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Original Article

A common genetic variant as an effect modifier for primary angle closure glaucoma

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Abstract: Background: Epidemiological studies provide evidence of a genetic basis for primary angle closure glaucoma (PACG), and genome-wide association studies (GWAS) have identified various candidate genes as susceptibility loci. However, different results produced by previous studies make the role of a common genetic variant in the *COL11A1* gene (rs3753841) remains elusive. Thus, we carried out a meta-analysis, attempting to determine the association of rs3753841 with PACG. Methods: Potentially relevant studies were identified by systematical computer-based searches. Selection of eligible studies was undertaken by two investigators according to inclusion criteria. The DerSimonian and Laird's method was performed to estimate pooled odds ratios (risk of PACG) under distinct genetic models. Heterogeneity was measured using the chi-square-based Q statistic test and I^2 metric. Results: We found a significant association of *COL11A1* rs3753841 with PACG among 26,365 subjects (5,594 cases and 20,771 controls) with Asian or Caucasian ancestry derived from a total of 15 studies. The association was more pronounced in individuals with the GG genotype (GG vs AA: odds ratio 1.26, 95% confidence interval 1.13-1.41; GG vs GA + AA: odds ratio 1.24, 95% confidence interval 1.12-1.38). In the stratified analyses, the statistical significance was retailed in Asians and the studies without Hardy-Weinberg equilibrium. Conclusion: Our meta-analysis including the large-scale study suggest that *COL11A1* variant rs3753841 may confer higher susceptibility to PACG and provide additional insight into the mechanisms that underlie this most common subtype of glaucoma.

Keywords: PACG, higher susceptibility, *COL11A1*, genetic variant

Introduction

About 76 million people, increasing from 44 million in the year 2000, will suffer from blindness in 2020 [1]. Glaucoma with multiple features including increased intraocular pressure, obstructed iridocorneal angle and progressive optic nerve damage accompanied with peripheral visual field loss is a major cause of global irreversible blindness [2]. Primary angle closure glaucoma (PACG) representing the most common subtype of glaucoma is a complex heterogeneous disease and accounts for the vast majority of glaucoma-related visual losses. Epidemiological studies indicated a possible genetic basis for PACG [3, 4]. The possibility was explored in genome-wide association studies (GWAS) where a variety of susceptibility loci have been identified [5, 6]. Nonetheless, the role of many genetic variants in the etiology of PACG remains unclear.

The human *COL11A1* is an important candidate gene encoding one of the two alpha chains of type XI collagen. Genetic variations in the gene that would result in serious consequences have been linked to various aggressive diseases, such as osteoarthritis [7], lumbar disc disease [8], type II Stickler syndrome [9], and Marshall syndrome [10], and it is this identified linkage suggests that the genetic variants at *COL11A1* locus are determinants underlying individual susceptibility to human diseases, including PACG.

A non-synonymous variant rs3753841 in the coding region of *COL11A1*, whose overexpression has been described in ovarian cancer and breast cancer [11], has a C to T substitution leading to an amino acid shift from proline to leucine at 1323 position (NM_001854.3). Existing literature previously documented a causal association of rs3753841 with altered

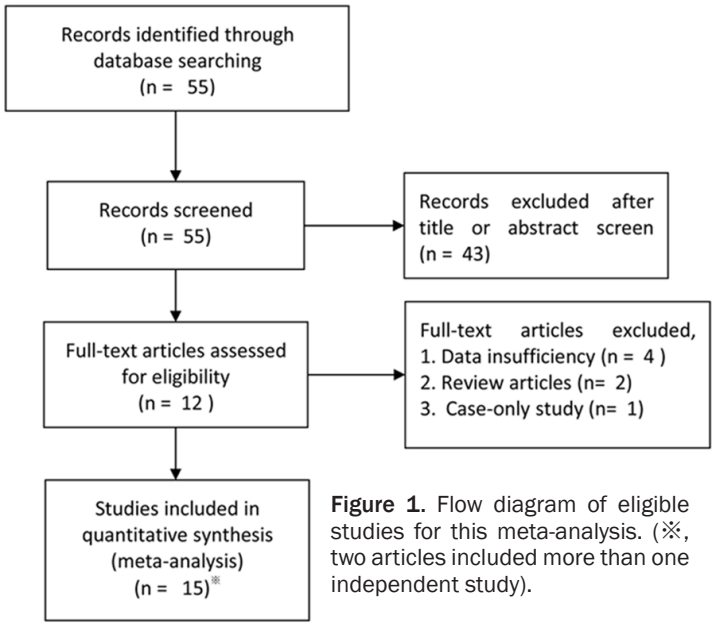

Figure 1. Flow diagram of eligible studies for this meta-analysis. (※, two articles included more than one independent study).

