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Genetic association of *BIN1* and *GAB2* in Alzheimer's disease: A meta-analysis and systematic review

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Aim: Heredity plays an important role in the pathogenesis of Alzheimer's disease (AD) especially for single-nucleotide polymorphism (SNPs) of susceptible genes, which is one of the significant factors in the pathogenesis of AD. The SNPs of *BIN1* rs744373, *BIN1* rs7561528 and *GAB2* rs2373115 are associated with AD in Asian and white people.

Methods: We included 34 studies with a total of 38 291 patients with AD and 55 538 controls of diverse races from four main databases. We used meta-analysis to obtain I^2-values and odds ratios of five genetic models in three SNPs. We carried out analysis of sensitivity, subgroup, publication bias and linkage disequilibrium test.

Results: The forest plots showed the odds ratio value of the three SNPs was >1 in white individuals, but not Asian individuals, in their genetic model. The funnel plot was symmetrical, and the D'-value was 0.986 between rs744373 and rs7561528.

Conclusions: *BIN1* rs744373, *BIN1* rs7561528 and *GAB2* rs2373115 are pathogenicity sites for AD in white people, and also rs7561528 belongs to a risk site in Asian people. The rs7561528 and rs744373 SNPs have strong linkage disequilibrium in Chinese people. In addition, apolipoprotein E ε4 status promotes them to result in the pathogenesis of AD. **Geriatr Gerontol Int 2021; 21: 185–191**.

Keywords: Alzheimer's disease, bridging integrator 1, GRB-associated binding protein 2, linkage disequilibrium, meta-analysis.

Introduction

Alzheimer's disease (AD) is a condition of central nervous system degeneration characterized by progressive cognitive and behavioral impairment, and by different severities of dementia. It is the most common type of dementia seen in individuals aged >65 years, accounting for 50–60% of senile dementia.[1] AD is a global disease accompanying higher morbidity among different ethnic groups.[2] Untreated patients have a progressive course accounting for either short- or long-term disability. The latest epidemiological survey shows that there are approximately 42 million AD patients worldwide, a number expected to double every 20 years on average until 2050.[3] The main pathological features of AD include the overphosphorylation of tau protein and the formation of neurofibrillary tangles caused by amyloid deposition, which has become an important reference index for the clinical diagnosis of AD. The etiologies of AD are multiple, with genetic factors accounting for 60–80%. It is known that there are >30 common susceptibility genes, and the site mutation caused by such genes' single-nucleotide polymorphism (SNP) has become a crucial etiology of AD.[4] Relevant research shows that more than half of susceptibility loci originate from the SNP of apolipoprotein E (*APOE*), and *APOEε4*$^+$ is involved in the nosogenesis of AD four- to fivefold more than APOEε4$^-$, which suggests that an array of other pathogenic genes cause AD. This genome-wide association study confirms that both bridging integrator 1 (*BIN1*) and GRB-associated binding protein 2 (*GAB2*) play an important role in the pathogenesis of AD.[5]

Bridging protein factor 1, encoded by *BIN1*, is an adaptor protein existing in brain tissue that regulates endocytosis and apoptosis, and maintains cytoskeletal integrity. In recent years, an increasing number of studies have found that *BIN1* is a late-onset AD susceptibility gene. The SNP of *BIN1* is connected with AD's etiopathogenesis generating a detectable gene locus mutation within AD patients. Meanwhile, *BIN1* contributes to the etiopathogenesis of AD through hyperphosphorylation of tau protein.[6] GRB-associated binding protein 2, encoded by *GAB2*, is a docking protein with a conserved, folded PH domain attached to the membrane and a large disordered region. It hosts interaction with signaling molecules, playing an important role in the processes of proliferation, survival, differentiation and apoptosis of the cell as a cytoskeletal protein. The SNPs of the *GAB2* gene increase the risk of AD, and it is closely related to the pathogenesis of AD.[7] Additionally, *GAB2* predisposes the problem by increasing the phosphorylation state of tau protein.[8]

Polymorphisms of susceptible genes influence the risk of AD. The polymorphisms of identical susceptible genes vary in different ethnic groups because of the variability of the population.[9] Clinical case–control studies on AD caused by SNPs of *BIN1* or

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GAB2 in different populations have been carried out for many years. Therefore, the present study collected pre-existing susceptibility loci (such as *BIN1* rs744373, *BIN1* rs7561528 and *GAB2* rs2373112) in different ethnicities through a variety of databases. We did not choose other loci of those two susceptible genes due to the limitation availability of case–control sample data,[10,11] and also the impact of those three SNPs on AD in different ethnicities is controversial, and without any study has yet given a definitive conclusion. We determined the relationship between the SNPs of *BIN1* and *GAB2* and the pathogenesis of AD by meta-analysis of these three susceptibility sites in different races, Which provids a new perspective for the clinical diagnosis of AD.

