·Meta-Analysis·

Genetic association of *COL1A1* polymorphisms with high myopia in Asian population: a Meta-analysis

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Abstract

• **AIM: To comprehensively evaluate the potential association of *COL1A1* polymorphisms with high myopia by a systematic review and Meta-analysis.**

• **METHODS: All association studies on *COL1A1* and high myopia reported up to June 10, 2014 in PubMed, Embase, Web of Science, and the Chinese Biomedical Database were retrieved. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were analyzed for single-nucleotide polymorphisms (SNPs) using fixed- and random-effects models according to between-study heterogeneity. Publication bias analyses were conducted by Egger´s test.**

• **RESULTS: A total of four studies from reported papers were included in this analysis. The Meta-analyses for *COL1A1* rs2075555, composed of 2304 high myopia patients and 2272 controls, failed to detect any significant association with high myopia. A total of 971 cases and 649 controls were tested for *COL1A1* rs2269336. The association of *COL1A1* rs2269336 with high myopia was observed in recessive model (CC *vs* CG+GG, *P* =0.03) and in heterozygous model (CG *vs* GG, *P* =0.04), but not in other models.**

• **CONCLUSION: This Meta-analysis shows that *COL1A1* rs2269336 (CC *vs* CG +GG) affects individual susceptibility to high myopia, whereas there is no association detected between SNPs rs2075555 and high myopia. Given the limited sample size, further investigations including more ethnic groups are required to validate the association.**

• **KEYWORDS:** *COL1A1*; high myopia; association; Meta-analysis
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INTRODUCTION

Myopia is the leading cause of visual impairment affecting about 500 million people worldwide. High myopia typically has a refractive error of 6.0 diopters (D) or worse, and it is complicated with an increased risk of pathological ocular disorders, such as cataract, glaucoma, chorioretinal degeneration, or retinal detachment [1-3]. The prevalence of high myopia is 2.8% to 9.1% in specific to the age and sex of the individual ethnic population [4-5]. It is significantly higher in younger Asians (70%) than in European descents (30%)[4,6].

High myopia is a multifactorial disease caused by environmental and genetic factors. Environmental factors such as near and prolonged reading could lead to the progression of myopia[7]. The twins and family-based genetic studies have shown that high myopia has high heritability[8-9]. To date, more than 20 known chromosomal loci and 25

candidate genes of high myopia have been reported, including *MYP1*- 2115q12-13, 21q22.3, 12q24, 4q21, 9q34.11 and 2q37 [10-12]. In the past five years, genome-wide association studies (GWAS) on high myopia have provided a very powerful tool to detect several susceptibility genes in myopia patients[13-19]. Many studies have shown that the collagen type I (*COL1A1*) gene plays an major role in the development of experimental myopia [20-23]. The *COL1A1* gene lies on 17q21 where the *MYP5* locus was identified [24]. The dysfunction of the *COL1A1* gene has been reported to be associated with disorders such as Ehlers-Danlos syndrome, systemic diseases with scleral thinning, and myopia [25-27]. SNPs in the *COL1A1* gene showed significant genetic association with high myopia in a Japanese group [28]. However, other reported studies on the association between SNPs in the *COL1A1* gene and high myopia risk in Chinese, Caucasian, even in Japanese population are inconclusive [29-32]. The association of the *COL1A1* gene with high myopia therefore is inconsistent and conflicting.

Most reported causing genes of high myopia are heterogeneous in different study groups. Such heterogeneity could be caused by different sample sizes and diversities in multiple ethnic cohorts. Meta-analysis, which combined all studies with the same criteria, could be helpful to comprehensively explain the association of the *COL1A1* gene with high myopia and provide some new clues for the research on high myopia. Therefore, in this study we conducted a systematic review and Meta-analysis of all association studies on *COL1A1* and myopia to determine the effects of *COL1A1* polymorphisms on high myopia.

MATERIALS AND METHODS

Searching Strategy A systematic literature search by the databases including PubMed, Embase, Web of Science, and the Chinese Biomedical Database were carried out to retrive all published articles on the association of *COL1A1* polymorphisms with myopia from their starting date to June 10, 2014. The keywords including "myopia", "myopic", "nearsighted", "near sight", "refractive error", "collagen type I", "COL1A1", "rs2075555", "rs2269336", "polymorphism (s)", "variant (s)", and "mutation (s)" were used for analysis. Reference lists of the identified studies and reviews were manually checked for additional articles, to confirm the studies not yet included in the electronic searches.

