Review Article

Genetic associations in *CHAT* and *COL11A1* with primary angle-closure glaucoma susceptibility: A systematic review and meta-analysis

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Genome-wide association studies (GWAS) have identified that single-nucleotide polymorphisms (SNPs) rs1258267 in *CHAT* and rs3753841 in *COL11A1* are associated with primary angle-closure glaucoma (PACG). The purpose of the study was to evaluate the association of *CHAT* rs1258267 and *COL11A1* rs3753841 with PACG. A comprehensive electronic database search was performed to include eligible studies, published from October 2010 to March 2022. By calculating summary odds ratios (ORs) and 95% confidence intervals (CI) under five genetic models, the risk of PACG related to these two SNPs could be estimated. Heterogeneity was measured with a Chi-square-based *Q* statistic test and the I^2 statistic. By the *Z* test, we analyzed the overall effect of OR. We used funnel plots and Begg's funnel plots to evaluate the publication bias of included studies. The meta-analysis was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist. There were eighteen studies associating *CHAT* rs1258267 with PACG indicating evidently decreased PACG risk in five genetic models. Thirty studies were included to demonstrate a notable increase in the risk of PACG-carrying *COL11A1* rs3753841 genotypes. Subgroup analyses showed that the association of *CHAT* rs1258267 and *COL11A1* rs3753841 with PACG was obvious in Asians, while no evidence was found to confirm this connection in Caucasians. This meta-analysis suggests that *CHAT* rs1258267 G/A polymorphisms could bring about a decreased risk of PACG susceptibility and *COL11A1* rs3753841 G/A polymorphisms could cause an increased risk. These effects mainly manifest in Asians.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1226_22

Quick Response Code:

Key words: *CHAT*, *COL11A1*, genetic variant, meta-analysis, PACG

Glaucoma is the leading cause of irreversible blindness worldwide.[1] The likelihood of severe bilateral visual impairment is three times higher in primary angle-closure glaucoma (PACG) than in primary open-angle glaucoma (POAG), especially among Asians.[2,3]

CHAT has been found to encode an enzyme choline O-acetyltransferase (CHAT) synthesizing the neurotransmitter acetylcholine (ACh), which plays a vital role in pupillary constriction and so on.[4] *COL11A1* in the trabecular meshwork (TM) is responsible for regulating the aqueous outflow pathway resulting in PACG susceptibility.[5]

Therefore, we performed a meta-analysis of these two SNPs to inquire into their influence on PACG susceptibility by including the nearest studies.

Methods

Searching strategy

We systematically searched PubMed, EMBASE, OVID, EBSCO, Elsevier Science Direct, Web of Science, VIP Chinese SCI-Tech Journal full-text Database, Wanfang, and China Biomedical Literature Database (CBM) during October 2010 to March 2022 using Chinese subject words "primary angle-closure glaucoma" and "gene polymorphism (s)," while English keywords were "PACG," "genetic," "*COL11A1*," "*CHAT*," "rs1258267," and "rs3753841." The search date ends on March 2022. We also screened the references cited in the publications matching the subject words listed above to obtain additional publications. The meta-analysis is guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist.

Inclusion and exclusion criteria

The inclusion criteria are: (1) Original research literature is a case-control study, (2) Using human patients diagnosed with PACG as cases, (3) Referring to the associations of *COL11A1* rs3753841 and *CHAT* rs1258267 with PACG, (4) Providing sufficient genotype data to estimate the odds ratio (OR) with 95% confidence interval (CI), (5) Newcastle-Ottawa Scale (NOS) ≥6. Abstracts from conferences, animal studies, full texts without raw data available for retrieval, non-case-control study, republished data, duplicate studies, and reviews were excluded.

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Received: 16-May-2022 Revision: 01-Aug-2022
Accepted: 22-Sep-2022 Published: 02-Feb-2023

Cite this article as: Wang S, Zhang G, Lu H. Genetic associations in *CHAT* and *COL11A1* with primary angle-closure glaucoma susceptibility: A systematic review and meta-analysis. Indian J Ophthalmol 2023;71:343-9.