Methods

Identification of eligible studies

To input as much data as possible, we selected four main databases from which to collect the data: CNKI, PubMed, ScienceDirect and Springer-Link. We also chose the journal with English or Chinese as their language type, as these were the languages our team was fluent in. The included literature that was published between 1 January 2007 and 1 May 2020. Additionally, we chose the keywords "BIN1 or bridging integrator 1," "GAB2 or GRB-associated binding protein 2," "single nucleotide polymorphism" and "AD or Alzheimer's disease." Having set inclusion and exclusion criteria, we used the retrieval data to identify eligible studies.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (i) case–control studies; (ii) susceptibility genes including *BIN1* or *GAB2*; (iii) case groups clinically diagnosed with AD; (iv) SNPs of susceptible genes; and (v) studies published as whole articles.

Exclusion criteria were as follows: (i) non-case–control studies; (ii) lack of confirmation of AD case; (iii) studies published as part of summaries, abstracts, books or case studies; (iv) animal research; (v) duplication of previous publications; and (vi) data scarcity.

Data extraction

After the qualified studies were obtained, their contents were extracted, including the first author, publication year, ethnicity of patients and controls, SNP, susceptibility genes and loci, *APOEε4* status and frequency, genotype, genotype frequency, mutation bases, major alleles, and Hardy–Weinberg equilibrium (HWE) evaluation results assessing factors such as the *P*-value in the case–control group. We calculated the HWE by genotype frequency in the original studies that had not detected or confirmed whether the controls conformed to the HWE or did not show the exact value. The required data can be obtained by contacting the author at the corresponding mailing address for the publication that provided the incomplete data. When relevant data cannot be attained, the research journal will be removed ($\chi^2 < 3.84$ or $P_{HWE} > 0.05$ with statistical significance).

Quality assessment

The quality of the included studies was accessed using a research article quality rating scale (Table S1) that formulates by adjusting the Newcastle–Ottawa Scale for assessing the risk of bias.[12] The total score is 9, with studies obtaining a total score of ≥7 being considered high-quality literature, whereas a total score of 5–6 is defined as medium quality and ≤4 belongs to low-quality literature. Only a small number of studies were input, and the research team took that limitation into consideration; therefore, sensitivity analysis or subgroup analysis was carried out on the low-quality studies instead of deleting them. Overall, the quality of the included literature was relatively high, with an average score of 6.9 according to the scale (Table S2).

Statistical analysis

The collected data were summarized, sorted and analyzed mainly using three software programs: IBM SPSS Statistics 23 (IBM Corporation, Armonk, NY, USA), Haploview 4.2 (Cambridge, MA, USA) and Stata 12.0 (StataCorp, College Station, TX, USA).

General characteristics of the entered data

APOEε4 can have carrier or non-carrier status, which affects the incidence of AD that was caused by genetic factors.[13] Consequently, combined the statistical data to analyze whether *APOEε4* status influence susceptibility genes SNPs (*BIN1* rs744373, *BIN1* rs7561528, and *GAB2* rs2373112) on pathogeny of AD.

Distribution of genotype and allele frequency

Separately combining the same genotype frequency and allele in *BIN1* rs744373, *BIN1* rs7561528 and *GAB2* rs2373115, we determined the corresponding odds ratio (OR) and $P_{\chi 2}$-value using Pearson's χ^2-test to acquire information on the distribution of genotype and allele frequency relating to the SNP results in the locus mutation.

Linkage disequilibrium test

All three SNPs (*BIN1* rs744373, *BIN1* rs7561528 and *GAB2* rs2373112) impact the pathogenesis of AD. Linkage disequilibrium (LD), also known as allele association, is used primarily to find candidate genes that are close enough to the disease-causing site to show disease-related loci.[14] Therefore, LD in the susceptibility loci of the same disease might occur. The author of the article (Xiao et al.) provided the raw data includes 459 cases and 751 controls, In using these raw data to calculate the haplotype frequencies of the two SNPs (*BIN1* rs744373, *BIN1* rs7561528) and the one SNP (*GAB2* rs2373115) in the patients and controls to figure out whether LD exists in the three SNPs by D'-value.

Meta-analysis

Calculation of genetic models

To evaluate the association between late-onset AD and SNPs of *BIN1* and *GAB2*, we selected four main genetic models: allele, dominant, recessive, heterozygote and homozygote. As the selected study described the genotype of the same SNP without identifying the genotype, we consolidated the same genotype with the same SNP in Asian and white individuals, as follows: for rs744373: allele model: G versus A; dominant model: GG + AG versus AA; recessive model: GG versus AG + AA; heterozygote model: AG versus AA; homozygote model: GG versus AA; for rs7561528: allele model: A versus G; dominant model: AA + AG versus GG; recessive model: AA versus AG + GG; heterozygote model: AG versus GG; homozygote model: AA versus GG; for rs2373115: allele model: G versus T; dominant model: GG + GT versus TT; recessive model: GG versus GT + TT; heterozygote model: GT versus TT; homozygote model: GG versus TT; *BIN1* rs744373 (C/T), *BIN1* rs7561528 (A/G), and *GAB2* rs2373115 (G/T; Table 1).