Inclusion and Exclusion Criteria The included articles were considered if they 1) analyzed the associations between *COL1A1* SNPs and high myopia; 2) compared high myopia cases and normal controls in defined populations; 3) gave an OR with 95% confidence interval (95% CI) or other available; and 4) were original research articles, not reviews or comments. Excluded articles were abstracts from conferences, full texts with no available data for retrieval and republished, duplicate studies.

Data Extraction Information were extracted from all included studies into data collection forms by two authors (Gong B and Shuai P) independently. Assessment of these studies were conducted by two authors (Gong B and Qu C) who were blinded to the article information such as the title, author and so on. Disagreements were resolved through discussion until a consensus was achieved. Otherwise, a third investigator was consulted to resolve the dispute. The following items were extracted from each study: first author's surname, year of publication, statistical data, ethnicity for subjects, whether the Hardy-Weinberg equilibrium (HWE) was examined in controls, genotyping method, total numbers of cases and controls, as well as total numbers of cases and controls for each *COL1A1* genotypes, respectively.

Statistical Analysis A pooled OR with 95%CI was used as index of the association of the SNPs in *COL1A1* with high myopia. For genotypic contrast, to analyze the association patterns, dominant, recessive, homozygous, and heterozygous were applied in the investigation of the disease association. Sensitivity analysis was carried out by eliminating one study at a time to see whether the results were influenced by a specific study. Heterogeneity was analyzed and measured using Cochran's Q statistic and I^2 statistic. A P value of Q-test >0.10 or $I^2<40\%$ indicated no or weak heterogeneity among studies, so the fixed-effect model was used to calculate the pooled ORs. Otherwise, if the P value for heterogeneity was $\leqslant 0.10$ or $I^2 \geqslant 40\%$, showing that there was a high degree of heterogeneity between studies, the random-effect model was used to evaluate the summary ORs. Egger liner regression test was used to evaluate the publication bias, where a value of $P<0.05$ was considered statistically significant. The HWE for each SNP polymorphism was tested by the χ^2 test. All statistical analyses were performed by the Review Manager software (RevMan, version 5.2; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen; 2012), and the STATA software (version 12.0, STATA Corp., College Station, TX, USA), as well as the Hardy Weinberg package (version 1.3) in R language (version 2.15.0, http://cran.r-project.org/). Two-sided P values <0.05 were considered statistically significant.

RESULTS

Literature Search and Characteristics A flow diagram showed the selection process of the included studies in this analysis (Figure 1). The initial strategy searched out 13 articles. Among them, three unrelated articles, and three review articles were. The full text of the remaining seven studies was retrieved and reviewed. Three articles were excluded after full-text review: one paper was excluded due to failure to extract sufficient data [33], one paper was not a case-control study [31], and one paper was experimental

Table 1 Characteristics of the eligible studies for the Meta-analysis

First author	Year	Ethnicity	SNP ID	Position (bp)[a]	Minor allele	Sample size		[b]MAF		Conclusion on high myopia association
						Cases	Controls	Cases	Controls	
Yumiko Inamori[28]	2007	Japanese	rs2075555	48274291	T	328	326	0.357	0.429	Associated
			rs2269336	48280356	C	329	330	0.397	0.464	Associated
Chung-Ling Liang[30]	2007	Chinese (Taiwan)	rs2075555	48274291	T	380	618	0.307	0.303	Non-associated
Hideo Nakanishi[29]	2009	Japanese	rs2075555	48274291	T	426	419	0.380	0.397	Non-associated
			rs2269336	48280356	C	417	418	0.438	0.458	Non-associated
Dingding Zhang[32]	2011	Chinese	rs2075555	48274291	T	697	762	0.370	0.350	Non-associated
			rs2269336	48280356	C	697	762	0.410	0.420	Non-associated

[a] Genomic positions are according to NCBI build 36; [b]MAF: Minor allele frequency.

