The most prevalent rare coding variants of TREM2 conferring risk of Alzheimer's disease: A systematic review and meta-analysis

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Abstract. Rare variants in the coding sequence of triggering receptor expressed on myeloid cells 2 (TREM2) have been identified in Alzheimer's disease (AD). They have been reported to be causative or confer risk of AD in several populations. However, the results are not conclusive. Therefore, a meta-analysis was performed to investigate the association between rare variants of TREM2 and the susceptibility to AD. Case-control studies meeting the inclusion criteria were identified by searching the PubMed, Embase and Web of Science databases. The association between four commonly analyzed variants of TREM2, p.Arg47His (R47H), p.Arg62His (R62H), p.Asp87Asn (D87N) and p.His157Tyr (H157Y), and the risk of AD were evaluated by meta-analyses with the fixed-effects model. Finally, a total of 26 datasets comprising 28,007 cases and 45,121 controls were included. There was no or low between-study heterogeneity in all comparisons. A significantly increased risk of AD was observed in carriers of R47H compared with non-carriers [odds ratio (OR)=3.88, 95% CI: 3.17-4.76, P<0.001], R62H (OR=1.37, 95% CI: 1.11-1.70, P=0.004) and H157Y (OR=4.22, 95% CI: 1.93-9.21, P<0.001). However, R62H only conferred a mild risk compared to R47H and H157Y (OR=1.37 vs. 3.88 and 4.22, respectively). D87N was not associated with AD susceptibility. Sensitivity analysis indicated that the association identified for R62H was not significant (P=0.192) when excluding a large-sample study. Subgroup analysis according to ethnicity revealed significant associations (R47H and H157Y) in Caucasians but not in Asians. In conclusion, rare coding variants of TREM2 were associated with an elevated risk of AD, particularly in Caucasians.

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Abbreviations: TREM2, triggering receptor expressed on myeloid cells 2; AD, Alzheimer's disease

Key words: TREM2, R47H, Alzheimer's disease, susceptibility, meta-analysis

Introduction

Alzheimer's disease (AD), the most prevalent form of dementia in the elderly, is characterized by the progressive loss of cognitive function. It is pathologically characterized by the extracellular accumulation of amyloid β proteins and intracellular formation of neurofibrillary tangles (1). Accumulating evidence has suggested an important role of the genetic component, which is estimated to be 60-80%, in the pathogenesis of AD (2). Numerous susceptible loci containing common variants [minor allele frequency (MAF) >5%] have been identified in recent decades (3). However, only the Ɛ4 allele of apolipoprotein E (APOE) is confirmed to be the most important variant conferring a 3- to 4-fold risk to AD (4). Furthermore, since most of the loci reside in the intronic or intergenic regions, the biological mechanisms remain difficult to interpret. With the advent of next-generation sequencing, more and more rare coding variants (MAF<1%) with a moderate effect on the risk of AD, including those in phospholipase Cγ2 (PLCG2), ABI family member 3 (ABI3) and triggering receptor expressed on myeloid cells 2 (TREM2), have been identified (5).

TREM2 is located on chromosome 6p21.1 and encodes a transmembrane protein on microglial cells. The protein is involved in the innate immunity within the central nervous system (CNS) by stimulating phagocytosis and inhibiting cytokine production (6). The association between TREM2 and AD was first suggested by findings indicating that homozygous loss-of-function variants of TREM2 caused autosomal recessive Nasu-Hakola disease, which is characterized by polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy and early-onset dementia (7). Subsequent genome-wide and exome-wide sequencing revealed that rare coding variants of TREM2 may confer a risk of AD (4,8). A rare missense variant, p.Arg47His (R47H, rs75932628), has been identified as a risk factor of AD in Caucasians (4,8), but not in African-American or Asian populations (9,10). Additional rare variants, including p.Arg62His (R62H, rs143332484), p.Asp87Asn (D87N, rs142232675) and p.His157Tyr (H157Y, rs2234255), have also been detected in

AD subjects and indicated to increase the susceptibility to AD (11,12). Furthermore, certain TREM2 mutations, such as p.Gln33stop, p.Tyr38Cys and Thr66Met, have been identified only in patients with AD but not in normal controls, and appear to be causative (13), However, due to the low frequency of these variants, studies with a small sample size may not have adequate power to identify the genetic associations (14-16). The results of association studies from different regions and ethnicities are not always consistent. Therefore, a meta-analysis for the genetic association between TREM2 rare coding variants and AD risk involving 73,128 individuals was performed.

