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 over-phosphorylation 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 nucleotide polymorphism (SNP) has become a crucial etiology of AD.5 Relevance of research shows that the site mutation caused by 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.6

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 e4 status promotes them to result in the pathogenesis of AD.7

Keywords: Alzheimer’s disease, bridging integrator 1, GRB-associated binding protein 2, linkage disequilibrium, meta-analysis.
**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, APOE4 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 (χ² < 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. 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**

APOE4 can have carrier or non-carrier status, which affects the incidence of AD that was caused by genetic factors. Consequently, combined the statistical data to analyze whether APOE4 status influence susceptibility genes SNPs (BIN1 rs744373, BIN1 rs7561528, and GAB2 rs2373112) on pathogenesis 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 P2-value using Pearson’s χ²-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. 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).
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. 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 $P > 50\%$ 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 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), Omounni et al., Liu et al. and the second iteration of

| SNP | Ethnicity | Allele model | Dominant model | Recessive model | Heterozygote model | P (OR) | 95% CI | $I^2$ (%) | PH OR (95% CI) | P (OR) | 95% CI | $I^2$ (%) | PH OR (95% CI) | P (OR) | 95% CI | $I^2$ (%) | PH OR (95% CI) |
|-----|-----------|--------------|---------------|----------------|-------------------|-------|-------|--------|---------------|-------|-------|--------|---------------|-------|-------|--------|---------------|
| rs744373 | Total | 23 | 0.008 | 1.13 (1.10–1.17) | 46.7 | 0.123 | 1.17 (1.12–1.22) | 26.2 | 0.037 | 1.12 (1.08–1.16) | 65.7 | 0.079 | 1.15 (1.10–1.21) | 31.1 | 0.018 | 1.10 (1.04–1.17) | 38.6 |
|      | PAN | 11 | 0.365 | 1.08 (1.02–1.14) | 28.8 | 1.14 (1.06–1.23) | 16.6 | 0.039 | 1.09 (1.04–1.13) | 58.6 | 0.079 | 1.14 (1.08–1.20) | 52.6 | 0.018 | 1.06 (1.00–1.12) | 52.6 |
|      | White | 12 | 0.006 | 1.19 (1.13–1.25) | 10.1 | 1.09 (1.03–1.15) | 16.2 | 0.029 | 1.11 (1.05–1.17) | 66.2 | 0.038 | 1.11 (1.06–1.16) | 56.8 | 0.018 | 1.09 (1.04–1.14) | 56.8 |
| rs2373115 | Total | 18 | 0.001 | 1.13 (1.07–1.17) | 33.2 | 1.19 (1.06–1.23) | 16.9 | 0.008 | 1.12 (1.06–1.18) | 68.2 | 0.079 | 1.15 (1.08–1.22) | 36.2 | 0.018 | 1.10 (1.05–1.15) | 36.2 |
|      | PAN | 9 | 0.002 | 1.13 (1.07–1.17) | 73.4 | 0.001 | 1.14 (1.06–1.23) | 14.9 | 0.016 | 1.11 (1.05–1.18) | 57.4 | 0.082 | 1.16 (1.09–1.24) | 48.7 | 0.016 | 1.13 (1.07–1.19) | 48.7 |
|      | White | 9 | 0.002 | 1.13 (1.07–1.17) | 73.4 | 0.001 | 1.14 (1.06–1.23) | 14.9 | 0.016 | 1.11 (1.05–1.18) | 57.4 | 0.082 | 1.16 (1.09–1.24) | 48.7 | 0.016 | 1.13 (1.07–1.19) | 48.7 |
| GAB2 | rs744373 | Asian | 7 | 0.001 | 1.13 (1.05–1.12) | 36.7 | 0.036 | 1.13 (1.05–1.12) | 16.6 | 0.039 | 1.10 (1.05–1.15) | 58.6 | 0.079 | 1.09 (1.04–1.14) | 52.6 | 0.018 | 1.09 (1.04–1.14) | 52.6 |
|      | White | 12 | 0.006 | 1.19 (1.13–1.25) | 10.1 | 1.09 (1.03–1.15) | 16.2 | 0.029 | 1.11 (1.05–1.17) | 66.2 | 0.038 | 1.11 (1.06–1.16) | 56.8 | 0.018 | 1.09 (1.04–1.14) | 56.8 |

Note: 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 three SNPs (Table S3).

The frequency of haplotype with GA was the largest in all (GA 0.643%; GG 0.234%; AG 0.122%; Table S5). 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 heterogeneous 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...
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 APOE4 status in all the inclusion studies, we only combined the groups with concrete data for counting. Consequently, the total genotype frequency of APOE4 status was less than the total sample that was included in the meta-analysis. The incentive effect of APOE4+ is the same for rs744373 and rs7561528 in white individuals, but contrary to the inhibitory effect of APOE4+ on the rs2373115 influence in AD. However, both GAB2 rs2373115 and APOE4+ 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 individuals and others are related to the differences of population genetics.21

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.
and white individuals, which might become another source of bias and even provide a new perspective for the emergence of disease.\textsuperscript{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.\textsuperscript{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,\textsuperscript{23} and the risk increases with patient age.\textsuperscript{24} Based on previous research, women are more likely to develop AD than men, and the age of onset influences the morbidity of AD.\textsuperscript{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 \textit{BIN1} rs744373 and \textit{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 \textit{BIN1} rs744373 and \textit{BIN1} RS2567518. Meanwhile, the distance between the two loci was relatively small, leading to the strong LD, whereas the loci of \textit{GAB2} rs2373115 was distant from the other two SNPs.\textsuperscript{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.

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### 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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