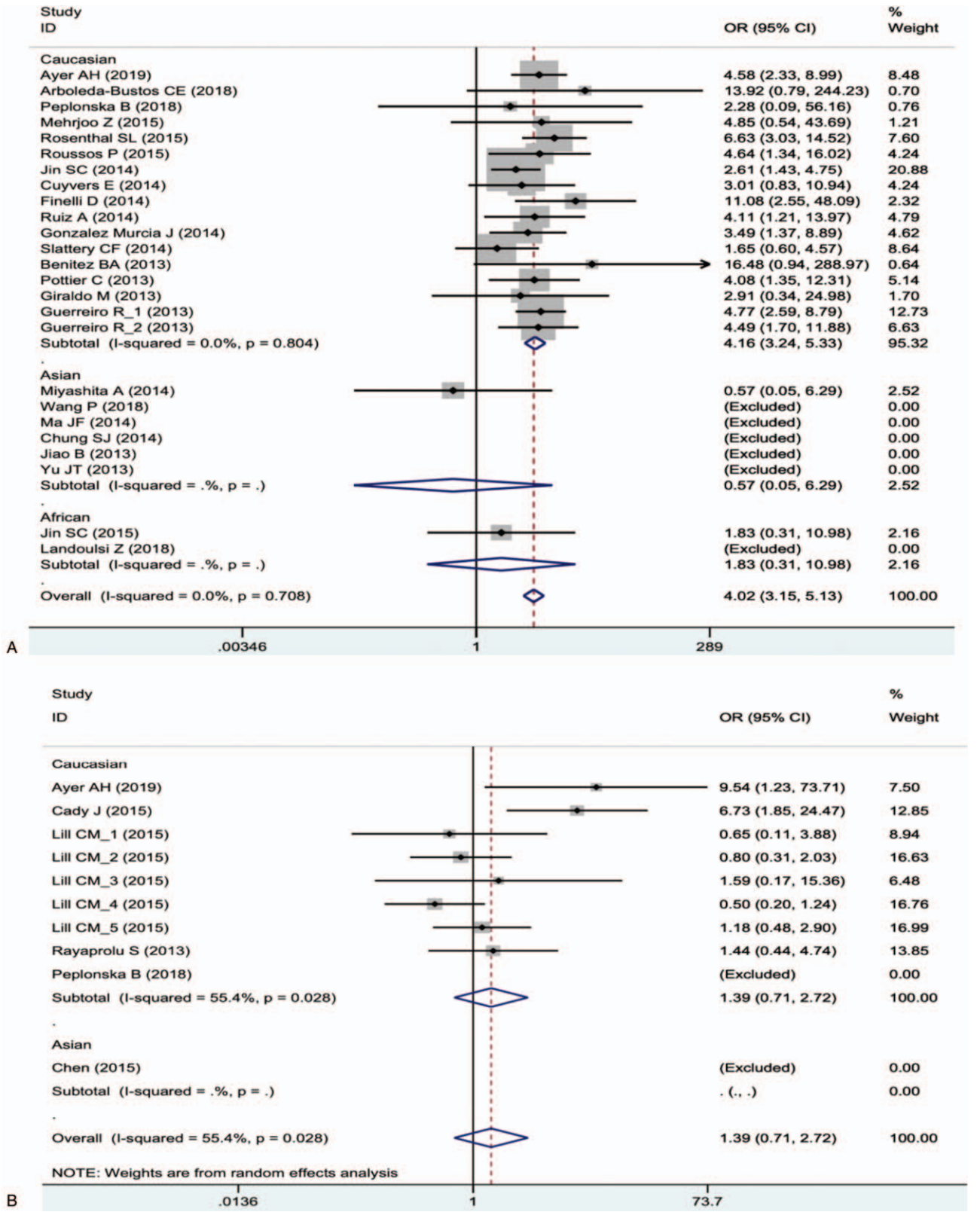

Figure 2. The forest plots of OR and 95% CI for *TREM2* variant R47H in 3 neurodegenerative diseases. Meta-analyses of data sets assessing the association between *TREM2* R47H and Alzheimer disease (AD; A), amyotrophic lateral sclerosis (ALS; B), and Parkinson disease (PD; C). The *x*-axis depicts the odds ratio (OR). Study-specific ORs (black diamond) and 95% confidence intervals (CI, lines) were calculated using an allelic model. A fixed-effect meta-analysis was calculated in AD and PD; a random-effect model was used in ALS. I^2 is an estimate of the amount of heterogeneity that is beyond chance. *TREM2* = triggering receptors expressed on myeloid cells 2.