Materials and methods

Search strategy. The PubMed, Embase and Web of Science databases were searched for articles investigating the association between TREM2 variants and the risk of AD using the following key words: ('TREM2' OR 'triggering receptor expressed on myeloid cells 2') and ('AD' OR 'Alzheimer's disease' OR 'Alzheimer disease') from inception to December 31, 2019. Additional articles were obtained by manually searching the reference lists of review and research articles.

Inclusion and exclusion criteria. For inclusion in the present meta-analysis, studies were required to meet the following criteria: i) Investigation of the association of TREM2 variants with the risk of AD in human subjects; ii) reporting on genotype data of at least one of the following four variants: R47H, R62H, D87N and H157Y; iii) studies with a case-control design with unrelated samples; and iv) providing sufficient data to calculate an odds ratio (OR) and corresponding 95% CI. If studies had overlapping samples, only the study with a larger sample size was included. Studies were excluded if they were based on family samples, used imputed data or provided insufficient genotype data.

Data extraction. A total of two independent researchers (RL and XW) extracted the following information: First author, publication year, ethnicity, sample size, genotype distribution in the case and control group and the genotyping method. Discrepancies between researchers were resolved by discussion.

Quality assessment. The present study used the Newcastle-Ottawa Scale (NOS) (17), which includes 8 items in 3 categories (selection, comparability and exposure), to assess the quality of all included studies. There are 9 stars in total, and studies having 7 or more stars were considered of high quality.

Statistical analysis. Since the four variants examined are rare in the general population, only the AD risk of carriers (heterozygous + homozygous variants) vs. non-carriers (homozygous wild-type) was compared. The OR was calculated as follows: OR=(no. of case carriers/no. of case non-carriers)/(no. of control carriers/no. of control non-carriers) and the 95% CI was determined to estimate the association strength of each variant with AD risk. Between-study heterogeneity was assessed by I^2 statistics, which indicated low, intermediate and high heterogeneity if I^2<25, 25-50 and >50%, respectively. The random-effects model was applied if there was high heterogeneity; otherwise, the fixed-effects model was used. Sensitivity analysis was performed to evaluate the impact of each study on the pooled effect size by excluding one study at a time. Publication bias was detected by Begg's funnel plots and Egger's test. All statistical analyses were performed by using STATA 12.0 (StataCorp LP). P<0.05 was considered to indicate statistical significance.

Results

Study selection. A total of 33 studies investigating the genetic association between rare TREM2 variants (R47H, R62H, D87N and H157Y) and the risk of AD were identified. However, 9 studies were excluded for the following reasons: A total of 5 did not provide any variant of interest in neither the case nor control groups (18-22), 3 used imputed data (5,23,24) and 1 did not provide genotype data (25). A total of two studies used a multi-stage strategy (8,26), and the datasets from discovery and replication stages were independently included in the quantitative synthesis. Finally, a total of 26 datasets from 24 studies (4,8-12,14-16,26-40) comprising 28,007 cases and 45,121 controls were eligible for the meta-analysis. Among these studies, 24 were for R47H (4 ,8-11,14-16,26-37,39,40), 12 for R62H (8,9,11,14-16,27,28,31,3 2,38,39), 11 for D87N (8,9,11,15,26-28,31,32,36) and eight for H157Y (8-12,26,31,36). A flowchart of the literature search is provided in Fig. 1. Regarding ethnicity, the majority of screened individuals were Caucasians (20 datasets) and the others were from African (2 datasets), Asian (2 datasets) or mixed populations (2 datasets). All studies were of high quality (≥7 stars) according to the NOS. The characteristics of all datasets included in the quantitative synthesis are listed in Table I.

R47H and risk of AD. A total of 24 datasets (26,847 cases and 43,609 controls) investigated the association between the R47H variant and risk of AD. Carriers of R47H accounted for 1.39% of AD patients and 0.35% of controls. There was no between-study heterogeneity (I^2=0) and the fixed-effects model was used. Compared with non-carriers, R47H carriers were more susceptible to AD (OR=3.88, 95% CI: 3.17-4.76, P<0.001; Fig. 2). Subgroup analysis of the datasets of Caucasian populations (20 datasets with 22,175 cases and 33,049 controls) revealed an increased risk of AD in R47H carriers (OR=3.93, 95% CI: 3.15-4.90, P<0.001, I^2=0; Fig. S1).

There were three studies reporting on the association between the R47H variant and the susceptibility to early-onset AD (EOAD), which onsets in patients below the age of 65 years. These 3 studies comprised a total of 1,758 cases of EOAD and 2,606 controls (26,27,36). The variant occurred in 2.22% of EOAD cases but only in 0.42% of controls, thus conferring a 4.86-fold increased risk (95% CI: 2.52-9.36, P<0.001, I^2=0; Fig. S2) to EOAD.