Table 2 The association between *COL1A1* rs2075555 and high myopia in different genetic model

Models tested	Pooled OR(95%CI)		*P*		Heterogeneity			Egger's test *P*>|*t*|
	FEM	REM	FEM	REM	*Q*	*P*	I^2 (%)	
C *vs* A	0.98 (0.89-1.09)	0.98 (0.89-1.09)	0.75	0.75	1.75	0.42	0	0.20
CC *vs* AA	0.96 (0.76-1.20)	0.97 (0.74-1.28)	0.71	0.83	2.92	0.23	31.6	0.40
CA *vs* AA	0.94 (0.78-1.13)	0.94 (0.77-1.14)	0.49	0.53	2.26	0.32	11.6	0.88
CC+CA *vs* AA	0.95 (0.80-1.13)	0.95 (0.77-1.18)	0.57	0.64	2.81	0.25	28.8	0.93
CC *vs* CA+AA	1.00 (0.86-1.17)	1.00 (0.86-1.17)	0.99	0.98	0.72	0.70	0	0.33

FEM: Fixed effect model; REM: Random effect model.

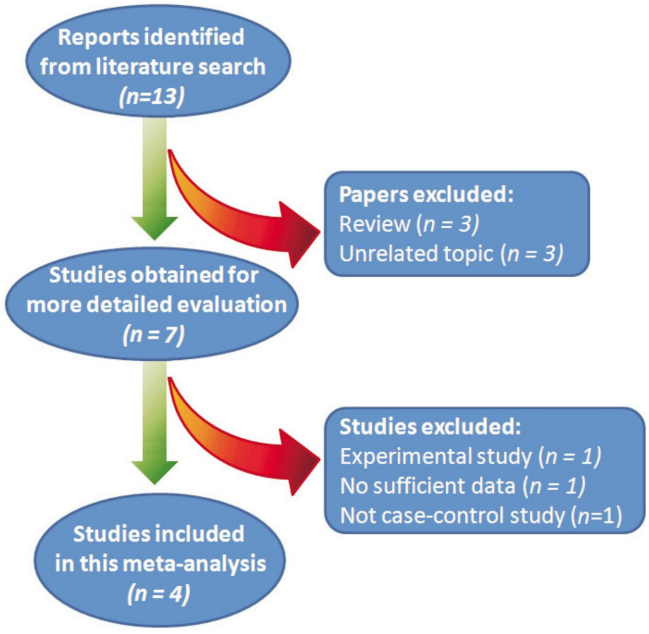

Figure 1 Flow diagram of article search for this Meta-analysis.

study [34]. Finally, four articles were identified to meet the inclusion criteria, thus were included for the Meta-analysis. All the studies were case-control studies. The analyzed SNPs were successfully genotyped and were within HWE in each included studies. In all the four articles, high myopia was defined as an axial length of 26 mm or longer and a refractive error of -6 D or worse. The characteristics of these articles are listed in Table 1.

Meta-analysis Results Four eligible studies provided results of the association of rs2075555 with high myopia, whereas in the study of Inamori *et al*[28], only patients with extreme myopia (refractive error of -9.25 D or less) was investigated. Therefore, a total of 4576 subjects (2304 high myopia patients and 2272 controls) from three studies (cases were defined as a refractive error of -6 D or less) were tested for rs2075555 in this study. Fixed-effects analyses did not show any significant association between high myopia and the SNP in all five genetic models and no significant heterogeneity among studies was detected (recessive model: CC *vs* CA+AA, OR=1.00, 95% CI 0.86 to 1.17, P=0.99, P_Q=0.70, I^2=0; dominant model: CC+CA *vs* AA, OR=0.95, 95% CI 0.80 to 1.13, P=0.57; P_Q=0.25; I^2=28.8%; heterozygous model: CA *vs* AA, OR=0.94, 95% CI 0.78 to 1.13, P=0.49; P_Q=0.32; I^2=11.6%; homozygous model: CC *vs* AA, OR=0.96, 95% CI 0.76 to 1.20, P=0.71; P_Q=0.23; I^2=31.6% and allelic model: C *vs* A, OR=0.98, 95% CI 0.89 to 1.09, P=0.75, P_Q=0.42; I^2=0, Table 2 and Figure 2). Figure 2 shows the forest plot of the allelic association.

