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Original Article

Association between *COL1A1* polymorphisms and high myopia: a meta-analysis

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Abstract: Background: Previous studies of the association between COL1A1 polymorphisms and high myopia risk have yielded conflicting results. To help resolve the discrepancies, we performed a meta-analysis to estimate the relationship between *COL1A1* polymorphisms and high myopia risk. Methods: We searched for case-control and cohort studies in MEDLINE, EMBASE, and OVID. Odds ratios (OR) with 95% confidence intervals (CI) were derived for single-nucleotide polymorphisms (SNPs). We also analyzed heterogeneity and publication bias. Results: This meta-analysis was based on five studies of rs2075555 (1,944 high myopia cases and 3,060 controls), and three studies of rs2269336 (1,454 high myopia cases and 1,512 controls). The combined results showed an association between rs2075555 and high myopia in the dominant (OR = 0.86, 95% CI = 0.71-0.99) and homozygote models (OR = 0.79, 95% CI = 0.64-0.97). In the recessive model for rs2269336, OR was 1.26 (95% CI = 1.05-1.50); in the heterozygote model, OR was 0.81 (95% CI = 0.69-0.96). Begg's and Egger's tests for rs2075555 showed no evidence of publication bias. Conclusions: This meta-analysis suggests *COL1A1* rs2075555 is a potential low risk factor for high myopia.

Keywords: COL1A1, polymorphisms, high myopia, meta-analysis

Introduction

Myopia is caused by lengthening of the ocular axis and focusing of light rays on the front of the retina; people with this condition can see close objects more clearly than distant ones [1]. It is a major global cause of visual impairment, has adverse social, educational, and economic consequences, and affects quality of life [2]. Epidemiological evidence suggests the prevalence of myopia has increased 28.1% and 19.4% in white and black populations [3, 4], whereas in Asians, the incidence has increased from 40% to 80% [5] and is still growing. As an extreme form of myopia, high myopia is usually defined as a refractive error of at least -6.00 diopter (D) or an axial eye length greater than 26 mm. This serious form of myopia is now considered the fourth most common cause of irreversible blindness [6]. Individuals with high myopia are predisposed to many pathologic ocular abnormalities such as cataracts, retinal detachment, glaucoma, chorioretinal degeneration, myopic foveoschisis, or choroidal neovascularization [7, 8], which may also lead to irreversible vision impairment or blindness. Epidemiological, experimental, and clinical studies provide convincing evidence that environmental and genetic factors each play a role in the occurrence of myopia. Less outdoor activity and more near-work activity are known risk factors for myopia [9]. High heritability in family-based and twin studies supports the theory that genetic factors are also responsible for high myopia [10-12]. Whole genome linkage analysis and genome-wide association studies have mapped more than 20 known chromosomal loci. [7, 13, 14] and candidate genes associated with high myopia have been reported, including collagen type I (*COL1A1*).

Published studies of the association between *COL1A1* and high myopia risk are inconclusive, and no meta-analyses have been conducted in this area. We performed a meta-analysis by using strict criteria to include or exclude poten-

tially relevant studies in order to examine the association between *COL1A1* variants and high myopia risk.

Methods

We performed a systematic review of the published literature. The study was performed according to the MOOSE guidelines and the PRISMA statement [15, 16] for meta-analysis of observational studies.

Search strategy

We performed systematic literature searches of MEDLINE (1966 to June 1, 2014), EMBASE (1980 to June 1, 2014), and OVID (1950 to June 1, 2014) with no language limitation and using medical subject headings (MeSH) or free text, with the following terms and keywords: "COL1A1", "polymorphism (s)", "variant (s)", "mutation (s)", and outcomes ("myopia", "refraction", "refraction error", "refractive error"). We also checked the reference lists of all relevant publications for other potentially relevant studies.

Selection criteria

Studies were included in the meta-analysis if they met the following criteria: (1) original case-control or cohort studies evaluating at least one *COL1A1* polymorphism and high myopia risk, and (2) providing sufficient data on each genotype and/or allele in both case and control groups. When the same patient population was included in several publications, we enrolled the most recent or complete study in our meta-analysis. Reviewers independently evaluated published quantitative estimates of the association between *COL1A1* and high myopia for inclusion in the meta-analysis. Studies that did not meet the above inclusion criteria were excluded during initial review. Any disagreement in extracted data was resolved by discussion.