R62H and risk of AD. The R62H variant was genotyped in 12 datasets comprising 8,525 AD cases and 9,539 controls. Pooled analysis using the fixed-effects model demonstrated a higher risk of AD in carriers than in non-carriers of R62H

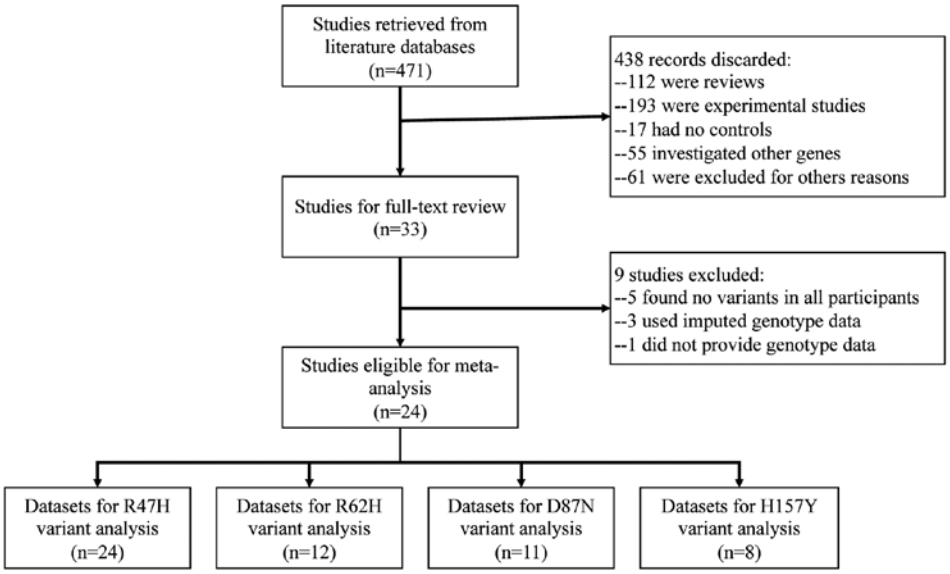

Figure 1. Flowchart of the literature search. TREM2, triggering receptor expressed on myeloid cells 2.

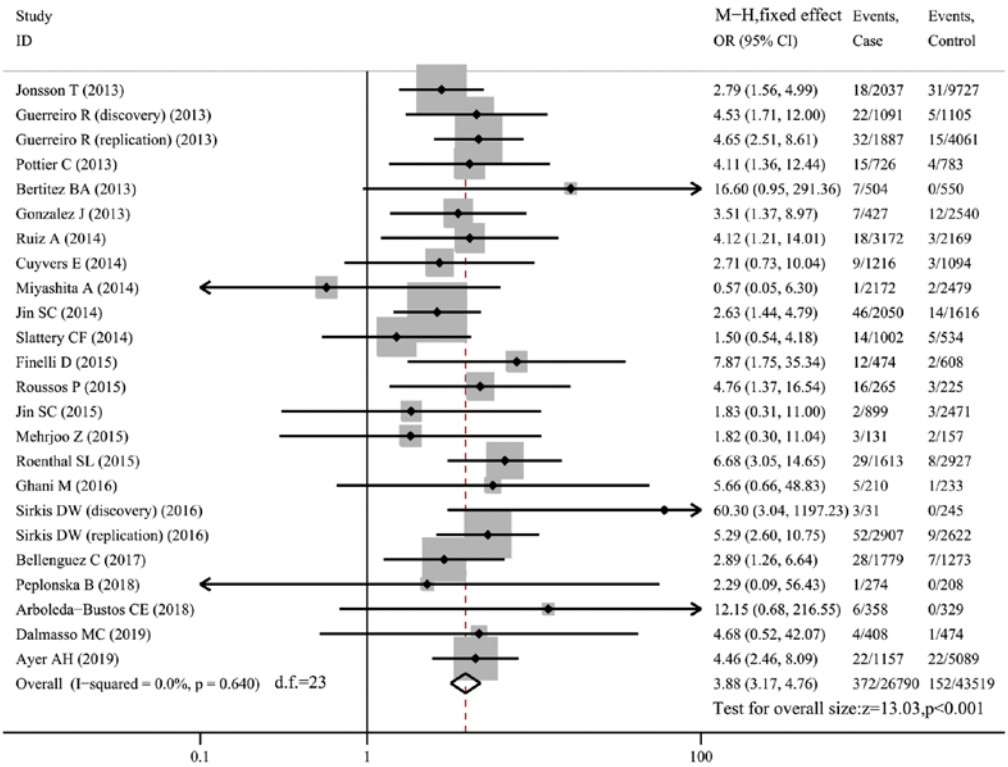

Figure 2. Forest plot for the association of triggering receptor expressed on myeloid cells 2 variant R47H with susceptibility to Alzheimer's disease. OR, odds ratio; M-H, Mantel-Haentzel method; d.f., degree of freedom.