Heterogeneity test and effect model selection

Although strict inclusion and exclusion criteria were established in the meta-analysis, all the studies included in the systematic evaluation were different. The discrepancy between the studies had to remain within certain limits, with the study conditions remaining similar to the actual situation. If the discrepancy exceeds this range, it should be reduced through a logical method.[15] The I^2-value, *P*-value and 95% confidence interval of different genetic models of three SNPs from *BIN1* and *GAB2* genes were observed under the fixed effects and random effects models, respectively, by forest plot. If $I^2 < 50\%$ or $P > 0.1$, there is no heterogeneity; in this case, the fixed effects model would be selected to merge the effect values. Otherwise, if $I^2 > 50\%$ or $P < 0.1$, the random effects model would be chosen because of the heterogeneity in the genetic model.[16]

Analysis of sensitivity and subgroup

If a certain study was noted to have obvious influence on the merged OR value, the study was considered to be sensitive to the merged OR value, and vice versa. There is no heterogeneity and the sensitivity of the literature is low when the study comes from the same population.[12] Sensitivity analysis is mainly carried out to reduce heterogeneity by changing important factors that affect the results. The present study showed that there is no essential change in the results before and after the analysis of different genetic models,[13] indicating that the meta-analysis results are relatively reliable. Otherwise, one could conclude that are important factors related to the gene model. The instrumental variables method was used to analyze the sensitivity of the gene model with consistency. The sensitivity analysis chart results were assessed by removing a group of data and combining the rest of data with the *P*-value. At the same time, subgroup analysis was carried out according to groups of Asian and white individuals to further explore the source of consistency. After deleting the maximum difference group, we observed heterogeneity again.[17]

Publication bias and trim and fill analysis

In meta-analysis, bias might occur in the process of literature retrieval and selection, as well as data extraction, which might cause the results to deviate from the actual value.[18] Therefore, the number of included studies on *BIN1* rs744373 and *GAB2* rs2373115 is relatively higher, and the *P*-value can be obtained by using the funnel plot method and Egger's rank correlation test method. $P > 0.1$ shows no publication bias. The trim and fill analysis was used to further adjust the publication bias as $P < 0.1$, but it merely makes an assessment for the influence of publication bias rather than represents the realistic bias.

Statement of ethics. The present study was carried out in accordance with the principles of Declaration of Helsinki, and the study protocol was approved by the General Hospital of Ningxia Medical University Research Ethics Committee (No. 2016–087).

Results

By adhering to the inclusion and exclusion criteria, and deleting the study that did not provide complete data, we finally obtained nine *BIN1* studies and seven *GAB2* studies, as well as one study covering both. All studies are listed in Figure S1.

Relevant data were extracted from the included studies. The *P*-value of HWE in the studies by Jiao *et al.* (covering *BIN1* rs744373), Omounmi *et al.*, Liu *et al.* and the second iteration of

Table 1 Results from the current meta-analysis in three single-nucleotide polymorphisms

