META-ANALYSIS

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Association Between Polymorphisms of 4 Common Genes and High Myopia Risk: A Comprehensive Analysis

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Background: Genome-wide association studies have been suggested single-nucleotide polymorphisms (SNPs) can influence susceptibility to high myopia (HM). To investigate the associations of multiple SNPs of 4 common genes and HM, we collected all related articles about these 4 common SNPs and risk of HM.

Material/Methods: PubMed and Wanfang databases were searched for articles published until Dec 10, 2025 using the keywords 'GJD2' or 'ZC3H11B' or 'MMP1' or 'MMP9', 'polymorphism' and 'myopia' or 'shortsightedness'. Odds ratios and 95% confidence intervals were used to examine the association between above 4 genes' SNPs and HM risk using Stata software.

Results: We performed a meta-analysis of data from 15 published articles. There were 2 SNPs in the GJD2 gene, 4 SNPs in the ZC3H11B gene, 1 in SNP in the MMP1 gene, and 1 SNP in the MMP9 gene. After analyses using Stata, significant results were detected: rs3743123 in the GJD2 gene was associated with a decreased overall HM risk. Additionally, similar trends were detected in all 4 SNPs in the ZC3H11B gene: rs4373767, rs4428898, rs10779363and rs7544369.

Conclusions: Our results suggest that the GJD2 gene rs3743123 and ZC3H11B gene 4 SNPs (rs4373767, rs4428898, rs10779363, rs7544369) polymorphisms are associated with risk of HM. Our results need to be confirmed by larger studies and mechanism research, which may aid in the early identification and prognostic evaluation of HM.

Keywords: Myopia, Degenerative • Polymorphism, Genetic

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/952771

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Introduction

Myopia prevalence has increased dramatically over recent decades. Globally, this upward trend is particularly pronounced in East Asia, making myopia a major public health concern [1-3]. As the most common cause of visual impairment, myopia results in an estimated global productivity loss of approximately US$250 billion annually [4-6]. To address the burden of eye diseases, it is imperative to develop comprehensive prevention and management strategies by elucidating the risk factors and pathophysiological mechanisms underlying them [7].

Emerging evidence underscores the substantial impact of genetic susceptibility on myopia and high myopia (HM). Polymorphisms in key genetic loci have been shown to significantly elevate susceptibility to this sight-threatening complication [8-10].

Genome-wide association studies (GWAS), when aggregated via meta-analysis, have identified numerous genetic loci significantly associated with both myopia and refractive error; however, the mechanisms by which genotypic identity confers myopia susceptibility remain unclear [11,12].

A previous meta-analysis systematically reviewed 76 studies (89 cohorts) encompassing 77 single-nucleotide polymorphisms (SNP) in 34 genes related to HM, identifying 22 SNPs in 13 genes (eg, ACAN, COL1A1, and CRYBA4) that are significantly associated with HM risk [13]. Additionally, 4 other common genes – GJD2, ZC3H11B, MMP1, and MMP9 – have also been implicated as risk factors for HM susceptibility.

Previous meta-analyses have been small, with insufficiently comprehensive subgroupings. The present study incorporated a larger number of relevant studies and provides a more specific and comprehensive analysis, enabling the derivation of conclusions with greater practical reference value. It is expected to provide essential molecular markers for the early detection of HM. Herein, we conducted pooled analyses of all case-control studies focusing on polymorphisms (rs634990, rs3743123, rs4373767, rs4428898, rs10779363, rs7544369, rs1799750, and rs17576) in these 4 common genes to assess their association with HM risk [14-24]. The aim was to generate stronger evidence regarding the existence of significant associations, which may be help in developing effective strategies to prevent HM.

Material and Methods

Study Selection and Data Extraction

The PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Wanfang (https://www.wanfangdata.com.cn/) databases were searched for all articles published as of Dec 10, 2025, using the keywords: 'GJD2 or gap junction protein delta 2' or 'ZC3H11B or zinc finger CCCH-type containing 11B' or 'MMP1 or matrix metallopeptidase 1' or 'MMP9', 'polymorphism' and 'myopia' or 'shortsightedness'. No language or publication year restrictions were imposed on the search. Additionally, the references of retrieved articles and reviews were manually searched to identify relevant studies. This study followed the established Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 reporting standards (**Table 1**) and included a detailed flow diagram [25]. This study was registered at PROSPERO (number 1365571; https://www.crd.york.ac.uk/prospero/). Finally, 2 independent reviewers from our research team screened the titles, abstracts, and full texts of retrieved articles to confirm eligibility for inclusion.

Eligible studies met the following criteria: (a) evaluated the correlation between HM risk and 1 or more of the selected polymorphisms; (b) were case-control studies; (c) included age- and sex-matched control groups; and (d) had an available full-text manuscript. Studies were excluded if they: (a) lacked a control population; (b) did not provide genotype frequencies; (c) were duplicate studies; or (d) there was clear evidence of bias. Data collected from eligible studies included the first author, publication year, country, ethnicity, different genes, different SNPs, genotypes in the case and control groups, source of controls, Hardy-Weinberg equilibrium (HWE) analyses of controls, and genotyping methods (eg, real-time PCR, TaqMan, MassARRAY).

Assessment of study quality

Study quality was assessed using the Newcastle-Ottawa Scale (NOS), which employs a star scoring system (range: 0-9 stars). A score of 9 stars indicates the highest methodological quality; scores of 5 to 9 are generally considered indicative of high quality, while scores of 0 to 4 suggest lower quality [26].

Statistical Analyses

Minor allele frequencies (MAF) for these 8 polymorphisms were assessed in 6 global populations using the 1000 Genomes Browser (https://www.ncbi.nlm.nih.gov/snp/), which reveals racial differences in polymorphism frequencies. The populations analyzed included Global (n=5008), African (n=1322), East Asian (n=1008), European (n=1006), South Asian (n=978), and American (n=694).

Odds ratios (ORs) and 95% confidence intervals (CIs) were used to examine the association between polymorphisms in the 4 common genes and HM risk, based on genotypic frequencies in cases and control subjects. Subgroup analyses were initially conducted based on the source of control subjects, separately assessing population-based (PB) and hospital-based (HB) studies.

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The significance of pooled ORs was assessed using the Z test [27]. For evaluating the consistency of the included studies, the Cochrane's Q test was first applied: if the *P* value of the Q test was >0.10, a fixed-effects model was used; otherwise, a random-effects model was used [28,29]. This was further validated using the I^2 test: if $I^2 \leq 50\%$, a fixed-effects model was used for all OR calculations; otherwise, significant heterogeneity was indicated, and a random-effects model was

Table 1. PRISMA flow checklist (2020).