in the whole sample (OR=1.37, 95% CI: 1.11-1.70, P=0.004, I^2=14.2%; Fig. 3) and in Caucasians only (OR=1.39, 95% CI: 1.11-1.74, P=0.004; Fig. S3). However, sensitivity analysis revealed that the association became insignificant (OR=1.17, 95% CI: 0.92-1.50, P=0.192, I^2=0; Fig. S4) when the study by Jin *et al* (11) was excluded, indicating that the study had a significant impact on the pooled effect size and was the main source of heterogeneity. In a subgroup analysis of Caucasian subjects after excluding the study by Jin *et al* (eight datasets with 13,436 subjects), no association was identified between the R62H variant and AD susceptibility (OR=1.17, 95% CI: 0.90-1.52, P=0.231, I^2=0; Fig. S5).

D87N and risk of AD. A total of 11 datasets (10,614 cases and 11,520 controls) were included in the meta-analysis on the association between the D87N variant and AD susceptibility. However, no significant associations were observed in the whole sample (OR=1.61, 95% CI: 0.94-2.76, P=0.081, I^2=0; Fig. 4) or in the Caucasian subgroup (OR=1.62, 95% CI: 0.94-2.82, P=0.084, I^2=0; Fig. S6).

Table I. Characteristics of all datasets included in the quantitative synthesis.

First author	Year	Ethnicity	Genotyping method	Sample size (cases/controls)	Variant	NOS score	Refs.
Jonsson	2013	Caucasian	Assay, Taqman	2037/9727	R47H	9	(4)
Guerreiro (discovery)	2013	Caucasian	NGS, Sequencing	1091/1105	R47H, R62H, D87N, H157Y	9	(8)
Guerreiro (replication)	2013	Caucasian	Taqman	1887/4061	R47H	9	(8)
Pottier	2013	Caucasian	Sequencing	726/783	R47H, R62H, D87N	7	(27)
Bertitez	2013	Caucasian	Sequencing	504/550	R47H, R62H, D87N	7	(28)
Gonzalez	2013	Caucasian	Taqman	427/2540	R47H	7	(29)
Ruiz	2014	Caucasian	Taqman, HRM, KASPar	3172/2169	R47H	8	(30)
Cuyvers	2014	Caucasian	Sequencing	1216/1094	R47H, R62H, D87N, H157Y	7	(31)
Miyashita	2014	Asian	Taqman	2190/2498	R47H, H157Y	8	(10)
Jin	2014	Caucasian	Taqman	2082/1648	R47H, R62H, D87N, H157Y	7	(11)
Slattery	2014	Caucasian	Sequencing	971/534	R47H, R62H, D87N	8	(32)
Finelli	2015	Caucasian	Sequencing	474/608	R47H	7	(33)
Roussos	2015	Caucasian	Sequencing	265/225	R47H	7	(34)
Jin	2015	African	Sequencing	906/2487	R47H, R62H, D87N, H157Y	8	(9)
Mehrjoo	2015	Caucasian	Sequencing	131/157	R47H, R62H	7	(14)
Rosenthal	2015	Caucasian	Taqman	1613/2927	R47H	8	(35)
Jiang	2016	Asian	NGS	988/ 1354	H157Y	8	(12)
Ghani	2016	Caucasian	NGS	210/233	R47H, D87N, H157Y	7	(36)
Sirkis (discovery)	2016	Caucasian	NGS	31/245	R47H, D87N	7	(26)
Sirkis (replication)	2016	Caucasian	NGS	2927/2633	R47H, D87N, H157Y	8	(26)
Bellenguez	2017	Caucasian	NGS	1779/1273	R47H	8	(37)
Peplonska	2018	Caucasian	Sequencing	274/208	R47H, R62H, D87N	7	(15)
Landoulsi	2018	African	Sequencing	172/158	R62H	7	(38)
Arboleda-Bustos	2018	Caucasian	KASPar	358/329	R47H, R62H	7	(16)
Dalmasso	2019	Mixed	Taqman	419/486	R47H, R62H	7	(39)
Ayer	2019	Mixed	Taqman	1157/5089	R47H	8	(40)

HRM, high-resolution melting; KASPar, KBioscience competitive allele-specific polymerase chain reaction genotyping system; NGS, next-generation sequencing; NOS: Newcastle-Ottawa Scale.

