·Meta-Analysis·

Association of COL1A1 polymorphism with high myopia: a Meta-analysis

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Abstract

• AIM: To investigate the association between collagen type I alpha 1 (COL1A1) gene and high myopia.

• METHODS: In this Meta-analysis, we examined 5 published case-control studies that involved 1942 high myopia cases and 2929 healthy controls to assess the association between the COL1A1 rs2075555 polymorphism and high myopia risk. We calculated the pooled odds ratios (ORs) of COL1A1 rs2075555 polymorphism in high myopia cases *vs* healthy controls to evaluate the strength of the association.

• RESULTS: Overall, there was no significant difference both in the genotype and allele distributions of COL1A1 rs2075555 polymorphism between high myopia cases and healthy controls: CC *vs* AA OR=1.10, 95% confidence interval (CI)=0.76-1.58; AC *vs* AA OR=0.98, 95%CI 0.80-1.20; CC/AC *vs* AA/OR=1.01, 95%CI 0.84-1.22; CC *vs* AC/AA OR=1.06, 95%CI=0.93-1.20; C *vs* A OR=1.06, 95%CI 0.91-1.23). In addition, in the stratified analyses by ethnicity, no significant associations were found in any genetic model both in European and Asia cohorts.

• CONCLUSION: Our results indicate that the COL1A1 rs2075555 polymorphism may not affect susceptibility to high myopia.

• **KEYWORDS:** collagen type I alpha 1; polymorphism; high myopia; Meta-analysis

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INTRODUCTION

Myopia is a common eye disorder that has been widely studied in recent years [1-3], particularly because of its increasing prevalence across populations worldwide [4]. According to epidemiological evidence, the incidence of myopia is increasing, especially in East Asia [3,5-6]. Previous studies have indicated that the greatest contributor to myopic refraction is the axial length [7], and when the elongation of the eyeball is excessive, high myopia occurs. High myopia is an extreme form of myopia that is characterized by a spherical equivalent of less than -6.00 diopters or an axial length greater than 26 mm. Many serious complications are associated with high myopia, including retinal detachment, glaucoma, cataracts, macular degeneration, and scleral staphyloma [8]. High myopia is one of the major causes of blindness in many countries and is an important public health problem worldwide[9].

Unfortunately, the pathogenesis of high myopia remains unclear. Although environmental factors such as near work, higher educational levels, and poor economic development levels have been implicated in the occurrence of high myopia [10-11], they cannot explain all cases. However, many studies suggest that genetic factors may be responsible for high myopia [12-14]. Recent reports have demonstrated that interactions of multiple genetic and environmental factors may contribute to the development of high myopia [15-16], and several genes have been confirmed to have an association with susceptibility to high myopia [12,14,17-19]. However, other studies have not been able to replicate the original findings for these genes [20-22]. In particular, the collagen type I alpha 1 (COL1A1) gene has been studied.

The COL1A1 gene is located on chromosome 17 (17q21.23), which contains the myopia 5 (MYP517q21-22) locus [23]. This gene encodes the major component (pro-α1 chains) of type I collagen. Mutations or single nucleotide polymorphisms (SNPs) of the COL1A1 gene may affect the

formation of COL1A1 products by altering COL1A1 gene expression, which as a result contributes to the susceptibility to collagen-related diseases such as osteoporosis, osteogenesis imperfecta, Ehlers-Danlos syndrome, and Marfan syndrome, as well as scleral thinning [24]. The COL1A1 gene also reportedly plays an important role in the development of animal myopia [25-26]. Recently, several studies performed in different regions investigated a genetic mutation in the COL1A1 sequence [rs2075555 (*homosapiens*), adenine to cytosine, A>C], as a candidate biomarker associated with high myopia [19,21,27-29]. However, the conclusions of these previous studies remain controversial and conflicting. To further investigate the role of COL1A1 rs2075555 polymorphism in high myopia, we performed a Meta- analysis involving all the relevant published studies available.

