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Associations of rs524952 and rs634990 gene polymorphisms in 15q14 with high myopia: A meta-analysis

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Purpose: Many studies have been conducted to investigate the association between the rs524952 and rs634990 polymorphisms and high myopia (HM). However, the results were conflicting. Thus, a meta-analysis was needed to reveal the real association between the two single nucleotide polymorphisms (SNPs) and HM.

Methods: All eligible studies published in Pubmed, Embase, China Biologic Medicine (CBM), the China National Knowledge Infrastructure (CNKI), the Cochrane Library, and the Web of Science from 2010 to March 2019 were examined.

Results: Six comparison groups in four studies with 5,293 subjects for the rs524952 polymorphism and five studies with 6,750 subjects for the rs634990 polymorphism were included. No statistically significant associations were observed between the rs524952 and rs634990 polymorphisms and HM under the allelic model, recessive genetic model, and dominant genetic model in this meta-analysis. Subgroup analysis was conducted by dividing the studies into two groups according to the case sample size, which showed that the association between the rs524952 polymorphism and HM was found only in a subgroup of fewer than 300 cases under the dominant genetic model (OR=0.64; 95% confidence interval [CI]:0.43–0.96). Sensitivity analysis for the rs524952 polymorphism suggested the results of this study were stable under all the genetic models. However, the association between the rs634990 polymorphism and HM turned out to be statistically significant in the allelic, recessive, and dominant genetic models after the omission of Qiang et al.'s study. No publication bias was found.

Conclusions: The results of this meta-analysis suggested the rs524952 and rs634990 polymorphisms may have nothing to do with the development of HM. The present results must be confirmed with larger-scale studies in the future.

Because of the increased time people spend on near-work, such as reading and writing, with education levels rising and less outdoor activity [1], the prevalence of high myopia has increased rapidly in recent years [2]. Thus, it has attracted attention globally, and researchers increasingly are focusing on this public issue. Susan et al. found an eightfold increase in high myopia (7.90 D) over 30 years (1971–1972 to 1999–2004). [3] Holden et al. performed a systematic review and meta-analysis of the prevalence of myopia and high myopia using data published since 1995. The authors estimated that by 2050 there will be 938 million people with high myopia (9.8% of the world's population) [4]. High myopia (HM), characterized as myopic eyes with a high degree of refractive error (≤–6D) or very long axial lengths (≥26 nm), is one of the main causes of legal blindness throughout the world [5,6]. Some sight-threatening eye diseases, such as glaucoma, macular hemorrhage, and retinal detachment, have also been found to be related to high myopia [7]. Therefore, it is urgent to utilize effective methods for preventing the development of HM or limit its progression.

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To date, the etiology of HM has not been completely clarified. Genetic factors and environmental factors have been considered to play an important role in the development of HM [8]. Genome-wide association studies (GWASs) have been widely used to detect possible genes related to the complex disease. Since the 15q14 locus was identified as associated with common myopia and reflective error with a GWAS conducted by Solouki et al. in 2010 [9], many types of research have been performed to evaluate the association between single nucleotide polymorphisms (SNPs) in 15q14 and HM [1,2,10-13]. The SNPs rs634990 and rs524952 are the most commonly studied SNPs on chromosome 15q14 associated with HM. Unfortunately, the results of the studies were inconsistent. Thus, this meta-analysis was conducted to investigate the associations between the rs634990 and rs524952 polymorphisms and HM.

METHOD

Data sources: All available studies were searched via various online databases, such as Pubmed, Embase, China Biologic Medicine (CBM), China National Knowledge Infrastructure (CNKI), the Cochrane Library, and the Web of Science from the first related literature in 2010 to 2019. The keywords "high myopia," or "myopia," or "near sight," or "refractive error,"

and mash terms for "15q14" or "rs524952" or "rs634990" were combined to search articles evaluating an association between the rs524952 and/or rs634990 polymorphism and high myopia. The literature search was performed by two different researchers to find all possible related publications. In addition, references cited by the retrieved studies were searched to trace back the original literature for complementing the final analysis.

Selection criteria: Studies were included if they met the following requirements [1]: focused on the relation of the rs524952 and/or rs634990 polymorphism with HM [2] and based on a case-control or cohort design with clear diagnostic criteria for HM (HM was diagnosed as a high degree of refractive error (≤-6D) or very long axial lengths (≥26 nm) [3]); provided relative risk (RR), odds ratios (ORs), and 95% confidence intervals (CIs) of the genotype frequency or original data in the case and control groups [4]; and published in English or Chinese. Studies were excluded if they met the following criteria: [1] was a review, case series, comment, or abstract [2]; did not provide sufficient data [3]; or the genotype distribution in the control group did not accord with Hardy–Weinberg equilibrium (HWE). If a study included two different groups of cases and controls, the results were treated respectively.