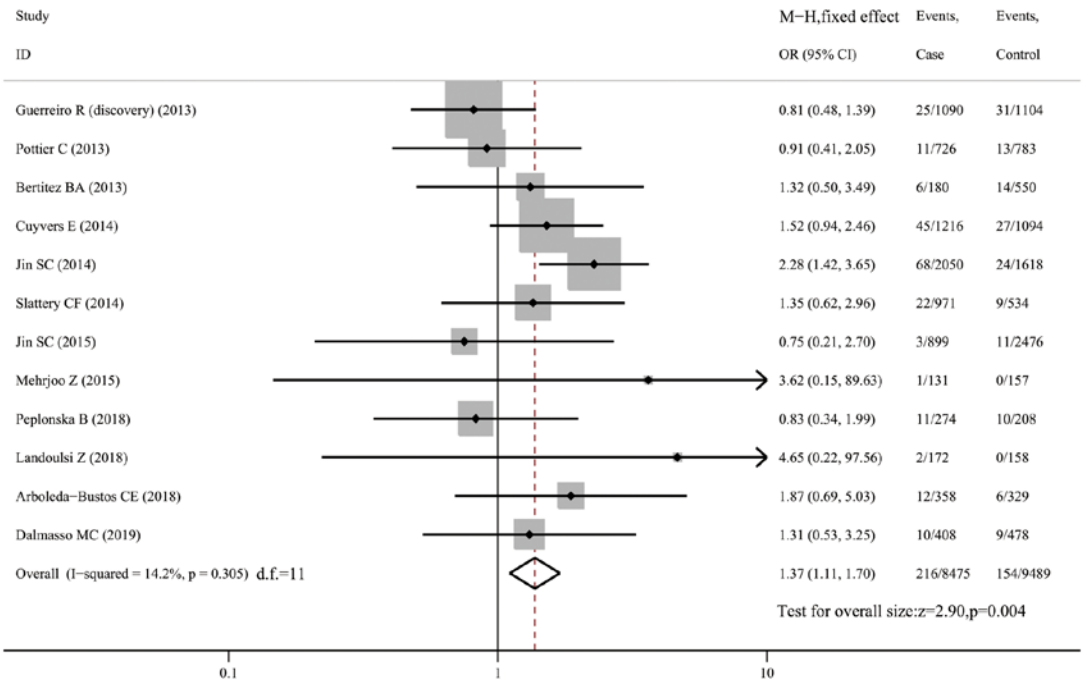

Figure 3. Forest plot for the association of triggering receptor expressed on myeloid cells 2 variant R62H with susceptibility to Alzheimer's disease. OR, odds ratio; M-H, Mantel-Haentzel method; d.f., degree of freedom.