A total of 971 cases and 649 controls from two studies were tested for *COL1A1* rs2269336. The recessive model (CC *vs* CG + GG) showed a significant association with high myopia (OR=1.21; 95% CI, 1.02 to 1.45; P=0.03; P_Q=0.90; I^2=0; Table 3 and Figure 3E). The heterozygous model (CG *vs* GG) also showed a modest association with high myopia (P=0.04, closed to 0.05) in a fixed-effects model, whereas the random-effects analyses did not show any association between high myopia and the SNP in this model (OR=0.80; 95% CI 0.61 to 1.04; P=0.09; Table 3). The analyses in the other three modes showed no statistical association with high myopia (Table 3 and Figure 3).

Table 3 The association between *COL1A1* rs2269336 and high myopia in different genetic model

Models tested	Pooled OR(95%CI)		*P*		Heterogeneity		
	FEM	REM	FEM	REM	*Q*	P_Q	I^2, %
C *vs* G	1.05 (0.93-1.18)	1.05 (0.93-1.18)	0.41	0.41	0.19	0.66	0
CC *vs* GG	1.02 (0.80-1.29)	1.02 (0.80-1.29)	0.87	0.87	0.56	0.46	0
CG *vs* GG	0.79 (0.63-0.99)	0.80 (0.61-1.04)	0.04	0.09	1.37	0.24	27.1
CC+CG *vs* GG	0.88 (0.71-1.09)	0.88 (0.70-1.11)	0.23	0.28	1.16	0.28	13.9
CC *vs* CG+GG	1.21 (1.02-1.45)	1.21 (1.02-1.45)	0.03	0.03	0.01	0.90	0

FEM: Fixed effect model; REM: Random effect model.

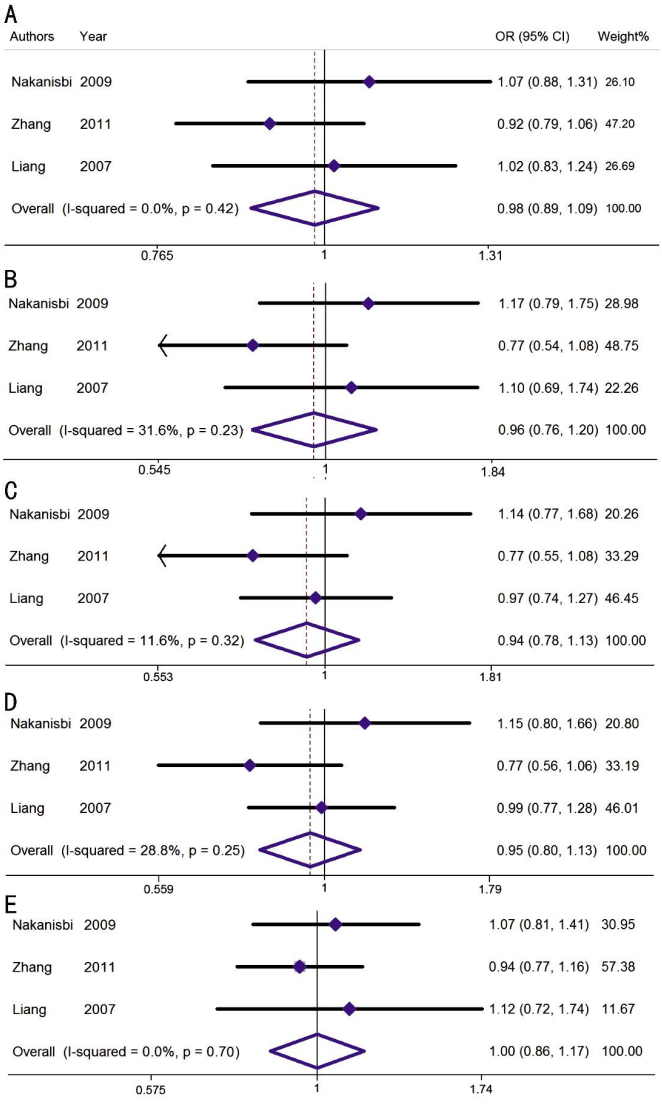

Figure 2 Forest plots of estimates of odds ratios of the association of *COL1A1* rs2075555 with high myopia A: Allelic model (C *vs* A); B: Homozygous model (CC *vs* AA); C; Heterozygous model (CA *vs* AA); D: Recessive model (CC+CA *vs* AA); E: Dominant model (CC *vs* CA+AA).