SNP	Ethnicity	*n*	Allele model			Dominant model			Recessive model			Heterozygote model			Homozygote model		
			PH	OR (95% CI)	I^2 (%)	PH	OR (95% CI)	I^2 (%)	PH	OR (95% CI)	I^2 (%)	PH	OR (95% CI)	I^2 (%)	PH*	OR (95% CI)	I^2 (%)
rs744373	Total	23	0.008	1.13 (1.10–1.17)	46.7	0.123	1.17 (1.12–1.22)	26.2	0	1.12(0.97–1.29)	65.7	0.079	1.15 (1.10–1.21)	31.1	0	1.20 (1.04–1.37)	58.6
	Asian	11	0.365	1.08 (1.02–1.14)	8.3	0.288	1.14 (1.06–1.23)	16.6	0	0.94 (0.74–1.21)	72	0.024	1.15 (1.06–1.25)	51.3	0.008	1.02 (0.82–1.26)	60
	White	12	0.006	1.16 (1.11–1.21)	58	0.101	1.18 (1.13–1.25)	36.2	0.029	1.29 (1.10–1.50)	48.7	0.413	1.15 (1.09–1.21)	3.2	0.018	1.36 (1.16–1.61)	52
rs7561528	Total	16	0	1.05 (0.96–1.16)	68.6	0	1.09 (0.97–1.23)	63.6	0.035	1.08 (0.91–1.27)	43	0.007	1.10 (0.99–1.23)	52.6	0.012	1.15 (0.95–1.39)	49.8
	Asian	7	0	0.94 (0.76–1.17)	75.4	0.001	0.96 (0.75–1.21)	72.4	0.282	1.03 (0.75–1.41)	19.3	0.012	0.96 (0.77–1.19)	63.4	0.089	0.99 (0.65–1.51)	45.3
	White	9	0.032	1.13 (1.03–1.24)	52.4	0.31	1.22 (1.12–1.32)	14.9	O.016	1.09 (0.88–1.35)	57.4	0.593	1.21 (1.13–1.31)	0	0.016	1.19 (0.95–1.48)	57.3
rs2373115	Total	18	0.001	1.13 (1.04–1.23)	59.2	0	1.27 (1.01–1.61)	68.2	0	1.52 (1.15–2.02)	94.9	0.082	0.96 (0.86–1.06)	33.6	0.008	1.21 (0.99–1.48)	50.3
	Asian	7	0.148	1.03 (0.95–1.12)	36.7	0.356	0.94 (0.83–1.06)	9.5	0.283	1.08 (0.98–1.20)	19.2	0.510	0.91 (0.81–1.02)	0	0.282	1.00 (0.86–1.16)	19.4
	White	11	0.008	1.20 (1.06–1.37)	58.1	0	1.77 (1.07–2.92)	71.4	0	1.89 (1.17–3.04)	96.5	0.111	1.25 (0.96–1.63)	36	0.028	1.51 (1.03–2.22)	50.4

n, The number of studies found in the literature; PH, *P*-value for heterogeneity; SNP, single-nucleotide polymorphism.

Harold *et al.* (covering *BIN1* rs756152) was <0.05, whereas the *P*-value of other groups was >0.05. However, due to the limitation of the small numbers of the included articles, we did not eliminate the above-mentioned studies. Also, the quality score of all studies covering *BIN1* and *GAB2* was >7 points, which means the quality of the included studies was high (Table 1).

The *APOEε4* status was divided in Asian and white individuals for subgroup analysis in cases and controls, both rs744373 and rs7561528 were discrepant in Asian and white individuals; for white individuals, the OR value was <1, but was the complete opposite in Asian individuals, which means *APOEε4*$^{+}$ promotes the involvement of those two SNPs in the pathogenesis of AD in white individuals rather than Asian individuals. However, the OR value of rs2373115 was >1 in Asian and white individuals. As a result, *APOEε4* status influences the pathogenesis of AD in three SNPs (Table S3).

In the heterogeneity test with different genetic models, we chose the effects model on the basis of the I^2-value. Except for the allele dominant and heterozygote models of *BIN1* rs744373, and recessive homozygote models of *BIN1* rs5671528 and heterozygote models of *GAB2* rs2373115, we selected the fixed effects model, whereas for all others, we selected the random effects model.

Therefore, the results suggested that the three SNPs were the pathogenicity site for AD, because the OR value of the three sites was >1, and the *P*-value was <0.05. For further study, individuals of different ethnicities with the same SNPs were divided into two groups of Asian and white individuals for subgroup analysis; the results showed: for rs744373, allele model OR 1.16, $P = 0.006$; recessive model OR 1.12, $P = 0.029$; and homozygote model OR 1.36, $P = 0.018$, which means the genetic model was the recessive model and rs744373 belongs to a risk pathogenicity site for AD in the group of white individuals, and that also shows homozygous mutation of G (GG); however, in the Asian group, the OR for the allele model was 1.06, $P = 0.408$, which signifies that the effect of rs744373 for AD was unclear. After rs7561528 was detected in white individuals, the OR for the allele model was OR 1.13, $P = 0.032$, the OR for the recessive model was 1.09, $P = 0.016$, and the OR for the homozygote model was 1.19, $P = 0.016$, rs7561528 belongs to a pathogenicity site for AD in the Caucasian group as well as its genetic model was recessive model with homozygous mutation of A (AA), whereas the rs7561528 of Asian individuals showed: allele model OR 0.94, $P = 0$; dominant model OR 0.96, $P = 0.001$; and heterozygote model OR 0.96, $P = 0.012$; however, the I^2-value of the five models in this SNP was >50%. Finally, for rs2373115, the following applied: allele model OR 1.20, $P = 0.008$; dominant model OR 1.77, $P = 0$; and recessive model OR 1.89, $P = 0$ in white individuals, showing that rs2373115 belongs to a pathogenicity site for AD and the genetic model was the dominant model for white individuals, which presents as heterozygous mutation of G (GG, GT or TG). Nevertheless, the effect of rs2373115 on AD in Asian individuals is uncertain due to the detection results: allele model OR 1.09, $P = 0.43$ (Table 1).