Data extraction

The reviewers independently extracted essential data using a standardized data collection form. Discrepancies in data interpretation were resolved by arbitration. The following data were extracted from each study: first author, publication year, country, participant ethnicity, gender, age, study size, specific *COL1A1* SNPs, genotyping method, extent of refractive degree and axial length for cases and controls, and number of eligible and genotyped cases and controls.

Statistical analyses

We evaluated the Hardy-Weinberg equilibrium (HWE) of genetic frequency distributions for the controls by using the χ^2 test, with $P < 0.05$ regarded as evidence of unequal genetic distributions. As for individual studies or non-HWE studies, we performed a none-way sensitivity analysis by sequential omission to test the robustness of the association. "A" was used to denote a major allele, and "a" to denote a minor allele. We selected the dominant model (aa + Aa vs. AA), recessive model (aa vs. AA + Aa), homozygote comparison model (aa vs. AA), and heterozygote comparison model (Aa vs. AA) to dissect the association patterns. The odds ratios (ORs) and 95% confidence intervals (95% CIs) were used as the common measure across studies in fixed-effect (using the Mantel-Haenszel method) and random-effects models (using the DerSimonian and Larid method) [17]. The model was chosen according to the heterogeneity assumption by the Q test; $P > 0.10$ indicated a lack of heterogeneity. If $P < 0.10$, heterogeneity was considered significant and the random-effects model was used to calculate the pooled OR; otherwise, the fixed-effects model was employed. Cochran I^2 statistics quantifying the proportion of total variation attributable to between-study heterogeneity were also calculated [18]. I^2 represents the percentage of total variation across studies which were attributable to heterogeneity rather than chance. As suggested by Higgins et al., I^2 values of 25%, 50%, and 75% were considered as low, moderate, and high heterogeneity, respectively [19]. We generated a funnel plot of the overall OR, produced a standard error (ER) to detect publication bias, and used Egger's and Begg's regression tests. We conducted stratified analyses to identify associations between *COL1A1* and high myopia, and relevant study characteristics such as ethnicity were analyzed. All analyses described above were conducted using Stata 12 (StataCorp, College Station, TX). Statistical significance was defined as a *P*-value < 0.05.

Results

Five studies met the inclusion criteria [20-24], and our meta-analysis included 1,944 cases

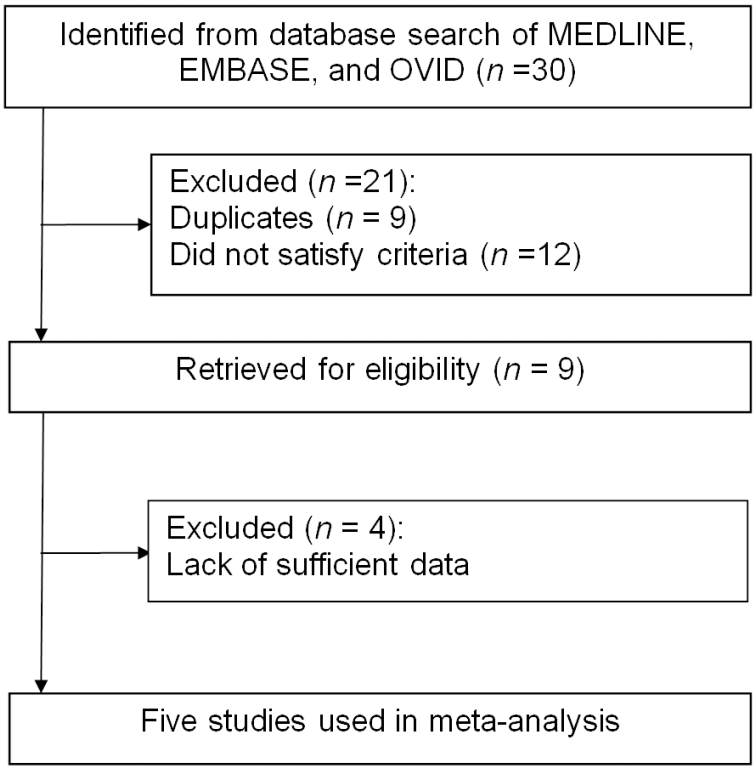

Figure 1. Flowchart of the study selection process.

and 3,060 controls. The included cases consisted of 1,057 males and 887 females. The study selection process is presented in **Figure 1** as a flow chart.