Section and topic	Item #	Checklist item	Location where item is reported
Title			
Title	1	Identify the report as a systematic review	1
Abstract			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge	1-2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses	1-2
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	2
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used	2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process	2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process	2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (eg, for all measures, time points, analyses), and if not, the methods used to decide which results to collect	2
	10b	List and define all other variables for which data were sought (eg, participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process	3
Effect measures	12	Specify for each outcome the effect measure(s) (eg, risk ratio, mean difference) used in the synthesis or presentation of results	3

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Table 1 continued. PRISMA flow checklist (2020).

Section and topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (eg, tabulating the study intervention characteristics and comparing against the planned groups for each synthesis [item #5])	3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions	3
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses	3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used	3
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (eg, subgroup analysis, meta-regression)	3
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results	3
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	3
Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram	3
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	3
Study characteristics	17	Cite each included study and present its characteristics	3
Risk of bias in studies	18	Present assessments of risk of bias for each included study	4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (eg, confidence/credible interval), ideally using structured tables or plots	4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies	4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (eg, confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	4
	20c	Present results of all investigations of possible causes of heterogeneity among study results	4
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results	4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	4

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Table 1 continued. PRISMA flow checklist (2020).

Section and topic	Item #	Checklist item	Location where item is reported
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	4
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence	5
	23b	Discuss any limitations of the evidence included in the review	5
	23c	Discuss any limitations of the review processes used	5
	23d	Discuss implications of the results for practice, policy, and future research	5
Other information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered	None
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	None
	24c	Describe and explain any amendments to information provided at registration or in the protocol	None
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review	6
Competing interests	26	Declare any competing interests of review authors	6
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review	6

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ, 2021; 372: n71. doi: 10.1136/bmj.n71.

applied, followed by additional sensitivity and subgroup analyses to identify sources of heterogeneity [30]. For the 8 polymorphisms (rs634990, rs3743123, rs4373767, rs4428898, rs10779363, rs7544369, rs1799750, and rs17576) in the 4 target genes, associations between genotype and HM risk were assessed using 5 genetic models: dominant, heterozygote comparison, allelic contrast, homozygote comparison, and recessive.

To adjust for multiple comparisons, the stepdown Bonferroni method was applied to reduce the type I error (false positive) [31]. Begg's and Egger's tests were used to evaluate funnel plot asymmetry to detect publication bias [32], with $P<0.05$ considered statistically significant. The Pearson chi-square goodness-of-fit test was used to detect departures from HWE for the 8 polymorphisms, with $P<0.05$ as the significance cutoff. Stata v11.0 (StataCorp LP, TX, USA) was used to calculate the ORs, CIs, and to conduct Begg's and Egger's tests.

Results

Systematic Literature Review and Study Selection

Our systematic search strategy retrieved 164 potentially relevant articles from PubMed and Wanfang databases. After rigorous evaluation based on predefined inclusion criteria, 15 high-quality studies were selected for meta-analysis (**Figure 1**), including 2 case-control studies for rs634990, 3 case-control studies for rs3743123, 4 case-control studies for rs4373767, 3 case-control studies for rs4428898, 3 case-control studies for rs10779363, 3 case-control studies for rs7544369, 2 case-control studies for rs1799750, and 2 case-control studies for rs17576. The detailed characteristics of included case-control studies are listed in **Table 2**.

MAF reports for these 8 polymorphisms were assessed in the 5 different global populations from the 1000 Genomes Browser, which shows the different ratio in different races for different

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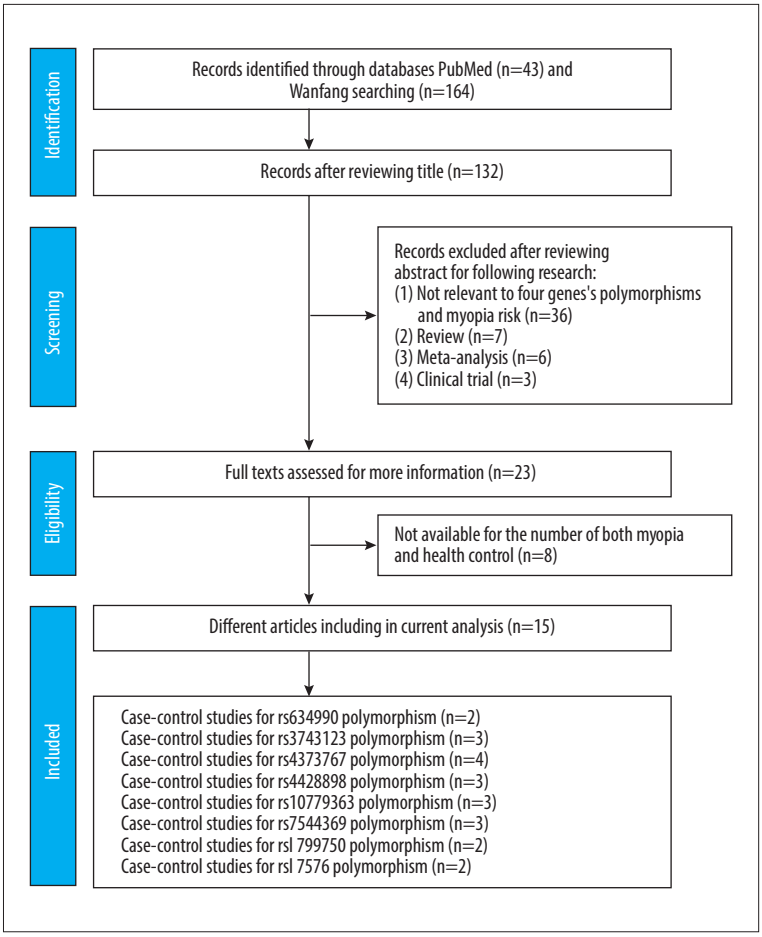

Figure 1. Flowchart depicting the systematic search strategy from different databases about the identification of studies investigating 4 genes' (*GJD2*, *ZC3H11B*, *MMP1*, *MMP9*) polymorphisms and HM risk.

polymorphisms (**Figure 2**). For example, the frequency from African in rs4428898 was the highest, however, was the lowest in rs4373767 (**Figure 2**).