The association of the SNPs with the pathogenesis of AD was evaluated using a forest plot. Only the allele models of *BIN1* rs744373, *BIN1* rs7561528 and *GAB2* rs2373115 are shown with the forest plot, because the maximum difference group was the same for their allele model of three SNPs (Fig. 1a–c). The results of the sensitivity analysis of rs744373, rs7561528 and rs2373115 show the resource of heterogeneity, with <50% of the I^2-value of three SNPs being identified as without heterogeneity (Figs S2,S3). We found that two groups (the third iteration of Lambert *et al.* and the first iteration of Reiman *et al.*) separately demonstrated a great difference from the total value of their own groups combining with the result of subgroup analysis. After deleting those two groups, we used the fixed effects model to determine that the I^2-value had plunged and the heterogeneity equaled <50% in all the allele models of rs744373 and rs2373115 (Figs S4,S5). Similarly for rs7561528, the I^2-value was decreased when the most heterogeneous group was deleted (Li *et al.*). Furthermore, the rs7561528 of the Asian group showed: allele model OR 1.02, $P = 0.02$ and dominant model OR 1.04, $P = 0.037$, and thus rs7561528 belongs to a risk pathogenicity site for AD in the Asian group as well as the white group.

Additionally, the funnel plot was symmetrical for rs744373 and rs7561528, and the *P*-value of Egger's rank correlation test was >0.1, which proves that no publication bias was associated between those two SNPs and AD in their genetic models, the difference was that the *P*-value of Egger's rank correlation test in rs2373115 was <0.1 in its genetic model, and the OR value was obviously different before and after the trim and fill analysis in rs2373115 genetic models. However, the *P*-value was >0.5, indicating no bias in the two groups after this case was divided into the Asian and white group for bias analysis, respectively (Table S4; Figs S6,S7).

The results of LD tests of three SNPs in *BIN1* and *GAB2* showed that LD does not exist between *GAB2* rs2373115 and two other SNPs (*BIN1* rs744373 and *BIN1* rs2567518). However, strong LD exists between *BIN1* rs744373 and *BIN1* rs2567518 (D' = 0.986; Fig. 2). The frequency of haplotype with GA was the largest in all (GA 0.643%; GG 0.234%; AG 0.122%; Table S5).

Discussion

BIN1 rs744373 polymorphism, *GAB2* rs2373115 polymorphism and *BIN1* rs7561528 polymorphism are associated with the pathogenesis of AD, and have been proven according to this meta-analysis. The *BIN1* rs744373, *BIN1* rs7561528 and the *GAB2* rs2373115 polymorphisms are risk pathogenicity sites for AD in the white population, and also the rs7561528 polymorphism is a risk site for AD in the Asian population, but the rs2373115 polymorphism remains unclear. Meanwhile, the genetic model of rs744373 and rs7561528 is a recessive model rather than rs2373115, which is a dominant model in white individuals. Furthermore, rs7561528 and rs744373 SNPs have strong LD in the Chinese population, so rs744373 might be the risk site for AD in the Asian population. We tested the heterogeneity, sensitivity, and subgroup and publication bias for all genetic models of the three SNPs. The influence of the three SNPs on AD has no definitive conclusion in Asian individuals yet. Despite rs744373 possibly being the risk site for AD in Asian individuals based on rs7561528 being a risk pathogenicity site that the domination model was genetic model in Asian individuals after deleting the group of Li et al., however, the genetic mutation of rs744373 in Asian was uncertain because of its insignificant heterozygous model and also few studies in Asian individuals accompanied by a comparatively high heterogeneity in the dominant model. Unlike the white individuals, most of the Asian individuals choose the control group from the hospital, which significantly increased the selection bias that means the specific areas population do not represent the whole Asian population; hence, the influence of the three SNPs on AD and the genetic model and mutation of rs7561528 in Asian individuals should be confirmed by larger and more detailed studies.[18] Due to the small sample number in other ethnicity except