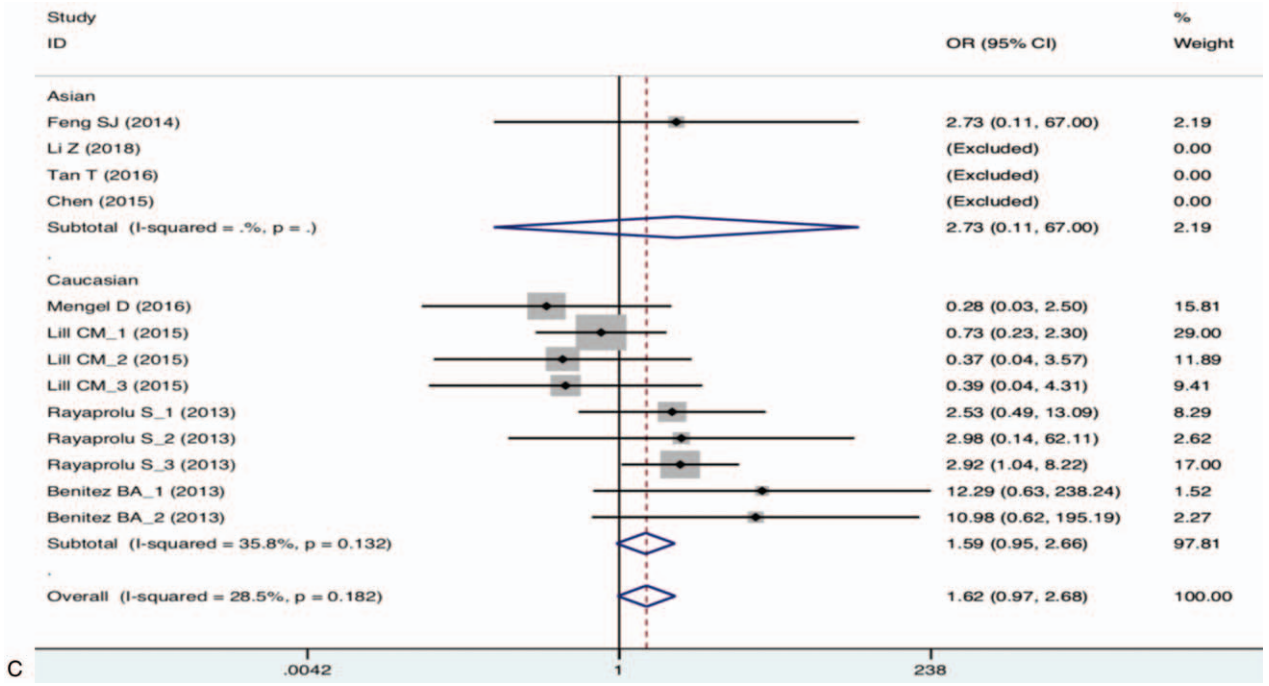

Figure 2. (Continued).

studies. While the total sample size of the AD group and control group in Asian people from 6 studies was in excess of 10,000,[13–18] the MAFs were not significantly different between AD patients and controls in Asian people, at 0.01% (1/10,260) and 0.02% (2/11,674), respectively. This result is consistent with the findings of another meta-analysis, which stated that R47H was not associated with AD in people from Asia or East Asia.[49,50] Although a recent study comprehensively analyzed the association between R47H and AD, with the cohort from Africa pooled into the Caucasian cohort,[50] we initially conducted a meta-analysis that included 2 studies on the association between R47H and AD in African people,[33,34] but this variant did not affect the AD risk for this population (0.09% [2/2142] in patients, 0.06% [3/5255] in controls). Therefore, for this variant, specific ethnicities appear to contribute to disease susceptibility.

Contrasting with the significant results observed for AD, our analyses, which combine recent and previously reported available association data for people living with PD, do not provide convincing statistical support for a role of the R47H variant in *TREM2* contributing to the risk of this disease, although an increase toward risk was found. In this meta-analysis of 9 studies, including 6402 PD patients and 7150 controls in Caucasian people,[26,37,39,40] no significant difference in the MAF distribution was found, which is consistent with the finding that it was also not associated with PD in northern European people but is inconsistent with the 3.88-fold increased risk for PD in non-northern European people found by another meta-analysis.[51] Alternatively, another meta-analysis identified that R47H increased the risk for PD by 3.59-fold in North American people but not in Europeans.[50] However, the subgroup analysis methods in these studies remain open to question,[51] as there seems to be no obvious difference in genetic background between northern European and non-northern European people or between North Americans and Europeans. In addition, the study from China included in the non-northern European group was not reasonable.[51] In the current meta-analysis, only 1 (1/9) study whose weight was 17% found a variant increase in the risk for PD (OR: 2.92, 95% [1.04–8.22]).[26] Therefore, no association between this variant and PD in Caucasian people could be accepted. In the ethnicity-specific analysis, while 4557 Asian people, including 2546 people with PD and 2011 controls, were analyzed,[41–44] only 1 PD patient carrying this variant was identified. We can therefore see that this variant may not be associated with the risk for PD.

This is the largest comprehensive assessment of the potential role of R47H in *TREM2* and ALS to date, since 6 papers comprising 10 studies were included.[24,26,36–38] No significant difference in MAF distribution was found between ALS and controls in the large sample size investigation, which included 7391 cases and 12,442 controls (0.29% [43/14782] and 0.27% [67/24884], respectively). Our results were consistent with the findings from another 2 meta-analyses involving fewer cohorts in which the variant was not found to be associated with ALS.[37,50] While it has been suggested that ALS and FTD may be within the same spectrum of disorders, our findings indicated differing pathogenesis to some degree since the recent meta-analysis found the variant to be associated with susceptibility to FTD in Caucasian people.[20]

In summary, much research has reported on the function of R47H in *TREM2*, which is linked to the pathogenesis of AD. Our study supports the notion that this variant may be involved in the development of AD, but not of PD and ALS. This, in turn, suggests that diverse pathogenesis may be involved in these different neurogenerative diseases.