Pooled analyses

A significant decreased association was detected between GJD2 rs3743123 polymorphism and HM risk: OR=0.78, 95% CI (0.67-0.91), $P_{heterogeneity}$=0.740, *P*=0.002, I^2=91.5% for A-allele vs G-allele, **Figure 3**; OR=0.72, 95% CI (0.60-0.87), $P_{heterogeneity}$=0.555, *P*=0.001, I^2=0.0% for AG vs GG, **Figure 4**; OR=0.73, 95% CI (0.61-0.87), $P_{heterogeneity}$=0.814, *P*=0.000, I^2=0.0% for AA+AG vs GG, **Figure 5**. No significant relationship was found for another polymorphism (rs634990) in the GJD2 gene (**Table 3**).

In the ZC3H11B gene, 4 polymorphisms were analyzed. For rs4373767, a decreased association was observed in 2 genetic models: OR=0.84, 95% CI (0.72-0.98), $P_{heterogeneity}$=0.270, *P*=0.027, I^2=23.2% for TC vs CC (**Figure 4**); OR=0.85, 95% CI (0.73-0.98), $P_{heterogeneity}$=0.239, *P*=0.026, I^2=28.8% for TT+TC vs CC (**Figure 5**). For rs4428898, this polymorphism was a decreased factor to HM: OR=0.87, 95% CI (0.77-0.98), $P_{heterogeneity}$=0.294, *P*=0.019, I^2=18.2% for G-allele vs A-allele (**Figure 3**); OR=0.82, 95% CI (0.69-0.97), $P_{heterogeneity}$=0.210, *P*=0.019, I^2=36.0% for GA vs AA (**Figure 4**); OR=0.82, 95% CI (0.69-0.96), $P_{heterogeneity}$=0.159, *P*=0.012, I^2=45.6% for GG+GA vs AA (**Figure 5**). For rs10779363, a significant relationship was found: OR=0.80, 95% CI (0.68-0.94), $P_{heterogeneity}$=0.2556, *P*=0.007, I^2=26.5% for CT vs TT (**Figure 4**); OR=0.82, 95% CI (0.71-0.96), $P_{heterogeneity}$=0.196, *P*=0.011, I^2=38.6% for CC+CT vs TT (**Figure 5**). Finally, for rs7544369, OR=0.86, 95% CI (0.76-0.97), $P_{heterogeneity}$=0.306, *P*=0.015, I^2=15.5% for C-allele vs T-allele (**Figure 3**); OR=0.81, 95% CI (0.68-0.96), $P_{heterogeneity}$=0.371, *P*=0.013, I^2=0.0% for CT vs TT (**Figure 4**); OR=0.81, 95% CI (0.69-0.95), $P_{heterogeneity}$=0.277, *P* = 0.009, I^2=22.2% for CC+CT vs TT (**Figure 5, Table 3**). To reduce the type I error, the Bonferroni method was used. Finally, no association was found both for rs4373767 and rs4428898 SNPs.

For the matrix metalloproteinase family (MMP1, MMP9) genes, no significant association was found (**Table 3**).

Publication bias and sensitivity analyses

The potential for publication bias was next evaluated with Begg's funnel plots and Egger's test. No publication bias was found in any of the 4 genes' polymorphisms (**Table 4, Figure 6**).

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Table 2. Characteristics of included studies about polymorphisms in 4 different genes and HM risk.

Author	Year	Country	Ethnicity	Gene	SNP	Case	Control	SOC
Kunceviciene et al [14]	2018	Lithuania	White	*GJD2*	rs634990	176	96	PB
Duan et al [17]	2013	China	Asian	*GJD2*	rs634990	300	290	HB
Liu et al [20]	2021	China	Asian	*GJD2*	rs3743123	445	445	PB
Liu et al [19]	2019	China	Asian	*GJD2*	rs3743123	265	268	PB
Liu et al [19]	2019	China	Asian	*GJD2*	rs3743123	312	309	PB
Mi et al [23]	2022	China	Asian	*ZC3H11B*	rs4373767	233	256	HB
Kuang et al [18]	2014	China	Asian	*ZC3H11B*	rs4373767	535	895	PB
Liu et al [22]	2019	China	Asian	*ZC3H11B*	rs4373767	605	211	PB
Liu et al [24]	2019	China	Asian	*ZC3H11B*	rs4373767	343	210	PB
Kuang et al [18]	2014	China	Asian	*ZC3H11B*	rs4428898	535	895	PB
Liu et al [22]	2019	China	Asian	*ZC3H11B*	rs4428898	603	209	PB
Liu et al [24]	2019	China	Asian	*ZC3H11B*	rs4428898	343	210	PB
Kuang et al [18]	2014	China	Asian	*ZC3H11B*	rs10779363	525	905	PB
Liu et al [22]	2019	China	Asian	*ZC3H11B*	rs10779363	1175	264	PB
Liu et al [24]	2019	China	Asian	*ZC3H11B*	rs10779363	343	210	PB
Kuang et al [18]	2014	China	Asian	*ZC3H11B*	rs7544369	532	906	PB
Liu et al [22]	2019	China	Asian	*ZC3H11B*	rs7544369	599	213	PB
Liu et al [24]	2019	China	Asian	*ZC3H11B*	rs7544369	343	210	PB
Liu et al [21]	2025	China	Asian	*MMP1*	rs1799750	302	143	PB
Nakanishi et al [15]	2010	Japan	Asian	*MMP1*	rs1799750	716	542	PB
Liu et al. 21]	2025	China	Asian	*MMP9*	rs17576	309	141	PB
Li et al [16]	2022	China	Asian	*MMP9*	rs17576	103	113	PB

Author	Case			Control			HWE	Genotype	NOS
	MM	MW	WW	MM	MW	WW			
Kunceviciene et al [14]	28	105	43	41	42	13	0.669	Real-Time PCR	8
Duan et al [17]	74	149	77	78	134	78	0.196	TaqMan SNP	7
Liu et al [20]	15	131	299	16	170	259	0.061	Agena MassARRAY	8
Liu et al [19]	5	92	168	15	99	154	0.861	Sequenom MassARRAY	8
Liu et al [19]	13	91	208	7	117	185	0.019	Sequenom MassARRAY	8
Mi et al [23]	56	108	69	60	120	76	0.347	MPCR	7

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Table 2 continued. Characteristics of included studies about polymorphisms in 4 different genes and HM risk.