Data extraction: Data extraction was implemented independently by two researchers, and inconsistencies were resolved through discussion and consultation. The following information was collected from each study: the name of the first author, the year of publication, the ethnicity of the study subjects, the sample size, the mean age for subjects in the case and control groups, and the distribution of genotype in both groups. For studies that included different groups of cases and controls, the data were extracted separately if possible.

Statistical analysis: Fisher's exact test or the chi-square test was used to assess the HWE of the control group, if the information was not provided by the original publications. The relations of the two gene polymorphisms and high myopia were assessed using pooled ORs and 95% CIs under the allelic model, recessive genetic model, and dominant genetic model. The chi-square-based Q statistic was used to estimate the heterogeneity between the studies, and a p value of less than 0.05 was considered statistically significant. The I^2 statistic was used to assess the degree of inconsistency in the meta-analysis. The range of the I^2 statistic is from 0% to 100% (more than 50% indicated that there was significant heterogeneity) [14]. If there was heterogeneity between the studies, then the ORs were pooled according to the random effect model. Otherwise, the fixed-effect model was applied to pool the effects. To assess the stability of the results, the sensitivity analysis was performed by removing each study in turn. As studies with a small sample size always lack sufficient power to detect the real association [15], subgroup analysis according to the sample size was used to reveal the true relation between the SNPs and HM, and detect the sources of heterogeneity. Egger's test and Begg's test were used to examine the publication bias. All these analyses were performed with STATA 12.0. A p value of less than 0.05 for the two-tailed tests was considered statistically significant.

RESULTS

Rs524952: A total of 35 papers were found with the search strategy, of which four studies met the inclusion criteria [1,11-13]. Among the other 31 studies, 11 studies were excluded as duplicate publications, and 13 did not meet the criteria after the title and the abstract were screened. Another seven studies were excluded for providing insufficient data. Two included studies explored the relation between the rs524952 polymorphism and high myopia based on two different groups of people. Chaoshan and Guangzhou populations were included in Jiao's study [1], and Hui and Han populations were included in Zhu's paper [11]. These different populations were considered separately in the present meta-analysis. Finally, a total of six comparison groups with 2,582 cases and 2,711 controls were available for this meta-analysis. The study selection process is presented in Figure 1, and the study details are displayed in Table 1.

Pooled meta-analysis and subgroup analysis: The evaluation of the association between the rs524952 polymorphism and HM is shown in Table 2. Heterogeneity was present among the studies in the overall comparisons (allelic model (A versus T): $p<0.1$, $I^2=90.0\%$; recessive genetic model (AA versus AT/TT): $p<0.1$, $I^2=85.1\%$; dominant model (AA/AT versus TT): $p<0.1$, $I^2=84.4\%$; respectively). Thus, the overall effect was pooled under the random-effects model. The meta-analysis suggested that the association between the rs524952 polymorphism and HM was not statistically significant in all genetic models (allelic model (A versus T): OR=0.95, 95% CI=0.72–1.24; recessive genetic model (AA versus AT/TT): OR=0.92, 95% CI=0.64–1.32; dominant model (AA/AT versus TT): OR=0.95, 95% CI=0.66–1.37; respectively). Subgroup analysis was conducted by dividing the studies into two groups according to the sample size of the cases in each study (cases≤300 and cases>300). However, the results revealed that there was no statistically significant association between the rs524952 polymorphism and HM in the subgroup with more than 300 cases. Similarly, in another subgroup (cases≤300), except the dominant genetic model (GG/GT versus TT, OR=0.64, 95% CI=0.43–0.96), there was also

Table 1. Characteristics of included studies for rs524952 and HM.