Data extraction and quality assessment

According to the above criteria, the data were retrieved and screened independently by two investigators. If these two investigators could not reach a consensus, disparities were settled by discussion. We extracted the following items from each qualified research: The surname of the first author, year of publication, study location, ethnicity, the total number of cases and normal controls, frequencies of *COL11A1* rs3753841 and *CHAT* rs1258267 polymorphism in cases and controls, and so on. These two investigators also used the NOS to evaluate the quality of the selected studies to ensure the NOS ≥6. The PRISMA 2020 checklist as additional file 1 guided this meta-analysis.[6]

Statistical analysis

The χ^2 test was used to evaluate whether the genotype distribution in controls was inconsistent with Hardy-Weinberg equilibrium (HWE). Under five genetic models, G vs. A, GG + GA vs. AA, GG vs. GA + AA, GA vs. AA, and GG vs. AA, a pooled OR and 95% CI was calculated to estimate the association between *COL11A1* rs3753841 or *CHAT* rs1258267 and PACG susceptibility. Heterogeneity among studies was measured with a Chi-square-based Q statistic test and the I^2 statistic. With $P > 0.10$ indicating an absence of heterogeneity, we used the Mantel–Haenszel method to calculate the pooled ORs in a fixed-effect model. On the contrary, the DerSimonian and Laird method was performed to calculate the pooled ORs in a random-effect model if the $P \leq 0.10$. I^2 statistic was used to estimate heterogeneity quantitatively ($I^2 > 50\%$ was considered as high-level heterogeneity, 25%–50% medium-level, and $I^2 < 25\%$ high-level). By the Z test, we analyzed the overall effect of OR and $P < 0.05$ showed that the results were statistically significant. We conducted subgroup analyses with respect to ethnicity or HWE deviation. By excluding each study, we conducted the leave-one-out sensitivity analysis to examine whether summary ORs were affected by one specific study. Funnel plots and Begg's funnel plot ($P \leq 0.05$ and $Z \geq 1.96$ indicated significant publication bias) were utilized to analyze publication bias qualitatively and quantitatively. All statistical analyses were performed by STATA (version 15.1, StataCorp LLC, College Station, Texas 77845, USA).

Results

Literature search and characteristics

The search process in our meta-analysis is described in Fig. 1. The initial search of databases identified 451 potentially relevant articles. After removing duplication and excluding substandard articles, a total of forty-eight[5,7-13] published studies provided 11373 cases and 36040 controls for the meta-analysis of rs3753841 and rs1258267 variants. All studies are made up of Asian and Caucasian ancestry, and Asian ancestry accounts for the main part. Furthermore, the HWE had been tested for all polymorphisms in the control groups and four of them show significant deviation. Additional file 2 presents more details of these studies.

Meta-analysis results

All forty-eight studies were pooled into this meta-analysis. The DerSimonian and Laird method was chosen for the G vs. A model of *CHAT* rs1258267 and three genetic models (G vs. A, GG vs. GA + AA, and GG vs. AA) of *COL11A1* rs3753841 because of medium-level heterogeneity ($P < 0.10$). The model selected for subgroup analysis was consistent with the pooled analysis. There were eighteen studies supplying results associating *CHAT*

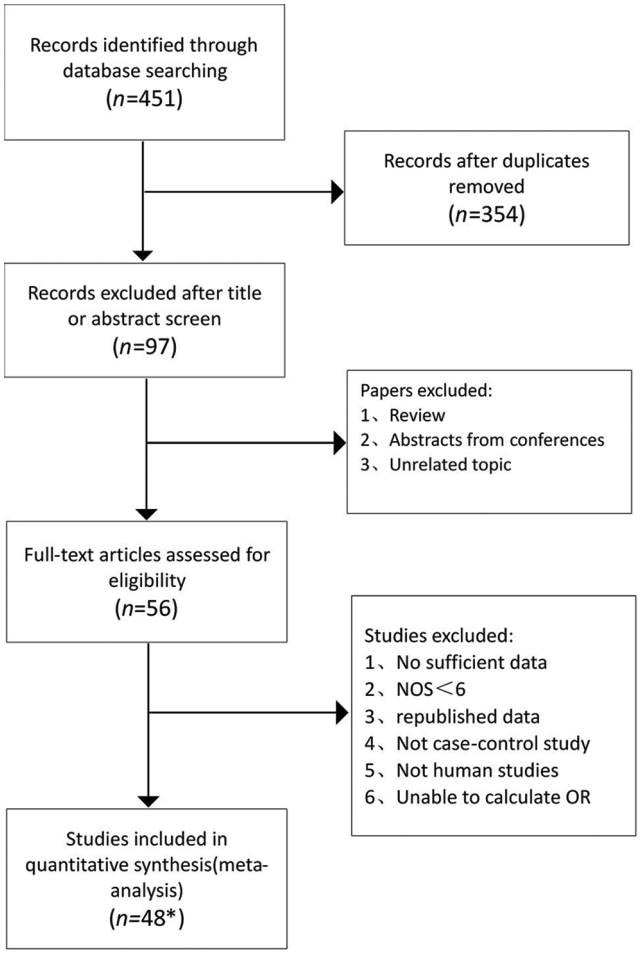

Figure 1: Flow diagram of included studies for this meta-analysis. (*four articles included more than one independent study)