Author	Case			Control			HWE	Genotype	NOS
	MM	MW	WW	MM	MW	WW			
Kuang et al [18]	56	212	267	100	370	425	0.154	TaqMan	7
Liu et al [22]	61	238	306	20	94	97	0.685	TaqMan	8
Liu et al [24]	49	158	136	35	115	60	0.094	TaqMan	8
Kuang et al [18]	56	212	267	100	370	425	0.154	TaqMan	7
Liu et al [22]	55	237	311	20	92	97	0.787	TaqMan	8
Liu et al [24]	48	163	132	37	116	57	0.096	TaqMan	8
Kuang et al [18]	55	205	265	96	375	434	0.266	TaqMan	7
Liu et al [22]	101	454	620	18	119	127	0.158	TaqMan	8
Liu et al [24]	47	162	134	35	116	59	0.083	TaqMan	8
Kuang et al [18]	51	207	274	94	371	441	0.226	TaqMan	7
Liu et al [22]	51	228	320	16	96	101	0.292	TaqMan	8
Liu et al [24]	40	170	133	35	115	60	0.094	TaqMan	8
Liu et al [21]	36	139	127	21	60	62	0.305	MassARRAY	8
Nakanishi et al [15]	74	313	329	60	227	255	0.378	TaqMan	8
Liu et al. 21]	18	119	172	8	51	82	0.984	MassARRAY	7
Li et al [16]	5	48	50	7	54	52	0.148	Sequenom MassARRAY	7

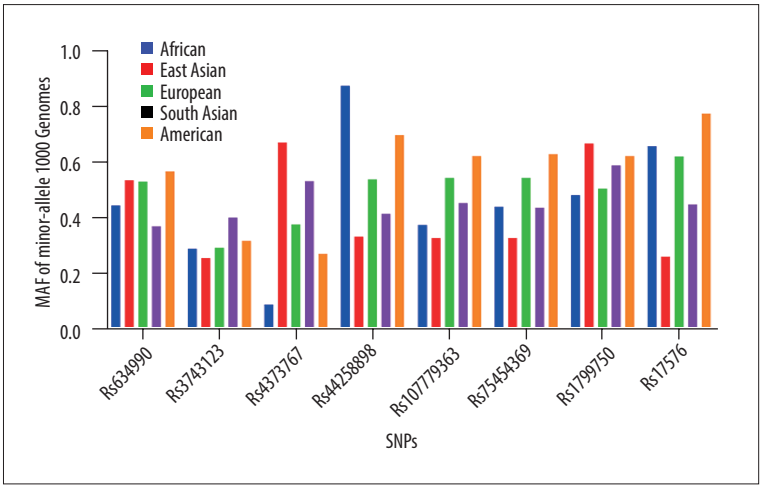

Figure 2. Minor (mutant) allele frequencies for 8 polymorphisms based on data from the online 1000 Genomes database.

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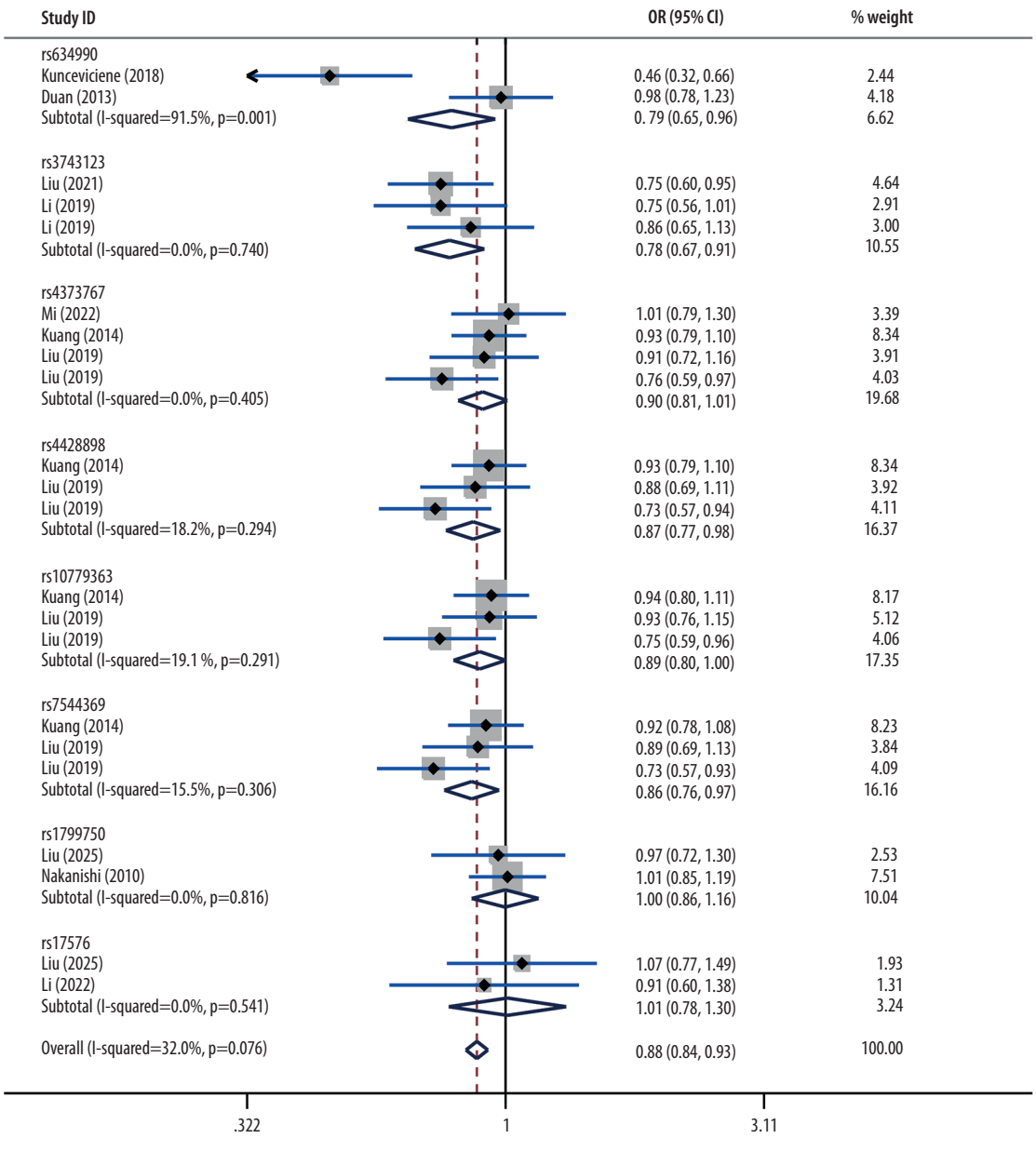

Figure 3. Forest plots corresponding to HM risk between the 8 polymorphisms in M-allele vs W-allele in total. The squares and horizontal lines respectively correspond to the study-specific ORs and 95% CIs, with square area being indicative of weight (the inverse of the variance). Diamonds additionally reflect the summary OR and 95% CI.