Study characteristics and quality

Main study characteristics are listed in **Table 1**. The most frequently studied genetic variants were rs2075555 and rs2269336, and our meta-analysis focused largely on these SNPs. All five included studies addressed the association between rs2075555 and high myopia risk (1,944 high myopia cases and 3,060 controls); three of these studies also addressed rs2269336 (1,454 high myopia cases and 1,512 controls). None of the studies of rs2075555 showed a deviation from HWE in the controls; for polymorphism rs2269336, however, one study had a deviation from HWE at a *P* value of 0.016.

Main analysis

Our meta-analysis of rs2075555 and rs2269336 in *COL1A1* and high myopia risk is presented in **Table 2**. For rs2075555 a reduced risk for high myopia was apparent in the dominant model (pooled OR = 0.86, 95% CI = 0.74-0.99; $P_{Heterogeneity}$ = 0.376, I^2 = 5.3%) or in homozygotes (pooled OR = 0.79, 95% CI = 0.64–0.97; $P_{Heterogeneity}$ = 0.261, I^2 = 24%); no association was observed between rs2075555 and high myopia risk in the other models (OR 0.90, 95% CI = 0.77-1.06; $P_{Heterogeneity}$ = 0.422, I^2 = 0% for the recessive model; OR 0.87, 95% CI = 0.75-1.02; $P_{Heterogeneity}$ = 0.593, I^2 = 0% for heterozygotes). rs2269336 studies revealed an increased risk in the recessive model (OR = 1.26, 95% CI = 1.05-1.50; $P_{Heterogeneity}$ = 0.123, I^2 = 52.2%) and a reduced risk in heterozygotes with a pooled OR of 0.81 (95% CI = 0.69-0.96; $P_{Heterogeneity}$ = 0.351, I^2 = 4.6%). No significant association was observed in other models (OR = 0.88, 95% CI = 0.75-1.03; $P_{Heterogeneity}$ = 0.164, I^2 = 44.6% and OR = 1.10, 95% CI = 0.89-1.36; $P_{Heterogeneity}$ = 0.091, I^2 = 58.2% for the dominant model and homozygotes, respectively).

Stratified analysis

Stratified analysis of the association between rs2075555 and high myopia risk showed a risk association of Asian ethnicity and rs2075555 in the dominant model and homozygotes (OR = 0.86, 95% CI = 0.74-0.99, $P_{Heterogeneity}$ = 0.238; OR = 0.79, 95% CI = 0.64-0.97, $P_{Heterogeneity}$ = 0.154, respectively). No statistical association was observed for the recessive model and heterozygotes (OR = 0.90, 95% CI = 0.77-1.06, $P_{Heterogeneity}$ = 0.276; OR = 0.87, 95% CI = 0.75-1.02, $P_{Heterogeneity}$ = 0.426, respectively).

Publication bias

Begg's and Egger's tests were performed to assess publication bias for *COL1A1* rs2075555, and both tests showed consistent results, indicating no publication biases in the dominant and recessive models (*P* = 0.462 for Begg's test and *P* = 0.838 for Egger's test in the domi-