Table 1: Overall analysis of the association between two SNPs and primary angle-closure glaucoma risk

Genetic models	OR (95%CI)	P	I^2 (%)	P_{het}
rs1258267				
G vs. A	0.80 [0.74, 0.86]	0.000	36.9%	0.059
GG + GA vs. AA	0.76 [0.72, 0.81]	0.000	16.4%	0.258
GG vs. GA + AA	0.78 [0.68, 0.90]	0.001	17.8%	0.240
GA vs. AA	0.77 [0.72, 0.82]	0.000	0.0%	0.604
GG vs. AA	0.71 [0.62, 0.82]	0.000	23.3%	0.178
rs3753841				
G vs. A	1.17 [1.12, 1.23]	0.000	38.1%	0.019
GG + GA vs. AA	1.18 [1.12, 1.23]	0.000	19.8%	0.169
GG vs. GA + AA	1.32 [1.20, 1.45]	0.000	42.3%	0.008
GA vs. AA	1.12 [1.06, 1.17]	0.000	6.7%	0.362
GG vs. AA	1.42 [1.28, 1.57]	0.000	41.1%	0.011

OR: Odds ratio; CI: Confidence interval; P_{het}: P value for heterogeneity

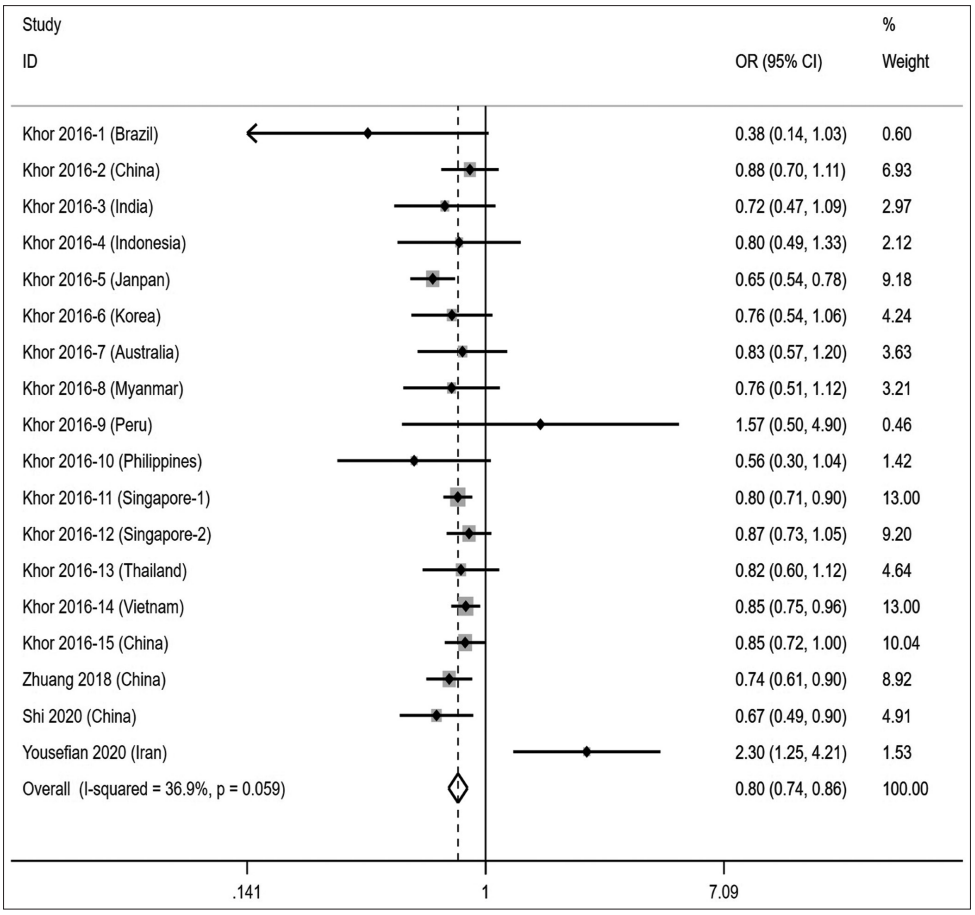

Figure 2: Forest plot (random-effect model) of the susceptibility of CHAT rs1258267 associated with PACG (G vs. A)