MATERIALS AND METHODS

Literature Search Strategy Potential articles were identified by a systematic search on the ISI Web of Science, PubMed, EMBASE, Wiley Online Library, and Science Direct databases up to December 15, 2013, using a combination of search terms: "collagen type I alpha 1" OR "COL1A1", "polymorphism" OR "variation" OR "mutation" AND "myopia" without language or publication date restrictions. All relevant publications and their reference were manually screened to identify eligible studies.

Selection Criteria Papers identified during the literature search had to meet the following inclusion criteria in order to be included in our study: 1) case-control or cohort design studies of humans; 2) evaluation of the association of COL1A1 rs2075555 polymorphism with high myopia; 3) sufficient published data available for our team to estimate odds ratios (ORs) of different genotype frequencies; 4) published original full-text literature. We excluded studies based on the following criteria: 1) insufficient reported data; 2) abstracts, review papers, and case-only studies; 3) duplication of previously published literature.

Data Extraction Three investigators (Jin GM, Zhao XJ, and Chen YX) independently extracted the data. Discrepancies between different investigators were adjudicated by another 2 investigators (Chen AM and Li Q), who reached consensus. The collected data included: name of the first author, publication date, geographical location, ethnicity, source of control, genotyping methods, genotype frequencies, matching variables, and the numbers of cases and controls.

Quality Assessment We employed the Newcastle-Ottawa scale (NOS), which has been described in detail in previous study [30] to evaluate the quality of the included studies by 2 investigators (Jin GM and Zhao XJ). A study scoring less than 3 stars was categorized as "low quality", while 4 to 6 stars and 7 to 9 stars were categorized as "moderate quality" and "high quality", respectively [31]. Discrepancies between investigators were resolved by discussion.

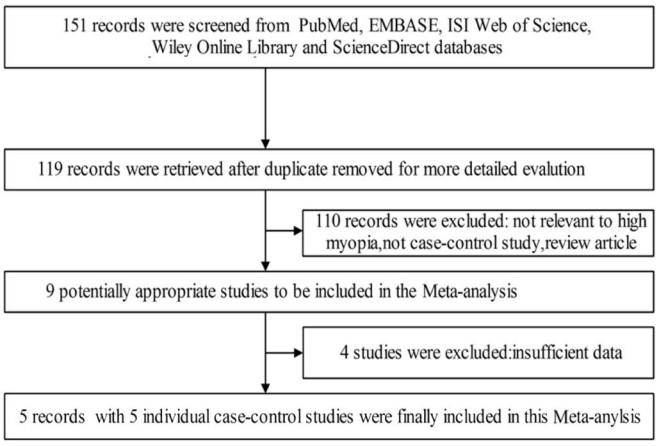

Figure 1 Flow chart for the selection of studies according to the criteria of this Meta-analysis.

Statistical Analysis The allelic frequency of COL1A1 rs2075555 was calculated, and Hardy-Weinberg equilibrium (HWE) was assessed for the control group in each included study. Pearson's χ^2 test was used, and significant disequilibrium was defined as $P<0.05$. The strength of the association between COL1A1 rs2075555 polymorphism and high myopia susceptibility was assessed by ORs with 95% confidence intervals (CIs). We used Z-test to judge the significance of the pooled ORs, and statistical significance was considered when $P<0.05$. The pooled ORs were calculated for 5 genetic models: allele model (C *vs* A); homozygote model (CC *vs* AA); heterozygote model (AC *vs* AA); dominant genetic model (AC/CC *vs* AA); and recessive genetic model (CC *vs* AC/AA). Stratified analysis in different genetic models was performed by ethnicity. Heterogeneity among included studies was evaluated by the χ^2-based Q test [32] and the I^2 index [33]; $P<0.10$ or $I^2>50\%$ were considered statistically significant. The random effects model was used to estimate the pooled ORs when obvious heterogeneity was present [34], otherwise the fixed-effects model was used [35]. The sources of the heterogeneity were identified by the Galbraith plot [36]. Sensitivity analyses that deleted 1 study at a time to reflect the effects of the individual study to the pooled ORs were used to estimate the stability of our results [37]. Publication bias of articles was assessed using Begg's funnel plots and Egger's test [38]. Significant publication bias was considered when $P<0.05$. All statistical analyses were performed with STATA 12.0 software (StataCorp LP, College Station, TX, USA).