Author	Year	Ethnicity	Sample size	Age (years)		Genotype distributions	
				cases	controls	Cases (AA/AT/TT)	Controls (AA/AT/TT)
Jiao et al.	2012	Chinese	608	22.2±1.7	21.7±1.5	69/161/70	125/143/40
Jiao et al.*	2012	Chinese	192	21.8±1.3	21.7±1.3	28/48/20	34/46/16
Hayashi et al.	2011	Japanese	2054	57.6±14.8	38.8±11.8	303/572/244	191/444/286
Zhu et al.	2014	Chinese	741	39.3±16.9	71.1±8.5	99/198/83	96/198/67
Zhu et al.*	2014	Chinese	234	41.0±17.6	70.2±7.4	33/57/17	38/70/19
Zhou et al.	2016	Chinese	1460	N	N	98/302/69	137/444/309

N: Not mentioned in the study *:to distinguish the two studies with the same author

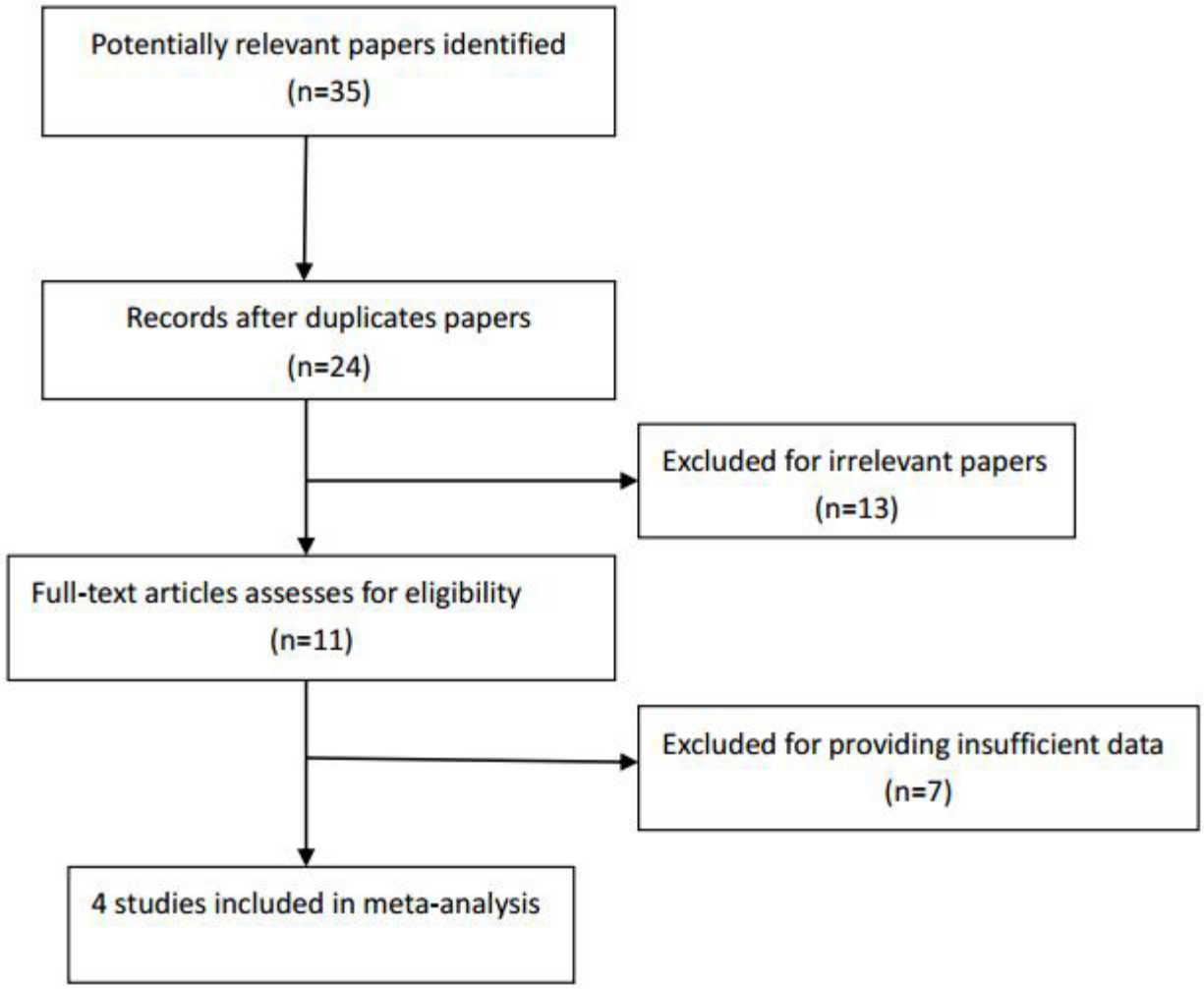

Figure 1. The study selection process for rs524952 and high myopia (HM). Flow diagram summarizing the systematic search and selection process for investigating the association between rs524952 and HM.