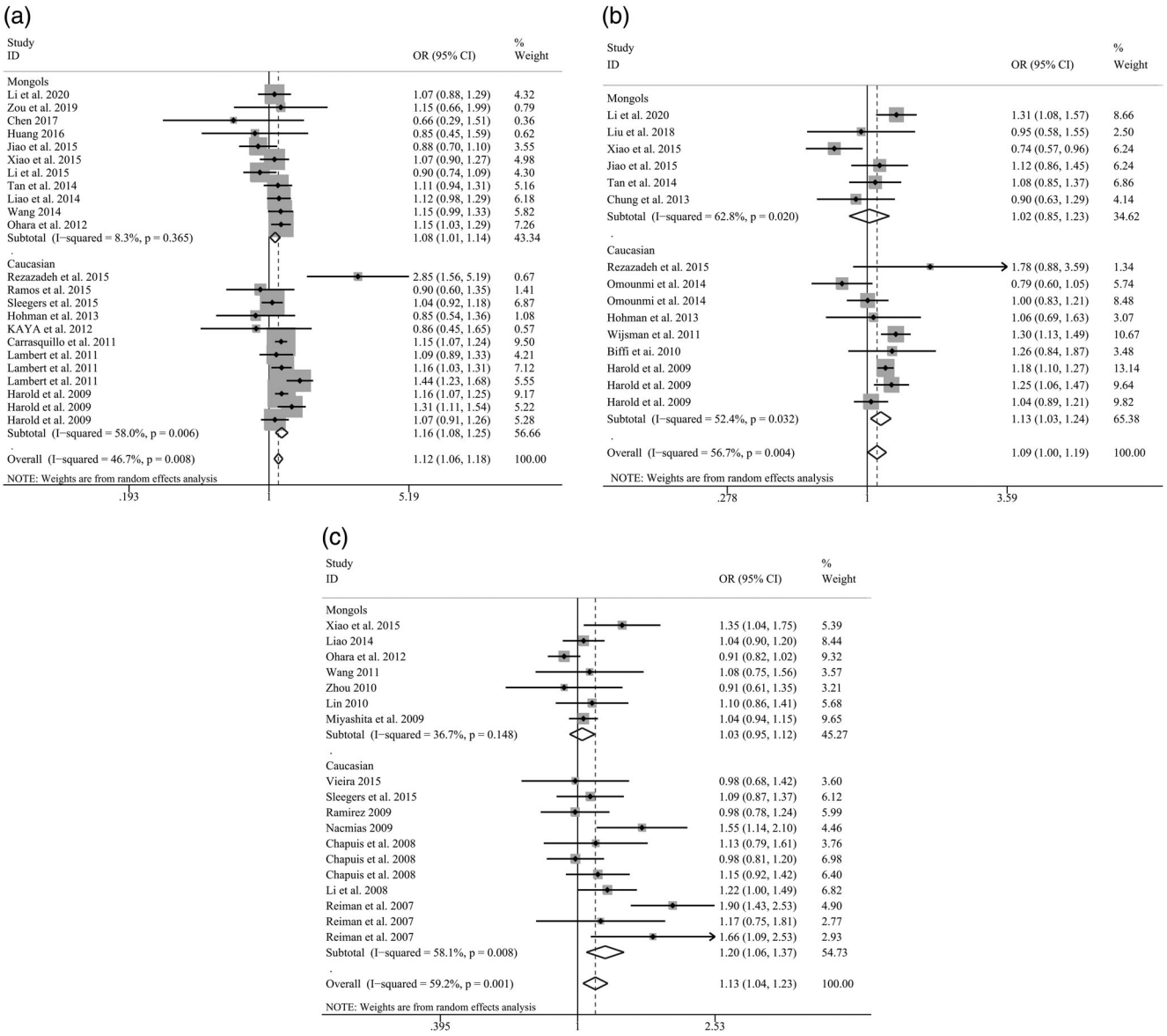

Figure 1 Forest plot of allele model comparison. (a) Forest plot of allele comparison of *BIN1* rs744373 for overall comparison (G *vs* A) with a random effects model. (b) Forest plot of allele comparison of *BIN1* rs7561528 for overall comparison (A *vs* G) with a fixed effects model after deleting the group of Li *et al*. (c) Forest plot of allele comparison of *GAB2* rs2373115 for overall comparison (G *vs* T) with a random effects model.

Chinese in Mongols group, like Japanese and Korean. Therefore, the conclusion of Mongols groups analysis was mainly for Chinese and much more other ethnicity need to be included for drawing a more definite subgroup analysis in Mongols group.

Given the fact we had incomplete data on the genotype frequency of *APOEε4* status in all the inclusion studies, we only combined the groups with concrete data for counting. Consequently, the total genotype frequency of *APOEε4* status was less than the total sample that was included in the meta-analysis. The incentive effect of *APOEε4*$^+$ is the same for rs744373 and rs7561528 in white individuals, but contrary to the inhibitory effect of *APOEε4*$^+$ on the rs2373115 influence in AD. However, both *GAB2* rs2373115 and *APOEε4*$^+$ were risk pathogenicity genes in AD in the white individuals, the results in rs2373115 was considered for the information bias that the included studies were published earlier than other two groups means the AD diagnosis criteria and strategies have some differences, while at the meantime, the existing sample data is too small in rs2373115 group should also not be ignored.[19]

Bias has been detected by Egger's rank and trim and fill analysis, caused by many factors, including information bias, selection bias and confounding bias.[20] A potential limitation was publication bias, in that studies obtaining optimistic results could be more easily published than those studies with unfavorable results. Nevertheless, the bias did not exist when dividing the two groups of Asian and white individuals in the rs2373115 genetic model. It is considered that the different SNPs might be associated with AD in diametric opposition from the same susceptibility genes because of the genetic differences among populations. We speculated that rs2373115 effects on AD by genetic differences between Asian