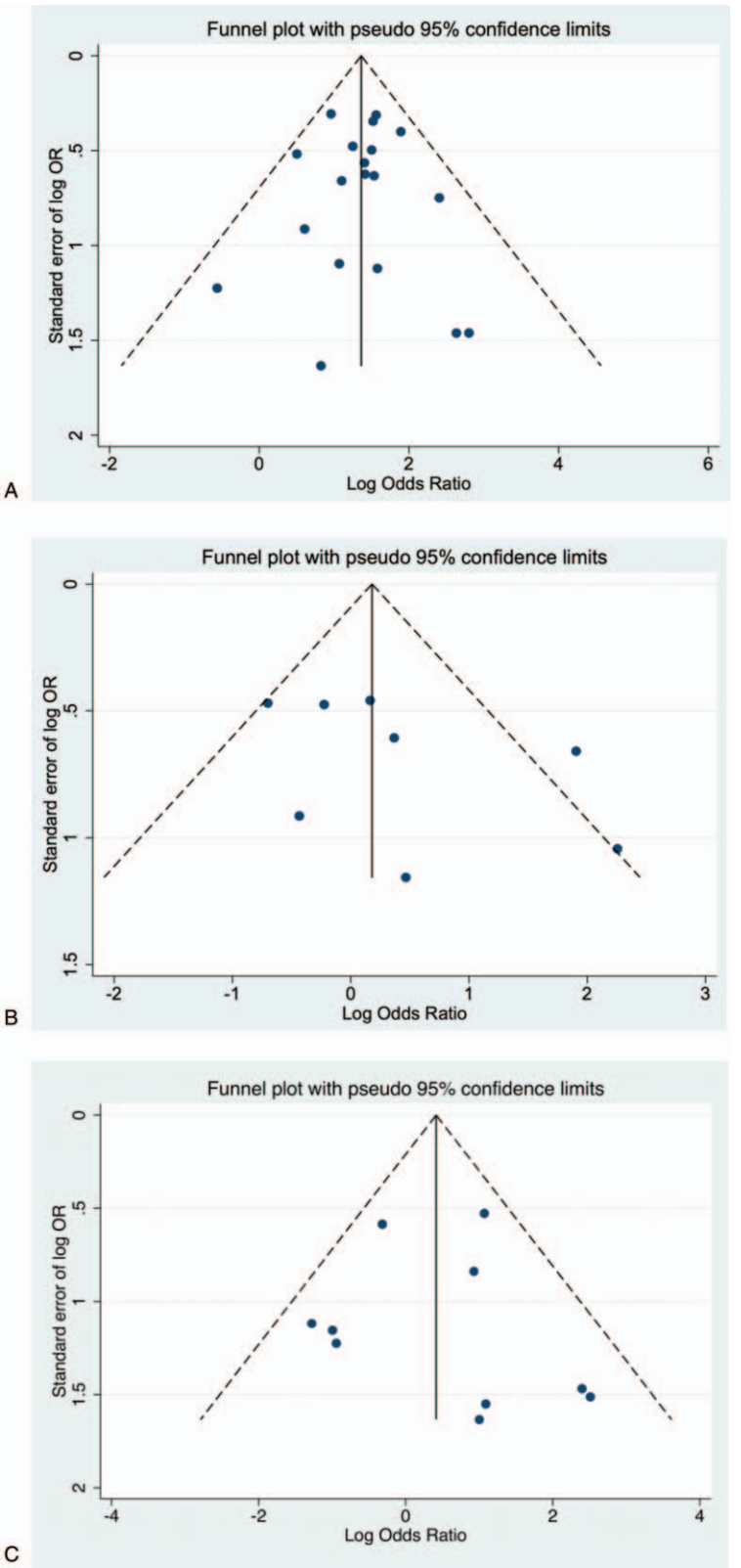

Figure 3. Egger funnel plot for publication bias analysis for *TREM2* variant R47H. A: Egger test for AD; B: Egger test for ALS; C: Egger test for PD. AD = Alzheimer disease, ALS = amyotrophic lateral sclerosis, PD = Parkinson disease, *TREM2* = triggering receptors expressed on myeloid cells 2.

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Author contributions

Data curation: Bin Zhang, Rui Li, Yufan Zhang.
Formal analysis: Bin Zhang.
Investigation: Bin Zhang, Rui Li.
Methodology: Bin Zhang and Xia Gao.
Project administration: Bin Zhang, Xia Gao.
Supervision: Xia Gao.
Writing – original draft: Bin Zhang.
Writing – review & editing: Xia Gao.
Xia Gao orcid: 0000-0003-3284-0138.

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