RESULTS

Characteristics of Eligible Studies Overall, 151 published articles were retrieved by our literature search strategy. From this group we ultimately analyzed 5 case-control studies that included four Asian studies and one European study and in total involved 1942 cases and 2929 controls. Figure 1 shows the literature selection process. Genotype frequencies in the

Table 1 Main characteristics of eligible studies included in the Meta-analysis

First author	Year	Region	Ethnicity	Genotyping method	Source	Matching
Inamori Y[19]	2007	Japan	Asia	Probe method	HB	Age, sex and ethnicity
Liang CL[29]	2007	Taiwan	Asia	TaqMan	PB	Age, sex and ethnicity
Vatavuk Z[28]	2009	Croatia	European	BeadChip assay	PB	NA
Nakanishi H[21]	2009	Japan	Asia	TaqMan	PB	NA
Zhang D[27]	2011	China	Asia	SNaPshot method	HB	Age and sex

HB: Hospital-based study; PB: Population-based study; NA: Not available.

Table 2 Distribution of COL1A1 rs2075555 genotypes among high myopia cases and controls included in the Meta-analysis

First author	No.		Case			Control			*P* for HWE
	Case	Control	AA	AC	CC	AA	AC	CC	
Inamori Y[19]	330	330	34	166	128	52	176	98	0.07
Liang CL[29]	471	623	36	161	183	53	269	296	0.46
Vatavuk Z[28]	17	794	0	5	12	19	210	565	0.92
Nakanishi H[21]	427	420	65	194	167	72	189	158	0.23
Zhang D[27]	697	762	91	333	273	79	374	309	0.03

COL1A1: Collagen type I alpha 1; HWE: Hardy-Weinberg equilibrium.

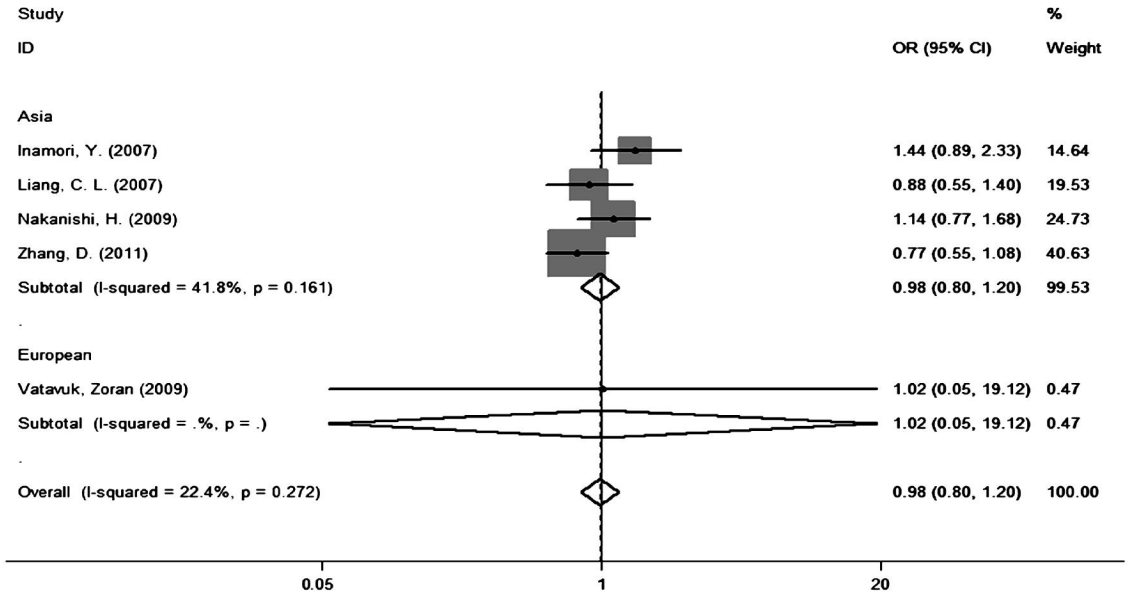

Figure 2 Forest plot of the association between COL1A1 rs2075555 polymorphism and susceptibility to high myopia in the heterozygote model (AC *vs* AA) in different ethnicities.

controls of one study showed significant deviation from the HWE, which required sensitivity analysis and evaluation of possible selection bias. As evaluated by the NOS, two studies were scored as "moderate quality" and three studies were scored as "high quality", indicating that the quality of the included articles was acceptable for the Meta-analysis. Individual characteristics of the studies, patients, and the control groups are shown in Tables 1 and 2.