COL11A1 expression [12]. Owing to the functional importance, intense interest has been focused on understanding the genetic contribution of this variant to the development of PACG. The first group concerning this topic is Vithana et al., showing that rs3753841 may contribute to the pathogenesis of PACG [12]. In contrast, subsequent groups, for example, Chen et al., failed to provide supportive evidence for the former findings [13]. Possible reasons that cause the discrepancy in the reported associations include non-homogeneous populations, distinct methodologies, and different sample sizes.

In this study, we used meta-analysis, an ideal statistical method frequently selected to assess genetic variants-associated disease risk when individual studies produced inconsistent results, attempting to determine the association of rs3753841 with PACG.

Materials and methods

Literature search and study selection

To identify the full-length studies that met all of the following criteria:

(i) Using human patients sustaining PACG as cases.

(ii) Healthy individuals comprised the control population.

(iii) The focus was the effects of *COL11A1* rs3753841 on the development of PACG.

(iv) Supplying sufficient genotype data by which risk of PACG could be estimated.

(v) Published prior to June 19, 2014.

(vi) Written in English or Chinese.

We carried out systematic literature searches via the PubMed, Embase, and ISI Web of Knowledge during March 10 and June 19, 2014. The search terms including ("*COL11A1*" AND "polymorphism" OR "polymorphisms" OR "variants" AND "PACG") and ("*COL11A1*" AND "polymorphism" OR "polymorphisms" OR "variants" AND "primary angle closure glaucoma") were used in the study. To obtain additional publications, we screened the references cited in the publications matching the key words listed above.

We excluded the studies that violated any of the previously described conditions. In addition, we selected the largest study with available data for calculation of odds ratios and 95% confidence intervals when the same case population was investigated in two or more studies.

Data extraction

Information on first author's surname, year of publication, study location, characteristics of cases and controls, ethnicity, total numbers of cases and controls, minor allele frequency (MIF) wherever available, matching variables, assays/platforms used in genotype determination, Hardy-Weinberg equilibrium whenever reported, and genotype frequency was collected independently by two authors for all studies eligible for the current meta-analysis. All data were crosschecked and disparities were settled by discussion with a senior author to reach an agreement.

Statistical analysis

The X^2 test was utilized to check whether the genotype distribution in controls was in consistent with Hardy-Weinberg equilibrium for the

Table 1. Characteristics of the selected studies evaluating PACG risk correlated with *COL11A1* rs375384

First author, year	No. of cases	No. of controls	Study location	Population	Matching variables	Genotyping assay/platform	HWE deviation
Duvesh-2013 [19]	176	360	India	Asian	Ethnicity-matched	TaqMan SNP assay	No
Shi-2013 [20]	337	456	China	Asian	Age-, gender-matched	TaqMan aenotyping assay	Yes
Vithana-2012-1 [12]	981	943	Singapore	Asian	Genetically-matched	Illumina 610K Quad BeadChip	No
Vithana-2012-2 [12]	297	1044	China	Asian	Genetically-matched	Illumina 610K Quad BeadChip	No
Vithana-2012-3 [12]	338	2537	India	Asian	Genetically-matched	Illumina 610K Quad BeadChip	No
Vithana-2012-4 [12]	83	3064	Malaysia	Asian	Genetically-matched	Illumina 610K Quad BeadChip	No
Vithana-2012-5 [12]	153	2017	Vietnam	Asian	Genetically-matched	Illumina 610K Quad BeadChip	No
Vithana-2012-6 [12]	1237	2271	China	Asian	Genetically-matched	Sequenom MassArray platform	No
Vithana-2012-7 [12]	298	1479	Singapore	Asian	Genetically-matched	Sequenom MassArray platform	No
Vithana-2012-8 [12]	80	309	India	Asian	Genetically-matched	Sequenom MassArray platform	No
Vithana-2012-9 [12]	165	175	Saudi Arabia	Caucasian	Genetically-matched	Sequenom MassArray platform	No
Vithana-2012-10 [12]	127	4702	UK	Caucasian	Genetically-matched	Sequenom MassArray platform	Yes
Awadalla-2013-1 [18]	232	288	Australia	Caucasian	Gender-, ethnicity-matched	Autoflex mass spectrometer	No
Awadalla-2013-2 [18]	106	204	Australia	Asian	Gender-, ethnicity-matched	Autoflex mass spectrometer	No
Chen-2014 [13]	984	922	China	Asian	Ethnicity-matched	MALDI-TOF	No

MALDI-TOF: matrix-assisted laser desorption ionization-time of flight mass spectrometry method.