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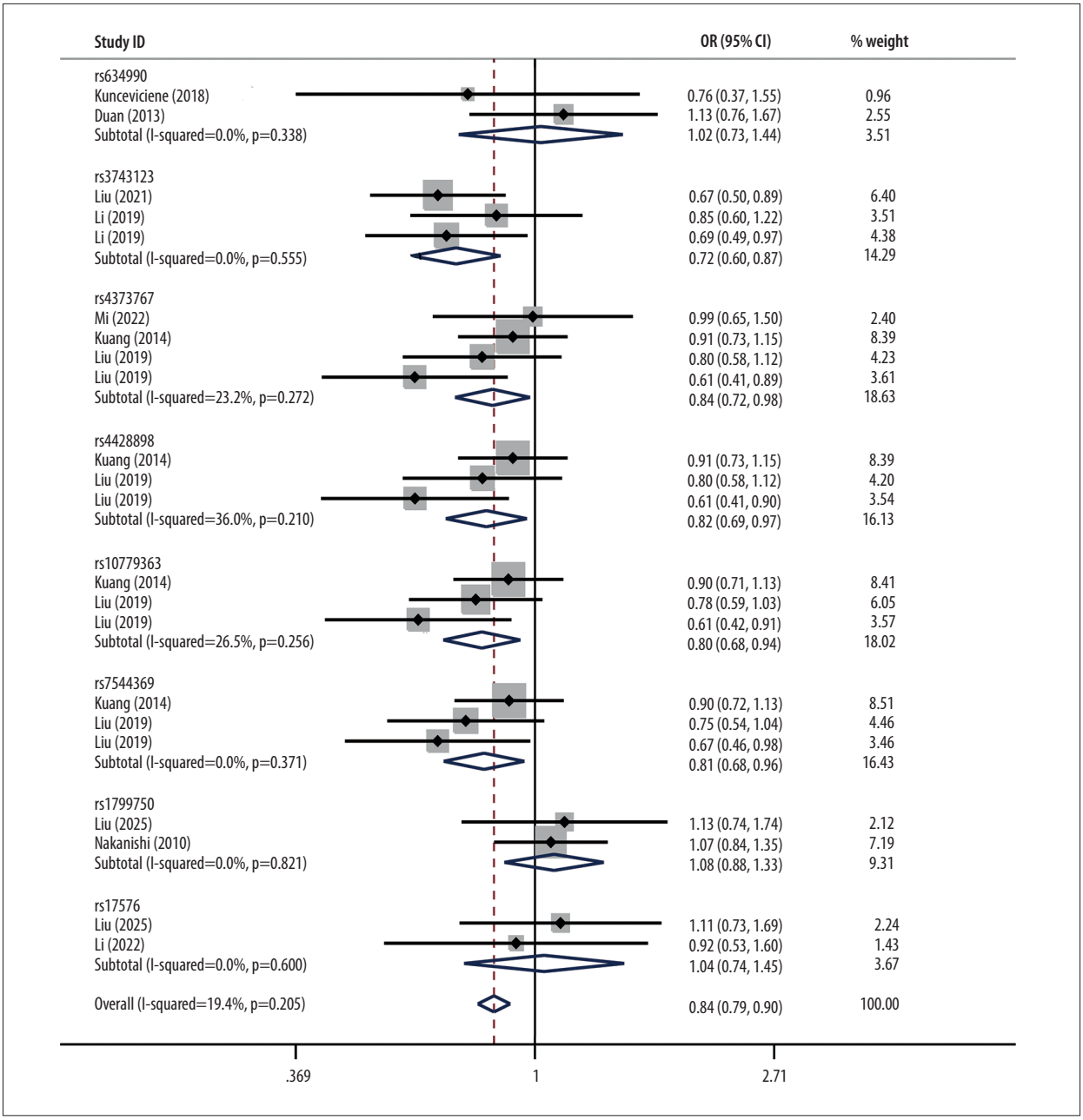

Figure 4. Forest plots corresponding to HM risk between the 8 polymorphisms in MW vs WW-allele in total.