Results of Meta –analysis The primary results of the Meta-analysis regarding rs2075555 polymorphism and high myopia risk are shown in Table 3. Overall, no obvious associations between rs2075555 polymorphism and high myopia susceptibility were found in any genetic models (CC *vs* AA: OR=1.10; 95%CI 0.76-1.58); (AC *vs* AA: OR=0.98, 95% CI 0.80-1.20); (CC/AC *vs* AA: OR=1.01, 95% CI 0.84-1.22); (CC *vs* AC/AA: OR=1.06, 95% CI 0.93-1.20); (C *vs* A: OR=1.06, 95% CI 0.91-1.23). In the stratified analysis by ethnicity, we found no significant associations between rs2075555 polymorphism and high myopia for any genetic models (Figure 2).

Test of Heterogeneity In our current Meta-analysis, significant heterogeneity was observed in 2 genetic models (CC *vs* AA and C *vs* A) (Table 3). The sources of the heterogeneity were assessed by the Galbraith plot of all included studies. Inamori *et al*'s [19] study was identified as the main source of heterogeneity for the association between rs2075555 polymorphism and high myopia susceptibility both in the CC *vs* AA and the C *vs* A models. The pooled ORs in these 2 models were not significantly influenced when this study was removed.

Table 3 Meta-analysis of COL1A1 rs2075555 polymorphism and susceptibility to high myopia

Comparisons	Population	N	Test of association				Test of heterogeneity		
			OR (95%CI)	Z	*P*	Model	χ^2	*P*	I^2 (%)
CC *vs* AA	Overall	5	1.10 (0.76-1.58)	0.49	0.62	R	10.10	0.04	60.4
(Homozygote)	Asian	4	1.10 (0.75-1.62)	0.50	0.62	R	10.08	0.11	70.3
	European	1	0.86 (0.05-15.1)	0.10	0.92	R	-	-	-
AC *vs* AA	Overall	5	0.98 (0.80-1.20)	0.16	0.87	F	5.15	0.27	22.4
(Heterozygote)	Asian	4	0.98 (0.80-1.20)	0.17	0.87	F	5.15	0.16	41.8
	European	1	1.02 (0.05-19.1)	0.01	0.99	F	-	-	-
CC /AC *vs* AA	Overall	5	1.01 (0.84-1.22)	0.12	0.90	F	7.76	0.10	48.4
(Dominant)	Asian	4	1.01 (0.84-1.23)	0.13	0.90	F	7.75	0.05	61.3
	European	1	0.88 (0.05-15.2)	0.09	0.93	F	-	-	-
CC *vs* AC/AA	Overall	5	1.06 (0.93-1.20)	0.86	0.39	F	5.55	0.24	27.9
(Dominant)	Asian	4	1.06 (0.93-1.20)	0.88	0.38	F	5.52	0.14	45.7
	European	1	0.97 (0.34-2.80)	0.05	0.96	F	-	-	-
C *vs* A	Overall	5	1.06 (0.91-1.23)	0.73	0.47	R	8.62	0.07	53.6
(Allele)	Asian	4	1.06 (0.90-1.24)	0.69	0.49	R	8.61	0.04	65.2
	European	1	1.07 (0.41-2.80)	0.14	0.89	R	-	-	-

COL1A1: Collagen type I alpha 1; OR: Odds ratio; R: Random-effect model; F: Fixed-effect model.