Two studies tested the association of *COL1A1* rs2075555 and rs2269336 with extreme myopia (axial length of 28 mm or higher and/or a refractive error of -9.25 D or less) in a total of 605 cases and 1092 controls [28,32]. The heterogeneity for the two studies was extremely high among five genetic models, in which I^2 were all more than 70%, so we did not conduct the Meta-analysis further (data not shown).

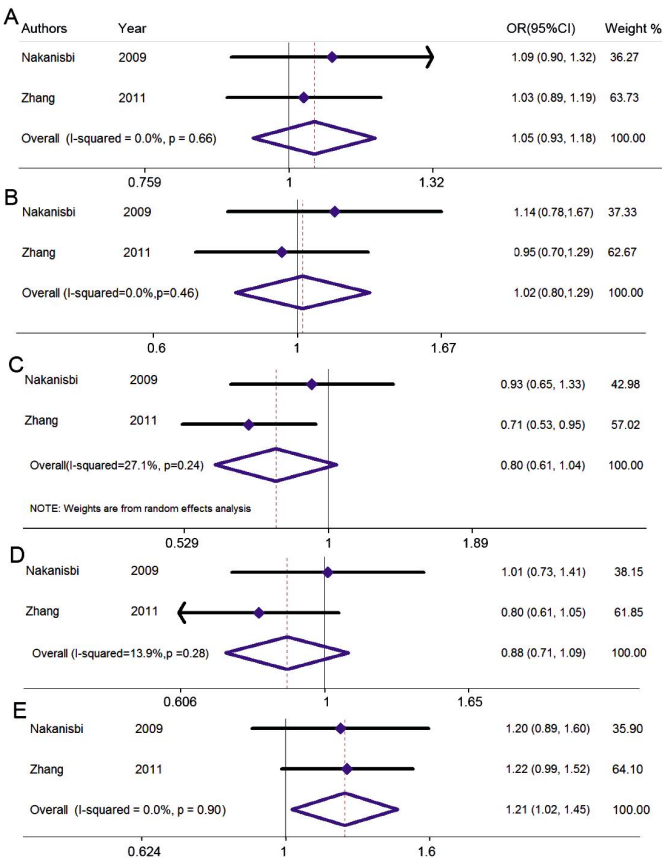

Figure 3 Forest plots of estimates of odds ratios of the association of *COL1A1* rs2269336 with high myopia A: Allelic model (C *vs* G); B: Homozygous model (CC *vs* GG); C: Heterozygous model (CG *vs* GG); D: Recessive model (CC+CG *vs* GG); E: Dominant model (CC *vs* CG+GG).

Publication Bias and Sensitivity Analysis Publication biases were evaluated by the Egger's test quantitatively. Egger's test for *COL1A1* rs2075555 reported from three studies did not detect any significiant evidence of publication bias in the overall analyses under all genetic models (Table 2). However, for *COL1A1* rs2269336, only two studies could be included in our research, we did not evaluate the publication bias for this SNP. We also assessed the effect of each study on the pooled OR when sequential omission of all the studies and found that the exclusion of any single study did not alter the significance of the final pooled OR.

DISCUSSION

Meta-analysis could provide a quantitative method to estimate and explain their diversity by pooling the data on the

same topic. By Meta-analysis of four published case-control studies, we distinguished the truth from the false and explored a more robust estimate of the effects of these polymorphisms on high myopia. The *COL1A1* polymorphisms have been reported to be a potential genetic risk factor for high myopia; however, conflicting results were revealed by several other studies. In this study, our Meta-analysis showed that there was a suggestive association between *COL1A1* rs2269336 and high myopia in recessive model but not in other models, suggesting that *COL1A1* rs2269336 may affect individual susceptibility to high myopia.

High myopia is a common, complex and multifactorial disease with obvious heritable trait. Identifying causative genes helps to understand the disease development and may help for prevention. More advances have been made in human myopia genetics, however, there is still much remaining unknown. To date, the importance of the genetic variation in high myopia has been well identified in twin, family and population studies, and more than 20 loci have been establised. Nonetheless, the responsible genes have not yet been identified. High myopia development is usually complicated with marked scleral thinning, scleral architecture alteration, and ocular axial elongating [35]. There was scleral collagen changese involved in the development of myopia[36-37]. The sclera component is composed of approximately 85% to 90% collagen, in which COL1A1 protein is the most prevalent[38].