Table 2. Meta-analysis of *COL11A1* rs375384 and PACG risk

Variables (No. of studies)	GG vs AA			GA vs AA			GG + GA vs AA			GG vs GA + AA			G vs A		
	OR (95% CI)	*P*	I^2 (%)	OR (95% CI)	*P*	I^2 (%)	OR (95% CI)	*P*	I^2 (%)	OR (95% CI)	*P*	I^2 (%)	OR (95% CI)	*P*	I^2 (%)
All (15)	1.26 (1.13, 1.41)	0.24	20.2	1.06 (0.99, 1.13)	0.99	0.0	1.07 (1.01, 1.13)	0.98	0.0	1.24 (1.12, 1.38)	0.09	37.0	1.10 (1.05, 1.15)	0.75	0.0
Ethnicity															
Asian (12)	1.30 (1.16, 1.46)	0.47	0.0	1.06 (0.99, 1.14)	0.98	0.0	1.07 (1.01, 1.14)	0.99	0.0	1.28 (1.15, 1.44)	0.27	18.3	1.11 (1.06, 1.16)	0.92	0.0
Caucasian (3)	0.98 (0.69, 1.40)	0.08	67.1	1.04 (0.81, 1.33)	0.40	0.0	1.02 (0.82, 1.26)	0.30	3.3	0.93 (0.67, 1.29)	0.07	68.0	1.07 (0.93, 1.22)	0.09	57.1
HWE deviation															
No (13)	1.28 (1.14, 1.44)	0.25	20.0	1.06 (0.98, 1.13)	0.97	0.0	1.07 (1.00, 1.14)	0.97	0.0	1.26 (1.13, 1.41)	0.09	39.8	1.11 (1.06, 1.16)	0.76	0.0
Yes (2)	1.07 (0.74, 1.54)	0.19	41.2	1.06 (0.85, 1.32)	0.60	0.0	1.04 (0.86, 1.27)	0.49	0.0	1.04 (0.73, 1.47)	0.23	29.2	1.04 (0.88, 1.23)	0.25	22.0

①: *P* values for heterogeneity test, ②: number of studies.

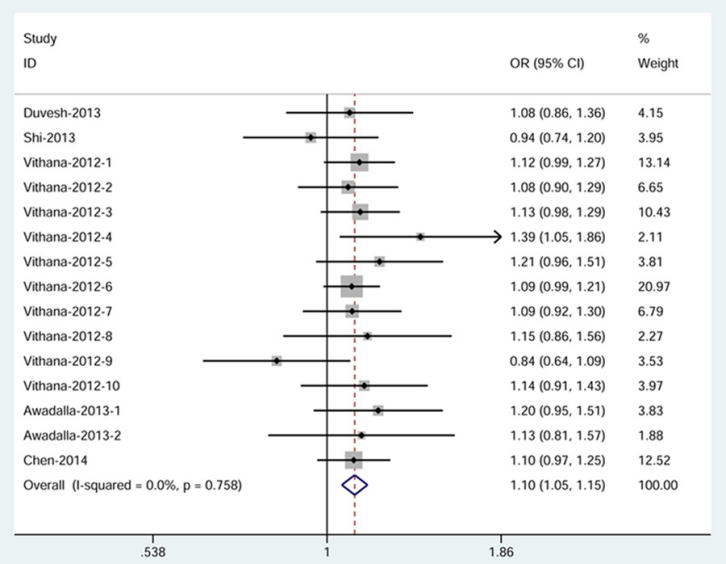

Figure 2. Forest plot (Fixed effects model) describing the association of *COL11A1* rs3753841 with susceptibility toward PACG. The rs3753841-G was associated with an increased risk of PACG (G vs A).

studies that did not report related data. When there was indication of Hardy-Weinberg equilibrium deviation, we performed the leave-one-out sensitivity analysis by excluding the outliers to examine the robustness of summary odds ratios. To assess the strength of association between *COL11A1* rs3753841 and PACG susceptibility, we estimated crude odds ratios with its 95% confidence intervals under GG vs AA, GA vs AA, GG + GA vs AA, GG vs GA + AA, and G vs A genetic models.