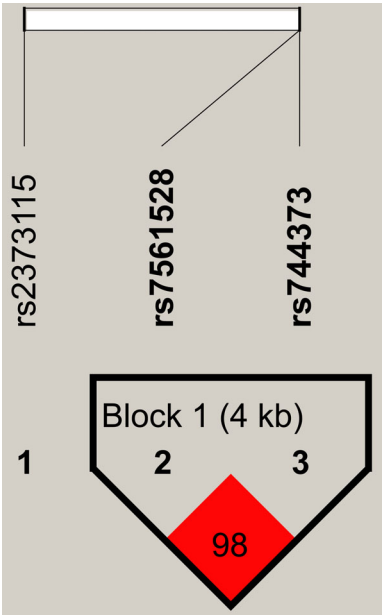

Figure 2 The linkage disequilibrium plot of *BIN1* rs744373, *BIN1* rs7561528 and *GAB2* rs2373115.

and white individuals, which might become another source of bias and even provide a new perspective for the emergence of disease.[21]

The heterogeneity of rs744373 and rs2373115 declined (G *vs* A and A *vs* G) when the third iteration of Lambert *et al.* and the first iteration of Reiman *et al.* were deleted, but not down to 0%, which means the heterogeneity of rs744373 and rs2373115 comes from both deleted groups, but the heterogeneity also comes from another source (Supplement). Therefore, an exploration of the multifactors in the meta-analysis is necessary.[22] Decreasing the heterogeneity increases the accuracy of the conclusion that the SNPs affect the incidence of AD. As the studies that are included can be a source of heterogeneity, deleting some groups lowers the heterogeneity of the genetic model. The average age of rs7561528 in the deleted group (Li *et al.*) was lower than the other three, which could be the reason why deleting this group decreased the heterogeneity. The age at onset plays an important role in determining the effectiveness of the etiological agent,[23] and the risk increases with patient age.[24] Based on previous research, women are more likely to develop AD than men, and the age of onset influences the morbidity of AD.[25] However, we could not obtain the relevant sex and age data of each sample individual, which might influence the accuracy of the statistics due to not checking the confounders.

For the LD test, there were four haplotypes in *BIN1* rs744373 and *BIN1* rs2567518, including GA, GG, AG and AA. The frequency of AA was 0.1% in the LD plot. However, it is not shown in Table S4, because the ratios of cases and controls were beyond computation. The D'-value was >0.5, which means the LD was strong in *BIN1* rs744373 and *BIN1* RS2567518. Meanwhile, the distance between the two loci was relatively small, leading to the strong LD, whereas the loci of *GAB2* rs2373115 was distant from the other two SNPs.[26,27] At the same time, according to the LD, the rs744373 might belong to the risk site in Chinese individuals, and we also speculated that LD might exist in other Asian and white populations, which should be further confirmed in future research.

Much more data were assessed in the present study than in previously published studies, making these results closer to the true value. Although not all ethnicities were included in the study due to the restrictions on sample sources, it still provides a direction for guiding the clinical detection and early prevention of AD.

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Disclosure statement

All the authors declare no conflict of interest.