The *COL1A1* gene has been reported to play a major role in the pathogenesis of experimental myopia [20-23] and mutations in this gene have been shown to be associated with myopia. Genetic polymorphisms in *COL1A1* showed significantly statistical association with high myopia in previous study[28], however, conflicting results were reported in several other studies[29-30]. Inamori *et al*[28] analyzed 10 SNPs in a Japanese group composed of 330 subjects with high myopia and 330 controls. This study found that the two SNPs were statistically associated with high myopia. However, a separate case-control study did not show significant association with the SNPs of the *COL1A1* gene and high myopia in a Taiwanese population [30]. Another study, which was composed of 427 high myopia cases and 420 controls, genotyped 8 tag SNPs of *COL1A1* [29]. This study showed that there was no significant association between *COL1A1* polymorphisms and high myopia in this Japanese group. Finally, in our previous study, we analyzed rs2075555 and rs2269336 SNP in the *COL1A1* gene in a Han Chinese population including 697 high myopia patients (276 cases of -9.25 D or less) and 762 controls. This study showed no significant association of the two SNPs with high myopia (P>0.05)[32]. Therefore, there was no obvious evidence that the association of *COL1A1* SNPs was significant in high myopia, probably because of small size samples and different ethnicities. Under this Meta-analysis, the association of *COL1A1* rs2075555 (a total of 2304 high myopia patients and 2272 controls) and rs2269336 (a total of 971 cases and 649 controls) was analyzed in Asian population. Our results did not detect any significant association of high myopia with *COL1A1* rs2075555, whereas *COL1A1* rs2269336 was detected to be associated with high myopia (P=0.03) in the recessive model (CC *vs* CG+GG). Therefore, our analyses could not conclude whether *COL1A1* rs2075555 is really a myopia-associated SNP and more replication data for *COL1A1* rs2269336 is needed to validate the association. Other factors including environment and different lifestyle, might play an important roles in these differences of association as well. Further analysis should be envaluated with more large-scale cohorts and case-control populations to confirm the association of *COL1A1* with high myopia. More studies with gene-environment interaction should also be further considered in the future.

This systematic review and Meta-analysis has sufficient power to anaylze all of the published genetics studies on *COL1A1* polymorphisms; however, we still should consider some potential limitations in the present study: 1) some relevant studies were excluded due to standard and stringent strategy for study inclusion, resulting in a small sample size that limited the statistical power of this analysis. The severity of myopia (refractive error -9.25 D or less) caused bias from non-differential misclassification[28] and different allele for the SNP was detected [33], therefore, the two studies were excluded in this Meta-analysis. 2) This Meta-analysis was analyzed with small number of studies and all the data were mainly based on the Asian populations due to publication limitation. For *COL1A1* rs2269336, only two articles reported its relationship with myopia, with one in Japanese population and one in Chinese population. Genetic mutation may differ between different ethnic groups and even different locations within the same ethnic group; therefore, it is difficult to explore whether this SNP is really associated with high myopia after combination of the two relevant studies. This limitation may affect the conclusions within Asian population and indicate the need for more studies in other ethnic group. 3) There was a high heterogeneity detected in the subgroup analysis for extreme myopia. It was possible that only two studies were included with small sample sizes and different clinical characteristics of patients. Other difficulties may be caused by the various definitions of the control groups. 4) High myopia is a multifactorial disease with complicated interactions between different genetic and other factors. Recently, the prevalence of high myopia has raised dramatically in the younger generation in east Asia;

however, the age and year of birth of included cohorts were not analyzed in this study. Therefore, confounding factors, such as age, sex, environment, and lifestyle, may influence our results. If the researchon gene-environment interactions across different ethnic subgroups could be carried out, we might get more conclusions about genetic association of *COL1A1* polymorphisms with myopia.

In conclusion, this Meta-analysis showed that *COL1A1* rs2269336 is associated with high myopia under recessive model but not in other models, suggesting that it may affect individual development of high myopia. Further investigations are needed to confirm the association and determine the roles of *COL1A1* in high myopia with larger sample sizes and more ethnic populations.

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