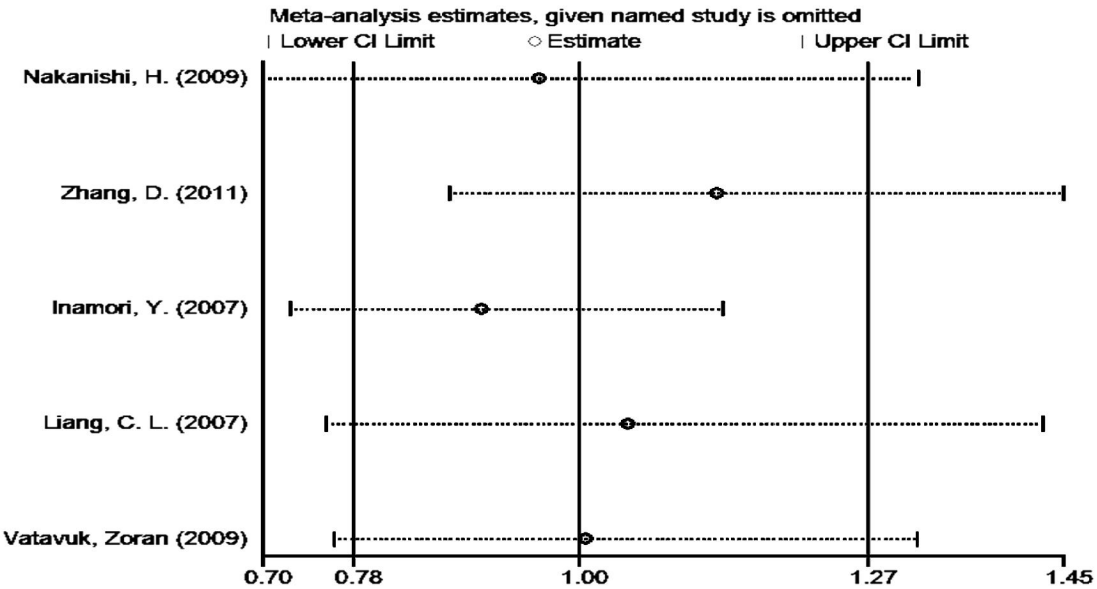

Figure 3 Sensitivity analysis performed to evaluate the influence of a single study on the pooled ORs in the heterozygote model (AC *vs* AA).

Sensitivity Analysis A single study included in the current Meta-analysis was excluded at the time of sensitivity analysis. Similar results were revealed, and pooled ORs were not obviously altered in any of the genetic models (Figure 3) shows the sensitivity analysis results in the CA *vs* AA model), suggesting the reliability and stability of our results.

Publication Bias Publication bias was evaluated using Begg's funnel plot and Egger's test. As Figure 4 shows, the funnel plot shape for the heterozygote model (CA *vs* AA) seems approximately symmetrical, which suggests that publication bias in this study can be neglected. In addition, Egger's test provides further statistical evidence of the funnel plots' symmetry (P=0.712). Overall, neither Begg's funnel plot nor Egger's test suggested any statistically significant publication bias in any genetic model. These results indicate that there is no evidence of publication bias in our Meta-analysis.

DISCUSSION

Although the association between COL1A1 rs2075555 polymorphism and high myopia has been reported many times in several geographic locations, the results generally were conflicting rather than consistent [18,20,27-29]. Different genetic backgrounds, sources of controls, and study designs may be responsible for these inconsistencies among different studies. An individual study with a small sample size may be underpowered to evaluate the relationship between gene mutation and high myopia, but pooling all eligible data by Meta-analysis can possibly provide more powerful and

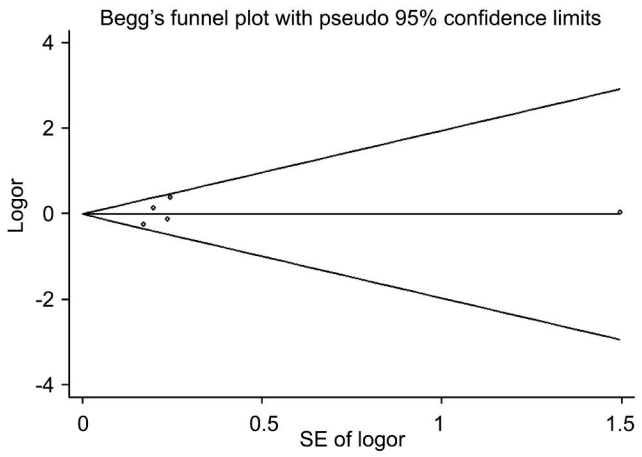

Figure 4 Begg´s funnel plot of COL1A1 rs2075555 polymorphism and high myopia susceptibility in the heterozygote model (AC *vs* AA).