Table 1. Study characteristics

Study (year)	Country	Ethnicity	Geno-typing method	SNP ID	Gender (M/F)		Age (mean ± SD, a)		Sample size		Refractive degree (diopter)		Axial length (mm)		HWE
					Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	
Zhang et al. (2011)	China	Asian	Dye termi-nator-based SNaPshot	rs2075555	317/380	352/411	34.3 ± 11.9	54.5 ± 9.2	697	762	≤ -6.00	> -1.0	≥ 26	NA	rs2075555: 0.09
				rs2269336											rs2269336: 0.05
Vatavuk et al. (2009)	Croatia	Caucasian	HumanHap Genotyping BeadChip	rs2075555	4/15	NA	NA	NA	19	925	≤ -6.00	NA	NA	NA	rs2075555: 0.922
Nakanisbi et al. (2009)	Japan	Asian	TaqMan	rs2075555	134/293	194/226	57.6 ± 14.1	44.3 ± 12.1	427	420	≤ -5.00	NA	≥ 26.5	NA	rs2075555: 0.234
				rs2269336											rs2269336: 0.655
Liang et al. (2007)	Taiwan	Asian	TaqMan	rs2075555	471/0	623/0	18-25	NA	471	623	≤ -6.0 D in one eye and ≤ –4.0 D in the other eye	≥ -1.5	NA	NA	rs2075555: 0.459
Inamori et al. (2007)	Japan	Asian	PCR	rs2075555	131/199	131/199	37.82 ± 11.97	37.82 ± 11.97	330	330	≤ -9.25	NA	27.78 ± 1.30	NA	rs2075555: 0.663
				rs2269336											rs2269336: 0.016

PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism; NA: Not applicable; HWE: Hardy-Weinberg equilibrium.

Table 2. Meta-analysis of *COL1A1* rs2075555 and rs2269336 and high myopia risk

SNPs	Models tested	Number of studies	Pooled OR (95% CL)	*P*	Heterogeneity		
					Q	PQ	I^2, %
rs2075555	Dominant model	5	0.86 (0.74, 0.99)	0.037	4.23	0.376	5.3
	Recessive model	5	0.90 (0.77, 1.06)	0.197	3.88	0.422	0
	Homozygote	5	0.79 (0.64, 0.97)	0.024	5.26	0.261	24.0
	Heterozygote	5	0.87 (0.75, 1.02)	0.076	2.79	0.593	0
rs2269336	Dominant model	3	0.88 (0.75, 1.03)	0.115	3.61	0.164	44.6
	Recessive model	3	1.26 (1.05, 1.50)	0.012	4.19	0.123	52.2
	Homozygote	3	1.13 (0.81, 1.59)	0.477	4.79	0.091	58.2
	Heterozygote	3	0.81 (0.69, 0.96)	0.016	2.10	0.351	4.6

"A", major allele; "a", minor allele; dominant model, aa + Aa vs. AA; recessive model, aa vs. AA + Aa; homozygote comparison, aa vs. AA; heterozygote, Aa vs. AA.

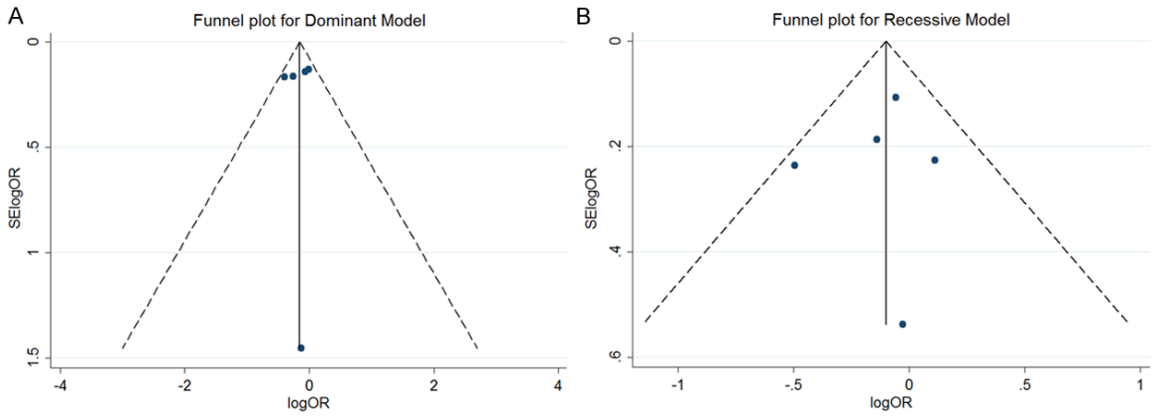

Figure 2. Publication bias analysis for rs2075555. A and B show the Begg's funnel plot of studies in the dominant and recessive models, respectively. The horizontal axis indicates the logOR and the vertical axis indicates the standard error of logOR (SElogOR). The vertical and sloping lines in the funnel plot demonstrate the fixed-effects summary OR, and the expected 95% CI for a given standard error, respectively.

nant model; P = 1.000 for Begg's test and P = 0.887 for Egger's test in the recessive model). The shape of the funnel plot of rs2075555 in **Figure 2** revealed no evidence of asymmetry in the dominant and recessive models.