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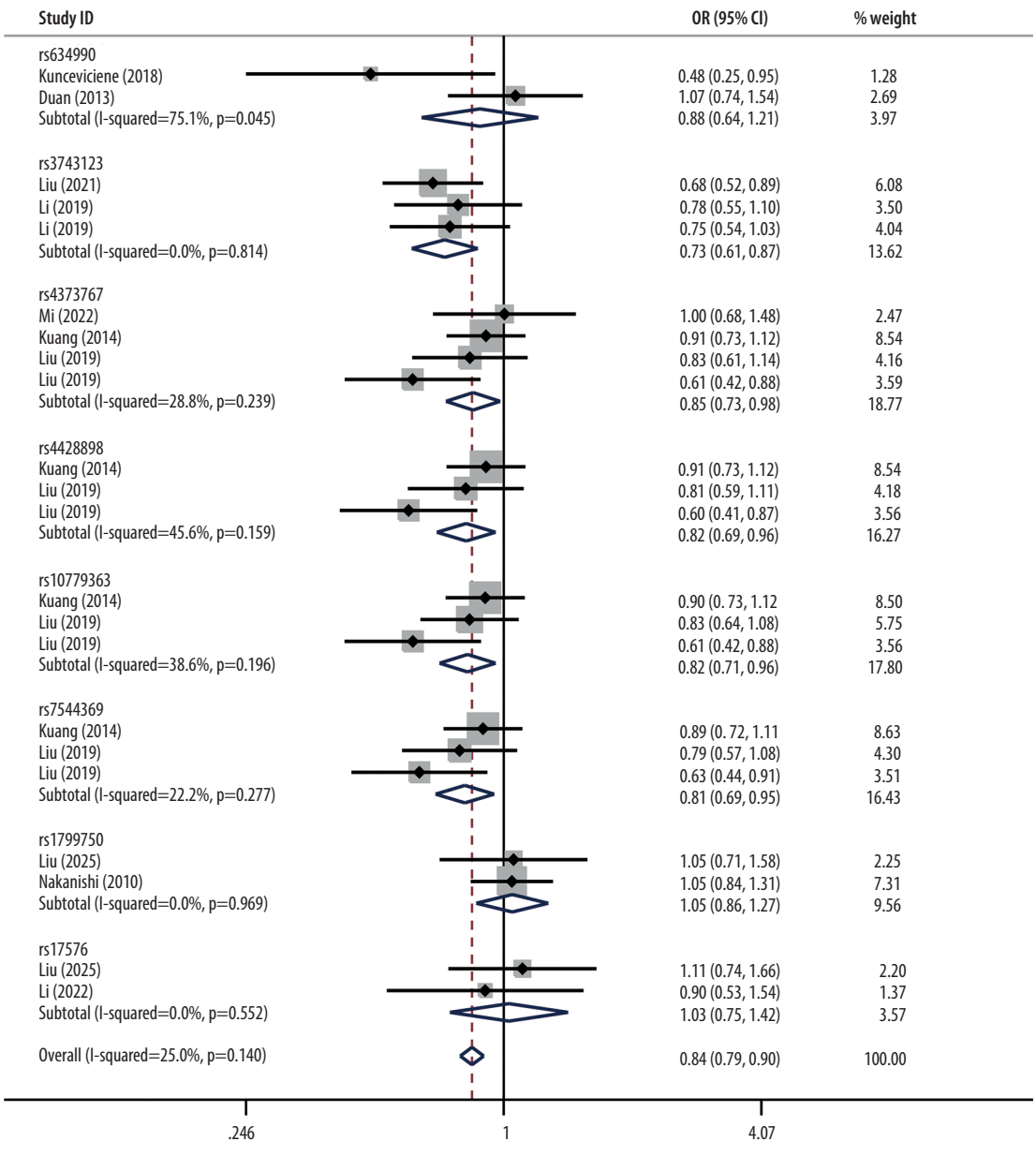

Figure 5. Forest plots corresponding to HM risk between the 8 polymorphisms in MM+MW vs WW in total.

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Table 3. Stratified analyses of 4 different genes' common polymorphisms on myopia risk.

Variables	N	Case/ Control	M-allele vs W-allele	MW vs WW	MM vs WW	MM+MW vs WW	MM vs MW+WW
			OR (95% CI)/ Ph/P/ Bon/I-squared	OR(95% CI Ph/P/ Bon/I-squared	OR(95% CI)/ Ph/P/ Bon/I-squared	OR (95% CI)/ Ph/P/ Bon/I-squared	OR (95% CI)/ Ph/P/ Bon/I-squared
rs634990							
Total	2	476/ 386	0.68 (0.34-1.34)/ 0.001/0.309/ 1/91.5%	1.02 (0.73-1.44)/ 0.338/0.888/ 1/0.0%	0.46 (0.10-2.08)/ 0.001/0.314/ 1/91.0%	0.76 (0.35-1.63)/ 0.045/0.479/ 1/75.1%	0.48 (0.14-1.66)/ 0.000/0.248/ 1/92.3%
rs3743123							
Total	3	1022/ 1022	0.78 (0.67-0.91)/ 0.740/0.002/ 0.010/0.0%	0.72 (0.60-0.87)/ 0.555/0.001/ 0.005/0.0%	0.76 (0.32-1.81)/ 0.060/0.539/ 1/64.4%	0.73 (0.61-0.87)/ 0.814/0.000/ 0.000/0.0%	0.85 (0.35-2.10)/ 0.045/0.726/ 1/67.7%
rs4373767							
Total	4	1716/ 1572	0.90 (0.81-1.01/) 0.405/0.067/ 1/0.0%	0.84 (0.72-0.98)/ 0.270/0.027/ 0.135/23.2%	0.87 (0.69-1.10)/ 0.530/0.243/ 1/0.0%	0.85 (0.73-0.98)/ 0.239/0.026/ 0.130/28.8%	0.96 (0.77-1.18)/ 0.883/0.681/ 1/0.0%
rs4428898							
Total	3	1481/ 1314	0.87 (0.77-0.98)/ 0.294/0.019/ 0.095/18.2%	0.82 (0.69-0.97)/ 0.210/0.019/ 0.095/36.0%	0.79 (0.61-1.03)/ 0.345/0.079/ 1/6.1%	0.82 (0.69-0.96)/ 0.159/0.012/ 0.060/45.6%	0.88 (0.69-1.13)/ 0.763/0.326/ 1/0.0%
rs10779363							
Total	3	2043/ 1379	0.89 (0.80-1.00)/ 0.291/0.052/ 1/19.1%	0.80 (0.68-0.94)/ 0.256/0.007/ 0.035/26.5%	0.88 (0.68-1.15)/ 0.202/0.358/ 1/37.5%	0.82 (0.71-0.96)/ 0.196/0.011/ 0.055/38.6%	0.99 (0.78-1.27)/ 0.408/0.953/ 1/0.0%
rs7544369							
Total	3	1474/ 1329	0.86 (0.76-0.97)/ 0.306/0.015/ 0.075/15.5%	0.81 (0.68-0.96)/ 0.371/0.013/ 0.065/0.0%	0.79 (0.60-1.04)/ 0.199/0.091/ 1/38.2%	0.81 (0.69-0.95)/ 0.277/0.009/ 0.045/22.2%	0.88 (0.68-1.13)/ 0.341/0.371/ 1/7.0%
rs1799750							
Total	2	1018/ 685	1.00 (0.86-1.16)/ 0.816/0.982/ 1/0.0%	1.08 (0.88-1.33)/ 0.821/0.451/ 1/0.0%	0.92 (0.67-1.27)/ 0.719/0.623/ 1/0.0%	1.05 (0.86-1.27)/ 0.969/0.642/ 1/0.0%	0.89 (0.65-1.20)/ 0.638/0.436/ 1/0.0%
rs17576							
Total	2	412/ 254	1.01 (0.78-1.30)/ 0.541/0.950/ 1/0.0%	1.04 (0.74-1.45)/ 0.600/0.822/ 1/0.0%	0.95 (0.47-1.91)/ 0.630/0.876/ 1/0.0%	1.03 (0.75-1.42)/ 0.552/0.863/ 1/0.0%	0.93 (0.47-1.85)/ 0.701/0.839/ 1/0.0%

P_h – value of *Q* test for heterogeneity test; *P* – *Z* test for the statistical significance of the OR; W – wild allele; M – mutant allele; Bon – *p* value in stepdown Bonferroni testing.