Table 2. Characteristics of included studies for rs634990 and HM.

Author	Year	Ethnicity	Sample size	Age(years)		Genotype distributions	
				cases	controls	Cases (CC/CT/TT)	Controls (CC/CT/TT)
Qiang et al.	2014	Chinese	1461	36.0±15.0	42.5±13.3	102/246/170	212/434/275
Hayashi et al.	2011	Japanese	2054	57.6±14.8	38.8±11.8	304/571/246	191/442/285
Zhou et al.	2016	Chinese	1460	N	N	97/291/177	137/442/308
Jiao et al.	2012	Chinese	608	22.2±1.7	21.7±1.5	71/156/73	39/144/125
Jiao et al.*	2012	Chinese	192	21.8±1.3	21.7±1.3	20/48/28	16/46/34
Zhu et al.	2014	Chinese	741	39.3±16.9	71.1±8.5	83/198/99	66/198/97
Zhu et al.*	2014	Chinese	234	41.0±17.6	70.2±7.4	17/57/33	19/70/38

N: Not mentioned in the study *:to distinguish the two studies with the same author

no statistically significant association between the rs524952 polymorphism and HM under the other genetic models. The summarized results are presented in Table 3.

Sensitivity analysis and publication bias: In this study, the associations between the rs524952 polymorphism and HM were not statistically significant in all genetic models after one study was omitted, suggesting that the overall meta-analysis estimates were stable. Egger's test and Begg's test were used to assess publication bias. No publication bias was observed, because the Egger test (p=0.21, 0.34, and 0.13, respectively) and Begg test (p=0.13, 0.13, and 0.26 respectively) results were not statistically significant under the allelic model, recessive genetic model, and dominant genetic model.

Rs634990: For the rs634990 polymorphism, the literature search resulted in 26 papers. After the title and the abstract were screened, 14 studies were excluded for not meeting the inclusion criteria: duplicated publication, review, and irrelevant to the topic. Another seven studies were excluded after the full text was read, two for providing no data about the rs634990 polymorphism with HM. Jiao et al. and Zhu et al. reported the allele (G rather than C, A rather than T) of the rs634990 polymorphism on the opposite strand from Qiang et al., Hiyash et al., and Zhou et al. Considering the two SNPs are in almost complete linkage disequilibrium, we included the two studies for this meta-analysis. Finally, a total of 3,099 cases and ,3651 controls of five studies with seven comparison groups were selected for this meta-analysis. The selection process is presented in Figure 2. The genotype frequencies in the control groups of the selected studies were all consistent with HWE, and the study details are shown in Table 2.

Genetic model statistical analysis: The evaluation of the association between the rs634990 polymorphism and HM is shown in Table 4 [1]. Allelic model (G versus T): The test for heterogeneity was statistically significant (p<0.1, I^2=75.0%), and the pooled odds ratio under the random-effects model was 1.12 (95% CI:0.96–1.31) [2]. Recessive genetic model (GG versus GT/TT): The pooled ratio was 1.24 (95% CI:0.98–1.57) under the random-effects model (p=0.007, I^2=66.0%) [3]. Dominant genetic model (GG/GT versus TT): The pooled ratio was 1.25 (95% CI:0.98–1.56) under the random-effects model (p=0.000, I^2=77.5%). Subgroup analysis was conducted by dividing the studies into two groups according to the sample size of the cases in each study (cases≤300 and cases>300). However, the results revealed that there was no statistically significant association between the rs634990 polymorphism and HM in the subgroup with more than 300 cases. Similarly, in another subgroup (cases≤300), there was also no statistically significant association between the

Table 3. The result of meta-analysis of the rs524952 polymorphism on the risk of HM.

Variables	N	Allelic model			Recessive genetic model			Dominant genetic model		
		OR(95%CI)	P value	I^2,%	OR(95%CI)	P value	I^2,%	OR(95%CI)	P value	I^2,%
Total	6	0.95(0.72–1.24)	0.000	90.0	0.92(0.64–1.32)	0.000	85.1	0.95(0.66–1.37)	0.000	84.4
Sample size										
cases<=300	3	0.75(0.52–1.44)	0.024	73.3	0.68(0.39–1.18)	0.025	72.9	0.64(0.43–0.96)	0.258	26.3
cases>300	3	1.15(0.93–1.42)	0.005	81.4	1.20(0.96–1.50)	0.131	50.8	1.22(0.87–1.72)	0.004	81.8