To select a more appropriate model to summarize the pooled odds ratios, we detected potential heterogeneity across studies using the chi-square-based Q statistic test as well as the I^2 metric, with *P* values above 0.05 and $I^2 < 50\%$ indicating absence of heterogeneity. In such a case, we used the Mantel-Haenszel method (a fixed effect model) [14] for estimations of summary odds ratios; otherwise, the DerSimonian and Laird method (a random effects model) was performed [15, 16]. Subgroup analyses were performed according to ethnicity and Hardy-Weinberg equilibrium. Publication bias was investigated by funnel plot and Egger's linear regression test [17], with obviously visual symmetry and statistical evidence of no funnel plot asymmetry suggesting lack of publication bias. All analyses were done with Stata software (version 12.0; StataCorp LP, College Station, TX). The values of $P < 0.05$ were considered statistically significant.

Results

Study characteristics

Fifteen studies (note: ten studies provided by Vithana et al. and two by Awadalla et al.) provided a total of 26,365 subjects (5,594 cases and 20,771 controls) with Asian or Caucasian ancestry for the meta-analysis of rs3753841 variant and PACG [12, 13, 18-20]. Although 55 titles were retrieved and screened, 50 were finally excluded due to various reasons as detailed in **Figure 1**. All studies had a moderate sample size, ranging from 310 in the Asian study conducted by Awadalla etr al. [18] to 4,289 in the Caucasian study by Vithana et al [12]. Most studies were for subjects of Asian ancestry (80%) and only 20% were performed in Caucasians. Different genotyping assays or platforms were selected in genotype determination, including TaqMan SNP (single nucleotide polymorphism) assay, TaqMan aenotyping assay, Illumina 610K Quad BeadChi, Sequenom MassArray platform, Autoflex mass spectrometer, and MALDI-TOF (matrix-assisted laser desorption ionization-time of flight mass spectrometry method). The included studies were similar in matching status, and two studies showed significant Hardy-Weinberg equilibrium deviation ([12]-the UK study, [19]). The detailed information was described in **Table 1**.

Quantitative synthesis

As shown in **Table 2**, we found that the rs3753841 genotypes were significantly associated with risk of PACG. We identified a 26% increase in the risk of PACG in individuals with the GG genotype (GG vs AA: odds ratio 1.26, 95% confidence interval 1.13-1.41). A 24% higher risk was indicated under the GG vs GA + AA model (odds ratio 1.24, 95% confidence interval 1.12-1.38). Using the GG + GA vs AA model and the G vs A model, we found a minor increase (odds ratio 1.07, 95% confidence interval 1.01-1.13; odds ratio 1.10, 95% confidence interval 1.05-1.15, **Figure 2**).

In a stratified analysis by ethnicity, significantly increased risk was observed in Asians under all

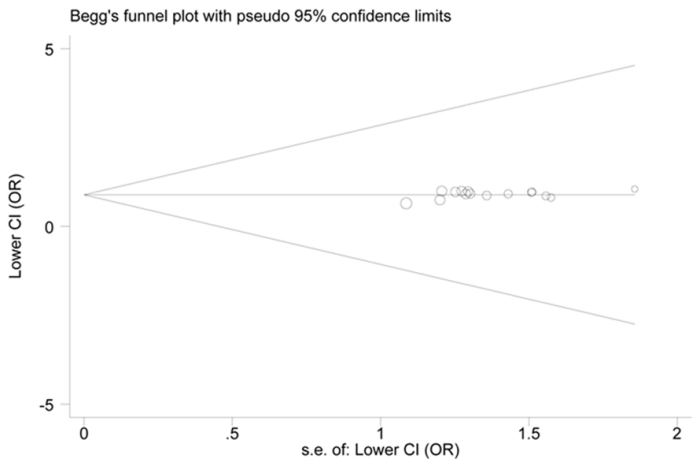

Figure 3. Funnel plot analysis to detect publication bias.

genetic models tested except for the GA vs AA model (odds ratio 1.06, 95% confidence interval 0.99-1.14). No statistical significance was indicated in Caucasians.

We then limited the pooling data to studies with no Hardy-Weinberg equilibrium deviation, the results were almost the same to the meta-analysis including all studies, with the exception that the association was lost in the GG + GA vs AA model (odds ratio 1.07, 95% confidence interval 1.00-1.14).