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Table 4. Publication bias tests (Begg's funnel plot and Egger's test for publication bias test) for 8 polymorphisms and HM risk.

	Egger's test					Begg's test	
Genetic type	Coefficient	Standard error	*t*	*P* value	95% CI of intercept	z	*P* value
M-allele vs W-allele	-2.228	0.970	-2.29	0.033	-4.260, -0.197	1.66	0.096
MW vs WW	-1.283	0.546	-2.35	0.029	-2.423, -0.143	1.21	0.225
MM vs WW	-0.729	0.356	-2.05	0.054	-1.471, 0.012	1.66	0.096
MM+MW vs WW	-1.369	0.559	-2.45	0.024	-2.537, -0.202	1.44	0.150
MM vs MW+WW	-0.659	0.457	-1.44	0.164	-1.612, 0.293	1.44	0.150

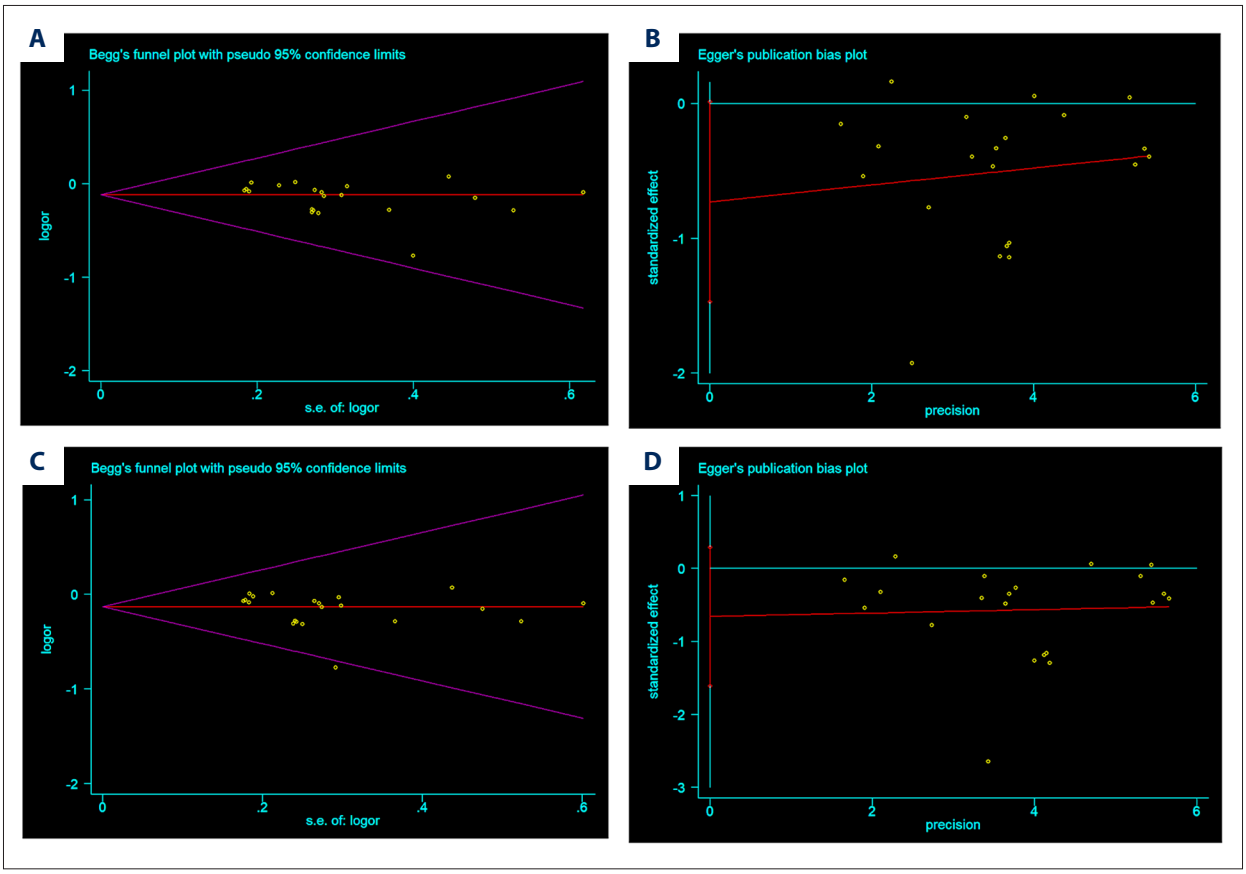

Figure 6. (**A**) Begg's funnel plot for publication bias test (MW vs WW). (**B**) Egger's publication bias plot (MW vs WW) for HM. (**C**) Begg's funnel plot for publication bias test (MM vs MW+WW). (**D**) Egger's publication bias plot (MM vs MW+WW) for HM.

Furthermore, to estimate the heterogeneity and delete studies that may influence the power/stability of the whole study, we applied sensitivity analysis, showing there were no sensitive case-control studies (**Figure 7**).

Discussion

Recent studies have identified SNPs associated with HM as significant genetic risk factors [10,33]. GWAS have discovered multiple susceptibility loci, particularly within or near genes involved in scleral remodeling and extracellular matrix organization, such as ARHGAP18, SNTB1, BMP2 and RASGRF1 [34-37]. Notably, advancements in large-scale biobank research and meta-analyses have enhanced the understanding of the polygenic architecture of this condition [33]. These investigations suggest that the cumulative effect of numerous common SNPs, combined with environmental stimuli such as prolonged near-vision work, contributes substantially to HM risk. Furthermore, functional genomic analyses are beginning to elucidate the biological pathways through which these variants influence axial elongation and scleral weakening.