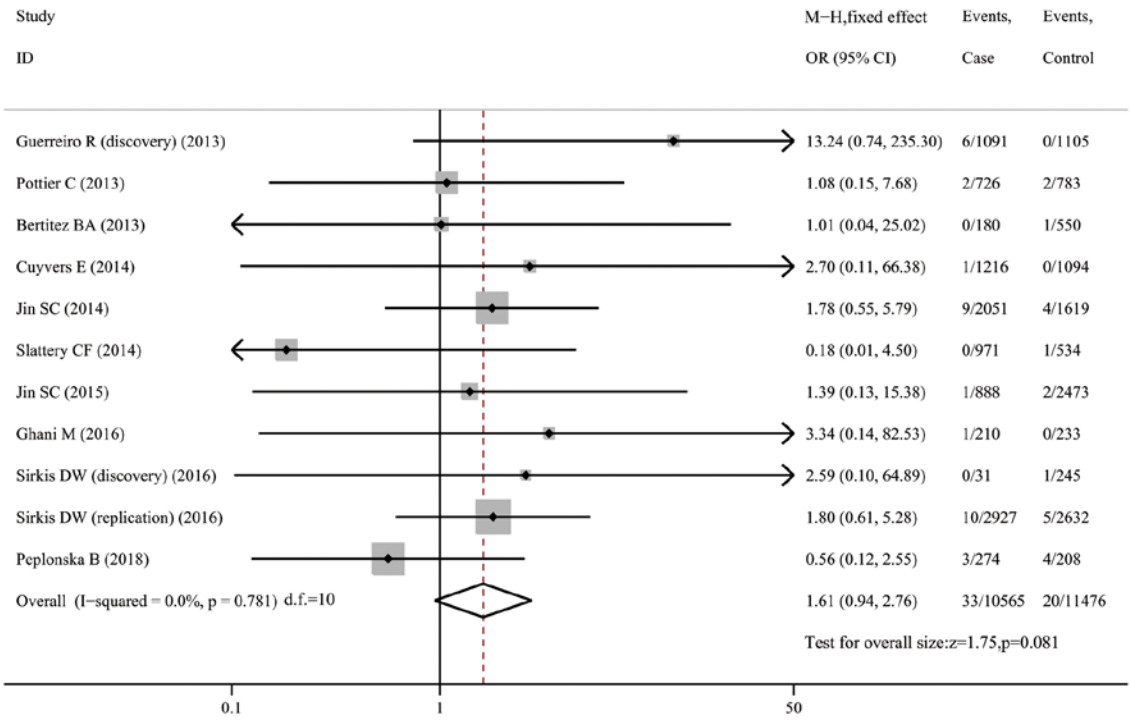

Figure 4. Forest plot for the association of triggering receptor expressed on myeloid cells 2 variant D87N with susceptibility to Alzheimer's disease. OR, odds ratio; M-H, Mantel-Haentzel method; d.f., degree of freedom.

H157Y and risk of AD. The H157Y variant was rare in AD cases (0.28%) and controls (0.05%). When pooling 8 datasets (10,096 cases and 10,099 controls) together, the analysis indicated that carriers of the H157Y variant were more predisposed to AD (OR=4.22, 95% CI: 1.93-9.21, P<0.001, I^2=0; Fig. 5). The variant conferred a 6.20-fold risk to Caucasians (95% CI: 1.60-24.04, P=0.008, I^2=0; Fig. S7) from 5 datasets, but was not associated with AD risk in Asians (OR=3.61, 95% CI: 0.61-21.37, P=0.157, I^2=55.1%; Fig. S8) from two datasets. Of note, in Caucasians, the variant was only found in AD patients (13/6,672) but was completely absent in normal controls (0/6,074).

Sensitivity analysis and publication bias. Sensitivity analysis demonstrated that none of the included datasets significantly

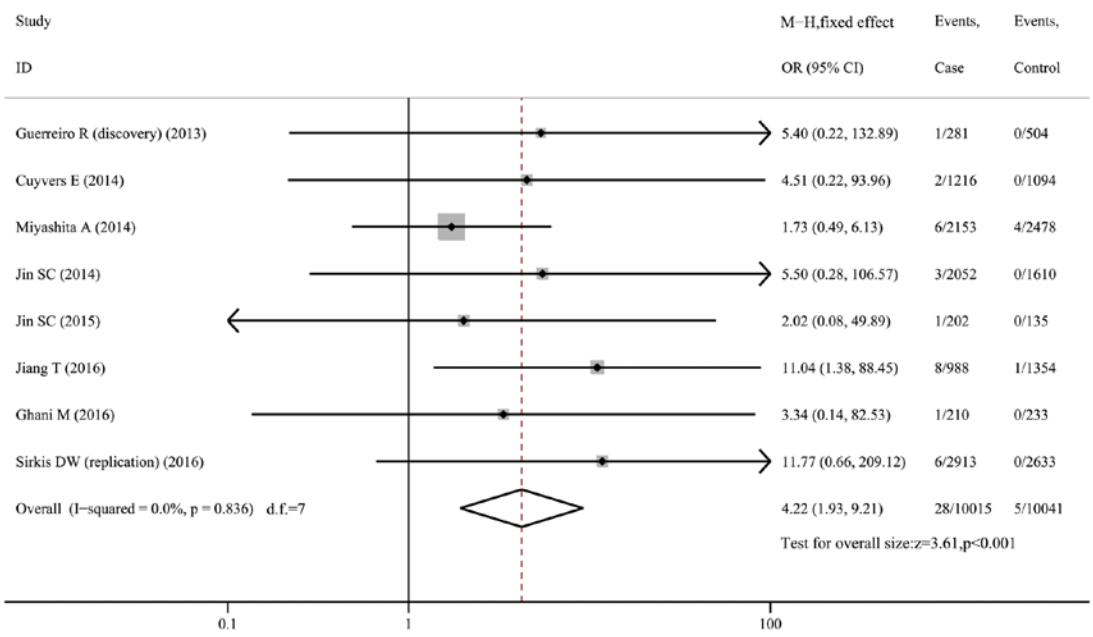

Figure 5. Forest plot for the association of triggering receptor expressed on myeloid cells 2 variant H157Y with susceptibility to Alzheimer's disease. OR, odds ratio; M-H, Mantel-Haentzel method; d.f., degree of freedom.