No significant between-study heterogeneity was detected in overall analyses ($P > 0.05$ and $I^2 < 50\%$, **Table 2**) and calculations of summary risk estimates were completed using a fixed effects model.

Sensitivity analysis

Robustness of our results was examined by performing meta-analysis while excluding the studies with significant Hardy-Weinberg equilibrium deviation. The sensitivity analyses results suggested that only the association estimated under the GG + GA vs AA model was disappeared. Therefore, our effect estimates were reliable (data not shown).

Publication bias

As shown in **Figure 3** (genetic model: G vs A), the studies were symmetrically scattered in the funnel plot ($P = 0.921$). To confirm the symmetry, we used Egger's test to provide statistical evidence. The derived data indicated no obvious publication bias in the meta-analysis ($P = 0.094$).

Discussion

The *COL11A1* gene, especially the genetic variations within the region, is of particular interest in the epidemiology field due to its role in modulating the risk of developing PACG, the most prevalent form of glaucoma and the leading cause of visual loss around the world [2]. The etiology of PACG has been thought to be multifactorial. Since Lowe et al. for the first time reported a causal association between family history and malignant progression of PACG [21], host genetic factors have extensively been investigated since then and many studies demonstrated data supporting the notion proposed by the former group [22, 23]. Family aggregation studies provided further evidence of a strong genetic predisposition to this disease. Amerasinghe et al. and Wang et al. found that the first degree relatives of PACG-free individuals compared to those of PACG patients have about 6~9 times lower risk of developing the malignancy [4, 24]. Concordant with previous findings, multiple candidate gene studies demonstrated evidence that genetic variations are critical components involved in the evolving stages of PACG [25, 26]. According to these data, it seems likely that *COL11A1* genetic variants, such as rs3753841, are underlying determinants of individual susceptibility to PACG.

To investigate the possibility, Vithana et al. carried out a large-scale study among different samples, most of whom were composed of Asian subjects, suggesting a significantly increased susceptibility towards PACG in all investigated populations [12]. This significant increase, however, was not replicated in most studies concerning the association of rs3753841 with PACG. Awadalla et al. investigated two populations, Caucasian from Australia and Asian from Nepal, and identified an association in the former population, but not in the latter [18]. The null results were also indicated in another two Asian studies from India and China, respectively [13, 19]. It is interesting that Shi et al. replicated the significant association in a Chinese population [20]. The most likely reason that results in the inconsistency

may attribute to sampling difference and ethnic variance.

To derive a more reliable estimate of the genetic association, we carried out a meta-analysis where 5,594 cases and 20,771 controls across 15 sample collections in Asia and Europe were incorporated. The combined risk estimates suggested that rs3753841 genotypes played a significant role in modulating individual susceptibility towards PACG, among Asians in particular. The results showed similar increases in the risk when analysis was limited to the studies with no Hardy-Weinberg equilibrium departure. While we confirmed the findings indicated among Asians in early-released studies with a relatively larger sample size, the exact role of rs3753841 remains to elucidated in future investigations, as our observations among Caucasian are inconsistent with previous studies. However, our findings of higher predisposition in Asians appear reasonable according to Alsbirk et al. suggesting higher incidence rate of PACG in Asians relative to Caucasians [27].

To the best of our knowledge, it is the first meta-analysis examining the association of *COL11A1* rs3753841 with the development of PACG. We expanded the sample to the largest by combining all available data published to date and thereby maximized the overall power. In addition to the sufficient number that makes our findings more reliable, lack of significant publication bias and between-study heterogeneity further ensured the reliability.

To better understand the findings in this study, several weaknesses are suggested to be noted. First, it is reported that ethnicity may have a key role in individual susceptibility of the disease being investigated, with higher incidence rate in Inuits and Asians, and lower in Caucasians. In this work, we only identified a sufficient number of studies for Asians, thus it remains indecisive whether rs3753841 contributes toward the susceptibility to PACG among subjects with other ancestries. Second, environmental risk factors that are frequently shown to increase the risk of human diseases after having interacted with genetic variants were not considered. Third, publication bias may be introduced, because only published data and the studies written in Chinese or English were included.

In conclusion, we support the notion that rs3753841 variant in the coding region of *COL11A1* was associated with risk of developing PACG, especially in Asian. Further analyses are also required to identify the genetic contribution of rs3753841 to the disease.

Disclosure of conflict of interest

None.

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