Table 2: Stratified analysis of *CHAT* rs1258267 based on ethnicity

Genetic models	OR (95%CI)	*P*	I^2 (%)	P_{het}
Asian				
G vs. A	0.80 [0.75, 0.84]	0.000	0.00%	0.524
GG + GA vs. AA	0.76 [0.71, 0.81]	0.000	0.00%	0.906
GG vs. GA + AA	0.76 [0.66, 0.88]	0.000	16.00%	0.274
GA vs. AA	0.77 [0.72, 0.82]	0.000	0.00%	0.992
GG vs. AA	0.69 [0.60, 0.80]	0.000	20.80%	0.222
Caucasian				
G vs. A	0.95 [0.40, 2.27]	0.917	83.20%	0.003
GG + GA vs. AA	0.91 [0.67, 1.25]	0.572	82.40%	0.003
GG vs. GA + AA	1.75 [0.76, 4.06]	0.189	0.00%	0.477
GA vs. AA	0.86 [0.62, 1.19]	0.359	80.00%	0.007
GG vs. AA	1.67 [0.73, 3.84]	0.227	0.00%	0.416

OR: Odds ratio; CI: Confidence interval; P_{het}: *P* value for heterogeneity

Table 3: Stratified analysis of *COL11A1* rs3753841 based on ethnicity

Genetic models	OR (95%CI)	*P*	I^2 (%)	P_{het}
Asian				
G vs. A	1.18 [1.13, 1.23]	0.000	24.70%	0.131
GG + GA vs. AA	1.18 [1.12, 1.23]	0.000	14.70%	0.254
GG vs. GA + AA	1.37 [1.25, 1.50]	0.000	29.50%	0.084
GA vs. AA	1.11 [1.06, 1.17]	0.000	9.80%	0.323
GG vs. AA	1.46 [1.33, 1.61]	0.000	27.60%	0.101
Caucasian				
G vs. A	1.07 [0.88, 1.32]	0.114	70.20%	0.009
GG + GA vs. AA	1.17 [1.00, 1.37]	0.051	50.10%	0.091
GG vs. GA + AA	1.04 [0.76, 1.43]	0.681	59.20%	0.044
GA vs. AA	1.17 [0.99, 1.39]	0.071	4.30%	0.382
GG vs. AA	1.14 [0.76, 1.70]	0.227	67.80%	0.015

OR: Odds ratio; CI: Confidence interval; P_{het}: *P* value for heterogeneity

rs1258267 with PACG and we found a 20% decrease in the risk of PACG under the G vs. A model (OR = 0.80, 95%CI = 0.74–0.86, *P* = 0.000, Fig. 2). Table 1 shows more than 21% decrease under other genetic models, especially GG vs. AA model (OR = 0.71, 95%CI = 0.62–0.82, *P* = 0.000). Subgroup analyses were carried out based on Asian and Caucasian ethnicities [shown in Table 2]. The results were obvious in Asians (GG vs. AA: OR = 0.69, 95%CI = 0.60–0.80, *P* = 0.000), while no statistical significance was manifested in Caucasians (G vs. A: OR = 0.95, 95%CI = 0.40–2.27, *P* = 0.917, Fig. 3).