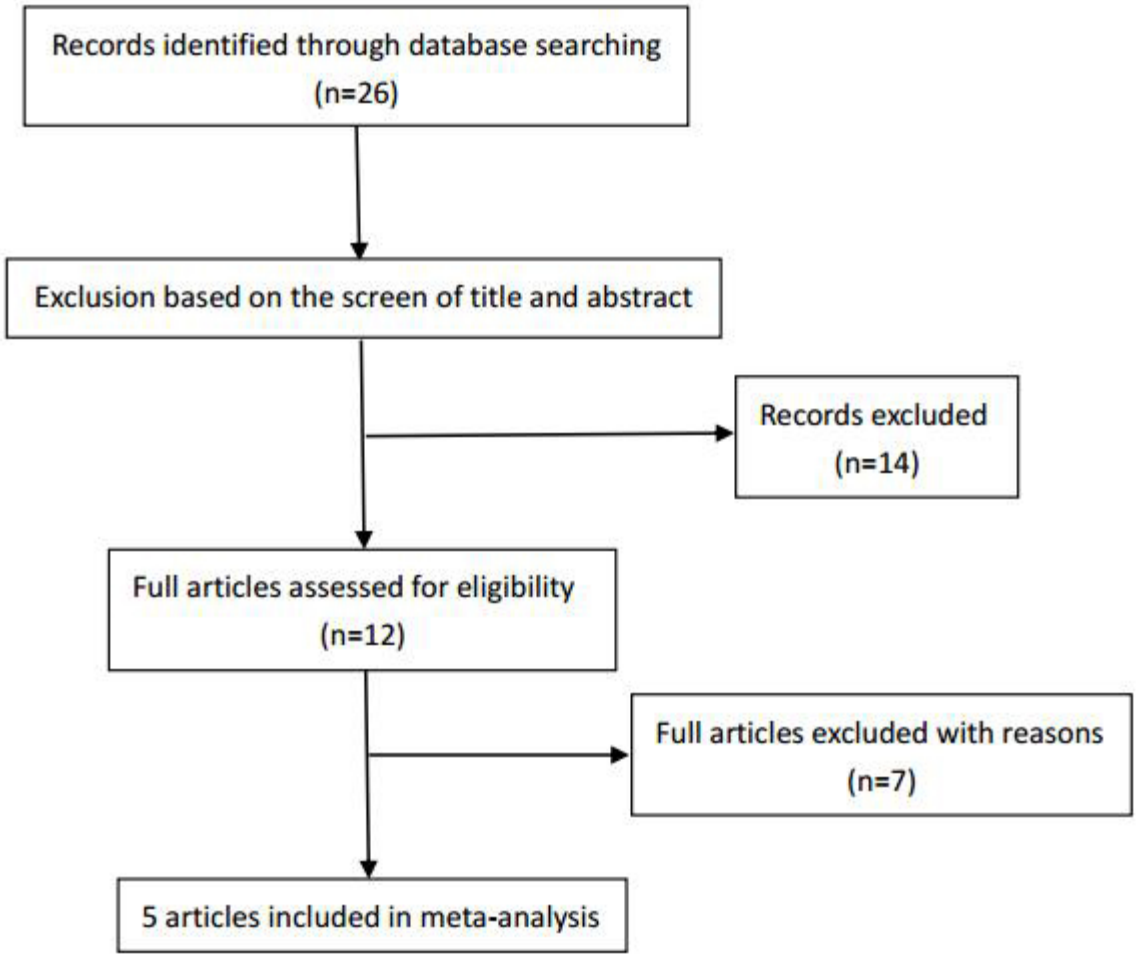

Figure 2. The study selection process for rs634990 and high myopia (HM). Flow diagram summarizing the systematic search and selection process for investigating the association between rs634990 and HM.

rs634990 polymorphism and HM under all genetic models. The summarized results are presented in Table 4.

Sensitivity analysis and publication bias: Sensitivity analysis showed that when Qiang et al.'s study was excluded, the association between the rs634990 polymorphism and HM turned out to be statistically significant in the allelic (OR=1.18, 95% CI:1.01–1.38), recessive (OR=1.36, 95% CI:1.36–1.14), and dominant genetic models (OR=1.35, 95% CI:1.07–1.70). A possible reason may be that the ORs in Qiang et al.'s study were statistically significantly lower than those in the other studies. Thus, the result was no longer not statistically significant when Qiang et al.'s study was excluded. The associations between the rs634990 polymorphism and HM were not

Table 4. The result of meta-analysis of the rs634990 polymorphism on the risk of HM.