credible evidence. The current Meta-analysis evaluating the possible effect of the COL1A1 rs2075555 polymorphism on high myopia susceptibility was based on a substantial amount of data from 5 individual case-control studies that included a total of 1942 high myopia cases and 2929 controls. Unfortunately, no valid association between COL1A1 rs2075555 polymorphism and high myopia was detected according to the pooled ORs in the different genetic contrast models. Population stratification is a factor that can lead to false evidence about the association between gene markers and high myopia. Previous studies have demonstrated that the prevalence of myopia varies according to ethnicity[39] and is much higher in the Asian population [40-41], especially in China[42]. Because of this, stratified analysis by ethnicity was performed but did not reveal a significant relation between the COL1A1 rs2075555 polymorphism and high myopia in either the Asian or European populations. The results of this study suggest that ethnicity is not a factor that influences the relationship between COL1A1 rs2075555 polymorphism and high myopia susceptibility.

A previous Meta-analysis performed by Nakanishi *et al*[21] showed a limited significance between COL1A1 rs2075555 polymorphism and high myopia susceptibility (OR=1.19; 95% CI 1.03-1.38, P <0.05) which is a result that is inconsistent with our findings. However, in their Meta-analysis, Nakanishi *et al* [21] combined data of their own with data from a previously published Japanese study that was the first reported positive association. As we know, the reported ORs in the first positive studies are usually higher than ORs reported in subsequent replication studies[43], so there was a possible correlation between COL1A1 rs2075555 polymorphism and high myopia susceptibility[19]. In addition, it is possible that publication bias affected the results in the first positive study, and the actual OR of the SNP was overestimated in their analysis, which included only 2 studies. Lastly, both of the studies included in their Meta-analysis were conducted in Japanese patients, and the sample size was too small to provide a powerful and precise estimate for COL1A1 rs2075555 polymorphism and high myopia risk. In contrast, our current Meta-analysis combined all the eligible published studies we could identify and used enhanced statistical methods to provide more reliable evidence that COL1A1 rs2075555 polymorphism does not contribute to high myopia susceptibility, even when different ethnicities are taken into consideration.

Several potential limitations of our Meta-analysis should be considered. Firstly, although a statistically significant publication bias was not found in all the genetic models, publication bias could still have occurred among the published articles meeting the inclusion criteria. Secondly, a lack of sufficient raw data such as age distribution and the sex of the patients included in the identified articles limited further exploration of potential interactions, and more precise and convincing analysis should be performed. Thirdly, all of the studies included in our study were conducted in Asians and Europeans cohorts, and, thus, conclusions from our Meta-analysis may be restricted to these two populations. However, some advantages of the current Meta-analysis can be highlighted. Firstly, based on the strict criteria of inclusion and exclusion, all the included studies were of acceptable quality, which significantly enhances the statistical power of our Meta-analysis. Secondly, we attempted to obtain adjusted estimates in different populations by performing a subgroup analysis between different ethnicities. Thirdly, no evidence of obvious publication bias was detected for any of the genetic models, which suggests that our results are unbiased and statistically reliable.

In summary, our Meta-analysis suggests that the COL1A1 rs2075555 polymorphism is not a risk factor for susceptibility to high myopia. Nevertheless, high myopia is a complex multifactorial eye disease that is influenced by both genetic and environmental factors as well as their interactions. Unfortunately, due to a lack of sufficient raw data from the included studies, interactions such as gene-gene, SNP-SNP, and gene-environment could not be evaluated. Further related research with larger sample sizes and enhanced designs are needed.

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