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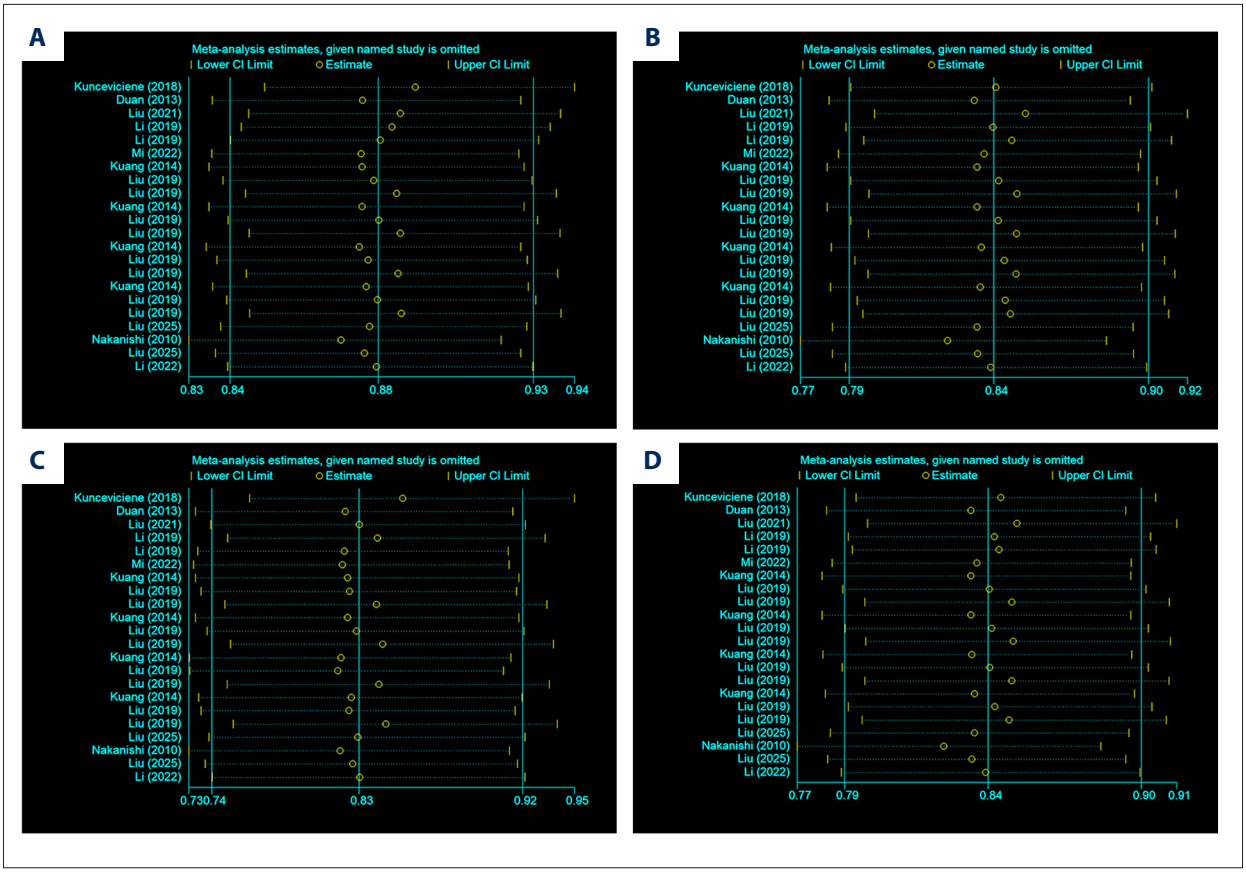

Figure 7. Sensitivity analysis of 8 polymorphisms and HM risk. (**A**) M-allele vs W-allele; (**B**) MW vs WW; (**C**) MM vs WW; (**D**) MM+MW vs WW.

The link to GJD2, which encodes connexin 36, underscores the critical role of gap junction communication in eye growth regulation, potentially affecting retinal signaling and scleral remodeling [38]. Similarly, the association with ZC3H11B, an RNA-binding protein, suggests a novel mechanism involving post-transcriptional gene regulation during eye development [39]. Most notably, the involvement of matrix metalloproteinases MMP1 and MMP9 points directly to extracellular matrix degradation and remodeling [40]. Dysregulation of these enzymes could weaken the structural integrity of the sclera, leading to its pathological elongation – a hallmark of HM. Given that these 4 genes have been implicated as important factors in the development of HM, we selected SNPs within these 4 genes to identify potential susceptibility SNPs for HM.

This meta-analysis is the first investigation to evaluate the association between 8 common SNPs across 4 genes and susceptibility to HM. The pooled data comprised a total of 9642 cases and 7941 controls, with the following distribution per SNP: rs634990 (476 cases, 386 controls), rs3743123 (1022 cases, 1022 controls), rs4373767 (1716 cases, 1572 controls), rs4428898 (1481 cases, 1314 controls), rs10779363 (2043 cases, 1379 controls), rs7544369 (1474 cases, 1329 controls), rs1799750 (1018 cases, 685 controls), and rs17576 (412 cases, 254 controls).

Based on the above data, the current analysis identified significant associations between HM risk and the rs3743123, rs4373767, rs4428898, rs10779363, and rs7544369 polymorphisms. These findings move beyond mere associations by suggesting potential mechanistic targets. The convergence of genes involved in cellular communication, genetic regulation, and structural integrity suggests that HM pathogenesis is multifactorial, resulting from subtle disruptions across interconnected systems. Translating this knowledge, the identified SNPs could serve as components of a polygenic risk score, enabling earlier identification of at-risk individuals. This paves the way for personalized preventive strategies, such as intensified monitoring and lifestyle interventions aimed at modulating environmental risk factors, ultimately contributing to a precision medicine approach for this vision-threatening condition.

The present study is subject to several limitations. First, despite the inclusion of all relevant literature, the overall sample size remains relatively modest. This limitation was further compounded when conducting subgroup analyses stratified by

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variables such as age, sex, ethnicity, axial length, and myopia severity. Second, the risk of high myopia associated with the identified polymorphisms is likely modulated by complex interactions, including gene-gene and gene-environment effects, as well as influences from other genetic variants. Future research should prioritize collecting detailed phenotypic and environmental data to clarify these relationships. Finally, elucidating the precise biological mechanisms through which these loci confer disease susceptibility would strengthen the rationale for genetic screening. Such mechanistic insights could facilitate the identification of clinically accessible biomarkers and reveal novel targets for therapeutic intervention.

Conclusions

The results of the present meta-analysis support a potential link between the GJD2 rs3743123, ZC3H11B polymorphisms, and an overall decrease in HM risk. Further large-scale studies with larger sample sizes, population stratification, environment factors, and mechanism research are needed to reliably clarify the association between HM susceptibility and these 4 genes' polymorphisms.

Statement of Ethics

A statement of ethics and a consent to participate are not applicable because this study is based exclusively on published reports.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Data Availability Statement

Further inquiries can be directed to the corresponding author Qianqian Yu at yuqianqianyk@163.com.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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