Variables	N	Allelic model			Recessive genetic model			Dominant genetic model		
		OR(95%CI)	P value	I^2,%	OR(95%CI)	P value	I^2,%	OR(95%CI)	P value	I^2,%
Total	7	1.12(0.96,1.31)	0.000	75.0	1.24(0.98,1.57)	0.007	66.0	1.25(0.98,1.56)	0.000	77.5
Sample size										
cases<=300	2	1.10(0.84,1.45)	0.447	0.0	1.19(0.71,1.97)	0.696	0.0	1.11(0.74,1.68)	0.433	0.0
cases>300	5	1.13(0.94,1.35)	0.000	83.5	1.26(0.95,1.66)	0.002	77.1	1.28(0.96,1.71)	0.000	84.4

statistically significant in all genetic models after the other six comparison groups were omitted.

Egger's test and Begg's test were used to assess publication bias. No publication bias was observed, because Egger's test (p=0.43, 0.38, and 0.95, respectively) and Begg's test (p=0.37, 0.23, and 1.00 respectively) were not statistically significant under the allelic, recessive genetic, and dominant genetic models.

DISCUSSION

Many studies investigating the pathogenesis of HM have indicated a genetic inherited susceptibility [9,16]. The SNP rs634990 was first found to be statistically significant with myopia in 15q14 which is located in gap junction protein delta 2 (GJD2; gene ID:57369, OMIM 607058) in a Dutch population-based study [16]. Moderate to high expression of GJD2 was observed in the retina of postmortem human eyes. A possible explanation of the potential function of GJD2 in the development of HM may be that GJD2 contributes to encoding connexin36 and forms gap functions, which play an important role in transmitting electrical signals in the mammalian retina [17]. Previous animal experiments on the mouse suggested that the deletion of connexin36 may result in the elimination of ON pathway signaling in the rod pathway, and then the mouse with a defective ON pathway highly developed myopia [18,19]. Thus, GJD2 was thought to be a candidate gene for high myopia. Rs524952 is the SNP in 15q14 which is adjacent to the SNP rs634990 with a distance of less than 200 bp. The SNP rs524952 was found to be associated with myopia in a previous meta-analysis [20]. Numerous studies have been conducted to investigate the association between the SNPs rs524952 and rs634990 and HM, but the results were inconsistent [1,2,11-13].

In the present study, no obvious association between the rs524952 polymorphism and HM under the allelic and genetic models were found. Heterogeneity should be considered an important factor influencing the reliability of the results. In this meta-analysis, statistically significant heterogeneity was found in all genetic models. A research focus on the global prevalence of myopia and high myopia from 2000 to 2050 showed that the prevalence of myopia varied by age group, and the high-prevalence age group was between 10 and 39 years [21]. Thus, heterogeneity may be related to the uneven distribution of age among the subjects. In the subgroup analysis, the results indicated that the pooled effects increased as the number of cases increased, and no statistically significant association was observed in the large case numbers group (>300) under allelic models or genetic models. In another subgroup (cases≤300), the statistically significant association between the rs524952 polymorphism and HM was observed only under the dominant genetic model (OR=0.64). The inconsistency in the conclusions between the two subgroups under the dominant genetic model indicated the different sample sizes of the studies may also be a possible cause of heterogeneity. Fen et al. showed that there is an interaction between the rs524952 polymorphism and education level on refractive error [22]. The association between the rs524952 polymorphism and HM under the dominant genetic model in the subgroup (cases≤300) may be affected by the education level, rather than a direct effect of the SNP itself. Associations with HM were not found for the rs634990 polymorphism under all genetic models. Similarly, no statistically significant results were observed in the subgroup analysis. However, the sensitivity analysis indicated that the association between the rs634990 polymorphism and HM was not robust in all genetic models.

To the best of our knowledge, the present meta-analysis was the first study to explore the association between the rs524952 and rs634990 polymorphisms and HM. However, several limitations should be recognized. First, the populations were composed only of Chinese and Japanese, and the lack of data from other regions may lead to results that are specific only to these particular populations. Second, the age of the subjects included in the studies varied greatly, which may contribute a potential source of considerable heterogeneity. Third, environmental factors also play an important role in the development of HM. However, we did not take these factors into consideration in this meta-analysis.

In summary, there is no evidence of a connection between the rs524952 and rs634990 polymorphisms and HM. Large-scale studies should be conducted in the future to confirm these results.

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