Discussion

Five studies of *COL1A1* and high myopia risk were included in this meta-analysis, including 1,944 high myopia cases and 3,060 controls. The studies addressed the association between two *COL1A1* polymorphisms and high myopia risk (rs2075555 and rs2269336). SNP rs2075555 is likely a low risk factor for high myopia, as the OR was 0.86 in the dominant model (95% CI = 0.74-$P_{Heterogeneity}$ = 0.376, I^2 = 5.3%; $P_{Heterogeneity}$ = 0.261, I^2 = 24.0% respectively). Further analysis of rs2269336 revealed an OR of 1.26 in the recessive model (95% CI = 1.05-1.50), and 0.81 in heterozygotes (95% CI = 0.69-0.96). Begg's and Egger's tests showed no evidence of publication bias for either polymorphism.

Previous studies have shown a significant genotypic association between *COL1A1* variants and high myopia in a Japanese population [20], although this finding could not be replicated by another Japanese population study [22]. No significant association between *COL1A1* polymorphisms and high myopia risk was observed in another Asian population [21]. Contradictory conclusions have also been drawn in other ethnicities [23, 25].

Dysfunction of type I collagen genes has been associated with disorders such as osteogenesis imperfecta [26] and ocular disorder [27-29]. *COL1A1*, which is located on chromosome

17q21 near MYP5 [30], has been demonstrated in experimental myopia models to play an important role in pathogenesis. The development of high myopia can be explained by altered scleral morphology associated with changes in collagen fibril ultrastructure and increased numbers of small-diameter collagen fibrils [27]. In selected collagen subtypes screened by RT-PCR and sequencing, *COL1A1* was present in the sclera, thus validating the possible relationship between *COL1A1* polymorphisms and risk of high myopia. Gentle et al. showed reduced type I collagen mRNA expression and scleral collagen accumulation in the sclera of myopic tree shrews [29], suggesting *COL1A1* variations control the development of myopia through scleral thinning, tissue loss, and altered tissue morphology. The findings of our meta-analysis showed that *COL1A1* rs2075555 was inversely associated with high myopia.

We found a converse interaction between rs2269336 and high myopia, with an OR of 1.26 in the recessive model (95% CI = 1.05-1.50), and 0.81 in heterozygotes (95% CI = 0.69-0.96). For the three enrolled studies of rs2269336, all of which were performed in Asian populations, one suggested a significant association with high myopia in Japanese [20]; the other two suggested no association [22, 24]. One of these studies had a deviation from HWE at a *P* value of 0.016 [20]. It is possible that this ambivalence is due to bias, as our analysis included a limited number of studies. Studies in other ethnic populations are required to clarify the role of these variations in high myopia risk.

The results of this meta-analysis should be treated with cautionary attention to its limitations. Among the five enrolled studies, one study conducted by Vatavuk et al [23]. Only included 19 cases of high myopia, and only one *COL1A1* polymorphism (rs2075555) was available in their scan, which failed to find an association for this polymorphism. Additional, larger studies should be evaluated, and a haplotype-based approach is needed for a more objective evaluation. Multiple hypotheses complicate the interpretation of this positive result, as it might be attributed to the small number of studies enrolled in the stratified analysis.

In conclusion, we found *COL1A1* rs2075555 is a potential low risk factor for high myopia, and identified a contradictory risk association for rs2269336. Larger, more comprehensive genetic and molecular biological studies are needed to determine the contribution of *COL1A1* to the incidence of high myopia.

Disclosure of conflict of interest

None.

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