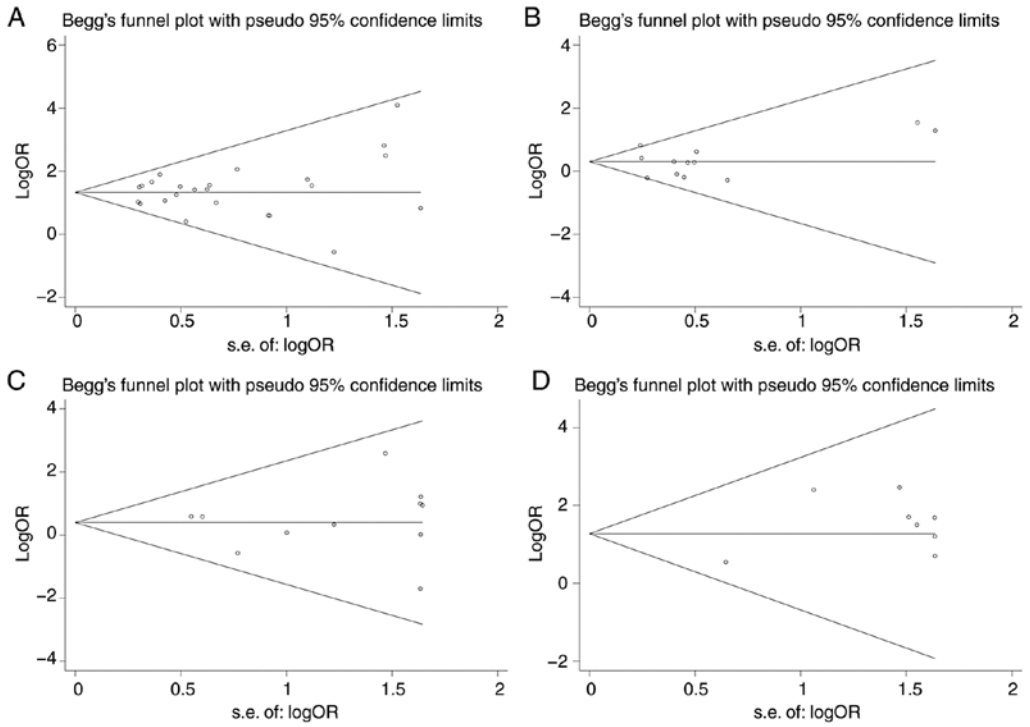

Figure 6. Symmetric funnel plots for the meta-analyses of (A) R47H, (B) R62H, (C) D87N and (D) H157Y. OR, odds ratio; M-H, Mantel-Haentzel method; d.f., degree of freedom.

affected the pooled effect size except the study of Jin *et al* (11) for the R62H variant as mentioned above. The funnel plots were symmetric for each mutation (Fig. 6) and Egger's test indicated that there was no publication bias (P>0.05).

Discussion

The present meta-analysis systematically investigated the genetic associations of four frequently reported rare variants of TREM2 with AD susceptibility. The results indicated that carriers of the R47H, R62H or H157Y variants were more vulnerable to AD.

TREM2 encodes a transmembrane immune receptor on microglial cells and exerts its effect by regulating the number of myeloid cells, enhancing phagocytosis and modulating the inflammation response in the CNS (6,41). Its pivotal role in neuroimmunology and neuroinflammation may indicate an implication of TREM2 in the pathogenesis of neurodegenerative

disease (41). Association studies have identified rare variants in the coding sequence of TREM2 as susceptibility markers for amyotrophic lateral sclerosis (42), Parkinson's disease and frontotemporal dementia (43), as well as AD. The involvement of TREM2 in the etiology of neurodegenerative diseases, particularly AD, is complex. Numerous studies have revealed that disease-associated variants (mainly R47H) of TREM2 impact amyloid pathology (44), modulate neuritic dystrophy (34), influence tau hyperphosphorylation and aggregation (45) and affect synaptic and neuronal loss (46). Although the pathogenic mechanism of TREM2 in AD may not have been conclusive, TREM2 variants are conclusively susceptibility markers for AD, as demonstrated by the present meta-analysis.