References

1 Lichtenstein ML, Fallah N, Mudge B *et al.* 16-year survival of the Canadian collaborative cohort of related dementias. *Can J Neurol Sci* 2018; **45**: 367–374.
2 Liu S, Sun YP, Gao XL, Sui Y. Knowledge domain and emerging trends in Alzheimer's disease: a scientometric review based on CiteSpace analysis. *Neural Regen Res* 2019; **14**: 1643–1650.
3 Marchini L, Ettinger R, Caprio T, Jucan A. Oral health care for patients with Alzheimer's disease: an update. *Spec Care Dentist* 2019; **39**: 262–273.
4 Morley JE, Farr SA, Nguyen AD. Alzheimer Disease. *Clin Geriatr Med* 2018; **34**: 591–601.
5 Han Z, Huang H, Gao Y, Huang Q. Functional annotation of Alzheimer's disease associated loci revealed by GWASs. *PLoS One* 2017; **12**: e0179677.
6 Franzmeier N, Rubinski A, Neitzel J, Ewers M. The BIN1 rs744373 SNP is associated with increased tau-PET levels and impaired memory. *Nat Commun* 2019; **10**: 1766.
7 Pan XL, Ren RJ, Wang G, Tang HD, Chen SD. The Gab2 in signal transduction and its potential role in the pathogenesis of Alzheimer's disease. *Neurosci Bull* 2010; **26**: 241–246.
8 Chen XX, Guo RR, Cao XP, Tan L, Tan L. The impact of GAB2 genetic variations on cerebrospinal fluid markers in Alzheimer's disease. *Ann Transl Med* 2018; **6**: 171.
9 Huang P, Hsieh SW, Chang YH, Hour AL, Chen HY, Liu CK. Differences in the frequency of Alzheimer's disease-associated genomic variations in populations of different races. *Geriatr Gerontol Int* 2017; **17**: 2184–2193.
10 Futao Z, Haina D. The bridging integrator 1 Gene rs7561528 polymorphism contributes to Alzheimer's disease susceptibility in East Asian and Caucasian populations. *Clin Chim Acta* 2017; **469**: 13–21.
11 Liu G, Wang T, Tian R *et al.* Alzheimer's disease risk variant rs2373115 regulates GAB2 and NARS2 expression in human brain tissues. *J Mol Neurosci* 2018; **66**: 37–43.
12 Margulis AV, Pladevall M, Riera-Guardia N, Varas-Lorenzo C, Hazell L, Berkman ND. Quality assessment of observational studies in a drug-safety systematic review, comparison of two tools: the Newcastle–Ottawa scale and the RTI item bank. *Clin Epidemiol* 2014; **6**: 359.
13 Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol* 2013; **9**: 106–118.
14 Skelly DA, Magwene PM, Stone EA. Sporadic, global linkage disequilibrium between unlinked segregating sites. *Genetics* 2016; **202**: 427–437.
15 Melsen WG, Bootsma MC, Rovers MM, Bonten MJ. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. *Clin Microbiol Infect* 2014; **20**: 123–129.
16 DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials* 2015; **45** (Pt A): 139–145.
17 Alexander PE, Bonner AJ, Agarwal A *et al.* Sensitivity subgroup analysis based on single-center vs. multi-center trial status when interpreting meta-analyses pooled estimates: the logical way forward. *J Clin Epidemiol* 2016; **74**: 80–92.
18 Kohn MA, Carpenter CR, Newman TB. Understanding the direction of bias in studies of diagnostic test accuracy. *Acad Emerg Med* 2013; **20**: 1194–1206.
19 Miller KD, Rahman ZU, Sledge GW Jr. Selection bias in clinical trials. *Breast Dis* 2001; **14**: 31–40.

20 Tripepi G, Jager KJ, Dekker FW, Zoccali C. Selection bias and information bias in clinical research. *Nephron Clin Pract* 2010; **115**: c94–c99.
21 Steinke D, Davey P. Association between antibiotic resistance and community prescribing: a critical review of bias and confounding in published studies. *Clin Infect Dis* 2001; **33** (Suppl 3): S193–S205.
22 Yashin AI, Fang F, Kovtun M *et al*. Hidden heterogeneity in Alzheimer's disease: insights from genetic association studies and other analyses. *Exp Gerontol* 2017; **107**: 148–160.
23 Tellechea P, Pujol N, Esteve-Belloch P *et al*. Early- and late-onset Alzheimer disease: are they the same entity? *Neurologia* 2015; **33**: 244–253.
24 Naj AC, Jun G, Reitz C *et al*. Effects of multiple genetic loci on age at onset in late-onset Alzheimer disease: a genome-wide association study. *JAMA Neurol* 2014; **71**: 1394–1404.
25 Podcasy JL, Epperson CN. Considering sex and gender in Alzheimer disease and other dementias. *Dialogues Clin Neurosci* 2016; **18**: 437–446.
26 Hrafnkelsson B, Helgason A, Jonsson GF *et al*. Evaluating differences in linkage disequilibrium between populations. *Ann Hum Genet* 2010; **74**: 233–247.
27 Xu H, Guan Y. Detecting local haplotype sharing and haplotype association. *Genetics* 2014; **197**: 823–838.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1 Literature quality rating scale included in the study.

Table S2 Characteristics of the selected studies.

Table S3 Influence of apolipoprotein E carrier between three single-nucleotide polymorphisms and Alzheimer's disease.

Table S4 Publication bias in three single-nucleotide polymorphisms.

Table S5 Haplotypes frequencies of two single-nucleotide polymorphisms in bridging integrator 1 between case and control.

Figure S1 Study selection.

Figure S2 Sensitivity analysis for the resource of heterogeneity in *BIN1* rs744373 (G *vs* A).

Figure S3 Sensitivity analysis for the resource of heterogeneity in *GAB2* rs2372115 (G *vs* T).

Figure S4 Forest plot after deleting two groups in *BIN1* rs744373 (G *vs* A).

Figure S5 Forest plot after deleting one groups in *BIN1* rs2373115 (G *vs* T).

Figure S6 Egger's plot for publication bias analysis for *BIN1* rs7561528 (A *vs* G).

Figure S7 Filled funnel plot with random effect model for GAB2 rs2373115 (G *vs* A).

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