R47H is the most frequently investigated variant in TREM2. The substitution of Arg by His leads to a marked reduction in soluble TREM2 levels (47) and the binding ability to cells, APOE and various lipids (45,48,49). However, whether it reduces the mRNA and protein expression in humans remains controversial (50). Furthermore, experiments have revealed that the heterozygous R47H variant may confer a loss of TREM2 function and enhance neuritic dystrophy around plaques, thus increasing the risk of AD (51), which was ascertained by epidemiological investigations in various populations (4,8,40). The R47H variant is enriched in AD cases (1.39%) but less prevalent in cognitively normal controls (0.35%). Most of the identified variants are heterozygous (98%, 514/524) and homozygous variants are detected in AD cases only. The present meta-analysis indicated an approximately 4-fold risk of AD in R47H carriers compared to non-carriers, indicating an effect size similar to that of the APOE Ɛ4 allele (4). However, APOE Ɛ4 is much more prevalent in populations and should still be the main genetic determinant of AD susceptibility.

In addition to risk, the R47H variant may also contribute to an earlier age of onset in AD. Slattery *et al* (32) reported a markedly younger age at onset in patients with the R47H variant than in those without the variant (55.2 vs. 61.7 years on average). Similar results were obtained in Icelandic and Dutch populations (4), implying an association between R47H and susceptibility to EOAD. In the present study, pooled analysis of 3 studies (27,28,37) suggested a higher prevalence (2.22%) of R47H in EOAD cases. Carriers had 4.86-fold risk of developing EOAD, which was even higher than the effect size observed in the total AD samples.

The R62H variant disrupts TREM2 recognition of cells and APOE (52) but does not alter the binding to lipid ligands (53). Jin *et al* (11) determined that it is associated with an increased risk of AD in a population of Americans of European descent (11). The present study revealed a mildly increased risk of AD in individuals harboring the R62H variant (OR=1.38, 95% CI: 1.11-1.70, P=0.004). However, the effect size may be largely attributed to the aforementioned study (11), as indicated by the sensitivity analysis. The association was no longer significant after excluding this study (P=0.192). A significant association was only observed in the study by Jin *et al* (11), but not in any other study. It should be noted that the study by Jin *et al* (11) had a large sample size (>3,700 subjects), and thus, it may have more statistical power than the other studies to identify the association of a rare variant with AD susceptibility. Therefore, more studies with a large sample size are required to confirm the association.

The D87N variant resides within the ectodomain proximal to the stalk region of TREM2. The mutation leads to enhanced interaction of TREM2 with certain ligands (53). However, the present study did not indicate any association of the variant with AD susceptibility when 11 datasets were pooled together. Of note, D87N was identified in 4 out of 5 patients in a family affected by AD (54). It may be enriched in familial cases in contrast to sporadic cases. Another variant, H157Y, is located on the stalk domain of TREM2 but has no impact on binding activity (53). Specifically, it is located at the TREM2 cleavage site by metalloprotease ADAM metallopeptidase domain 10 and results in increased shedding of TREM2 and reduced cell surface expression of TREM2 (55). In addition, *in silico* programs [SIFT (http://sift.jcvi.org/) and Polyphen2 (http://genetics.bwh.harvard.edu/pph2/)] predicted that the variant may have a deleterious/possibly damaging impact on functions of TREM2. The present analysis, comprising 10,096 cases and 10,099 controls, revealed a significantly increased AD susceptibility in carriers of H157Y, although the variant is rare in AD (0.28%).

In the present study, a subgroup analysis was performed with regard to ethnicity, indicating an ethnicity-specific pattern of TREM2 variants. R47H and R62H were mostly identified in Caucasians but rare in Asians. Only one study from Asian (10) reported a low frequency of R47H (0.06%), whereas the other studies did not (18-22). Therefore, R47H and R62H mutations were only associated with an increased risk of AD in Caucasians. Contrary to R47H and R62H, H157Y was more frequent in Asians. Miyashita *et al* (10) reported 10 carriers out of 4,631 participants, while Jiang *et al* (12) identified 9 carriers among 2,352 participants. However, the H157Y variant was not associated with AD risk in Japanese (10) but increased the risk in a Han Chinese population (12). Of note, in Caucasians, the H157Y variant was only harbored by AD cases but by none of the controls, indicating that H157Y was more likely to be a causative variant of AD in Caucasians.

In summary, the present meta-analysis, involving >73,000 individuals, supported that rare coding variants of TREM2 are associated with AD susceptibility and may be used as predictive markers for neurodegenerative disease.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RL designed and supervised the study; RL and XW performed literature search, study selection, data curation and formal analysis; RL and PH performed quality control of studies; RL and XW prepared the original draft; RL, XW and PH critically

revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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