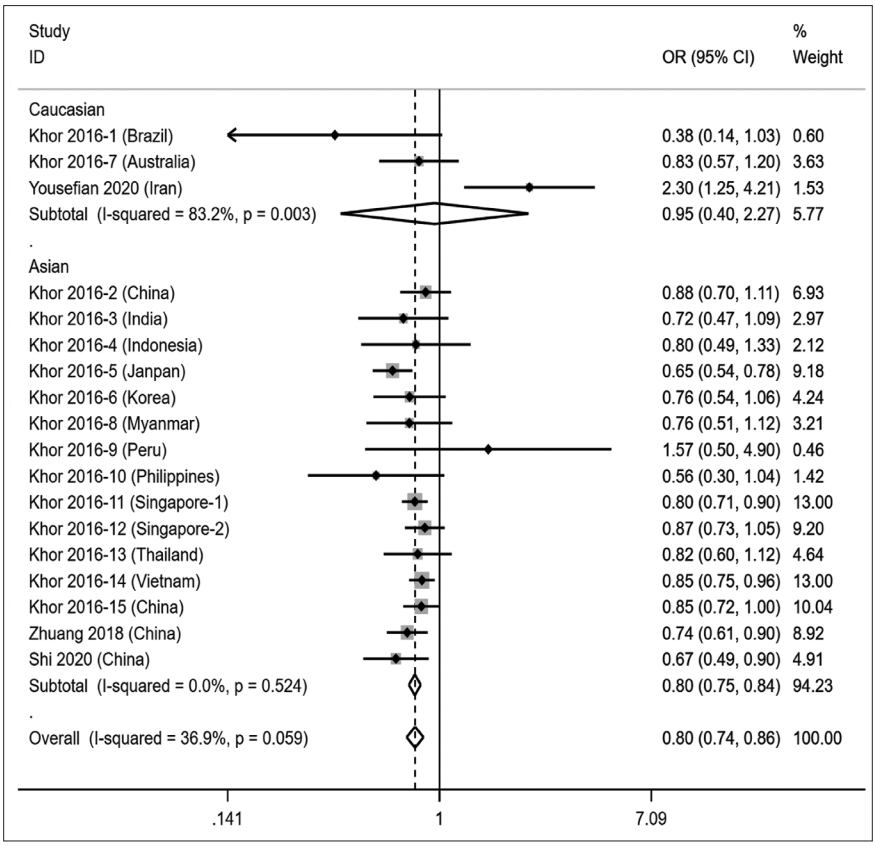

Figure 3: The results of CHAT rs1258267 analyzed based on Asian and Caucasian ethnicities (G vs. A)

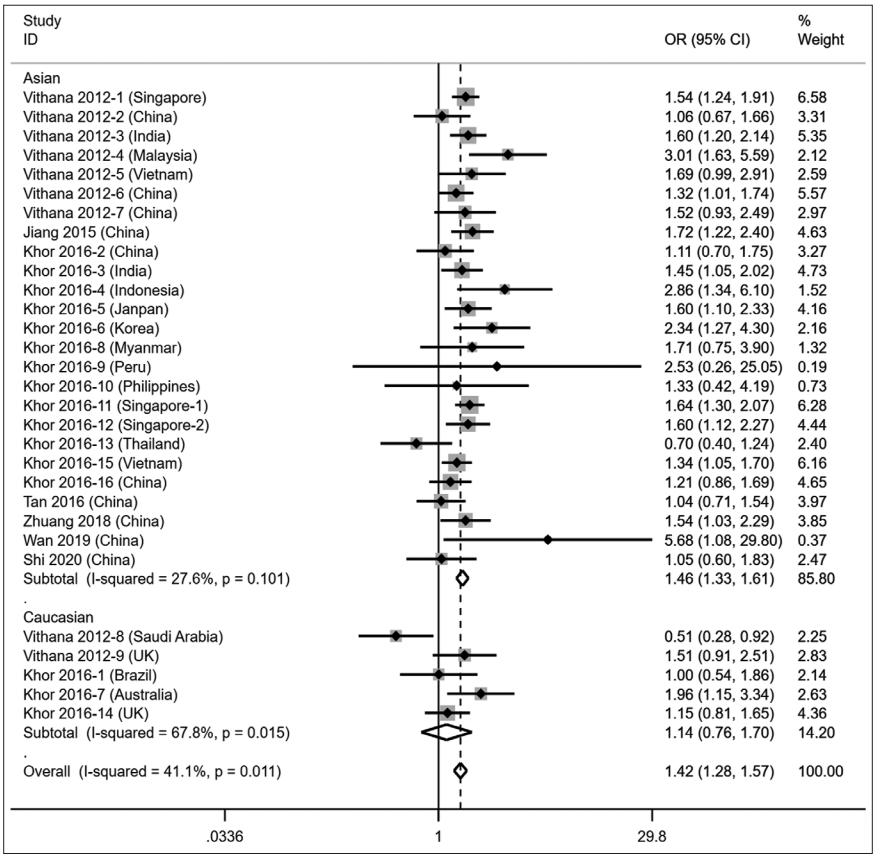

Figure 4: The results of COL11A1 rs3753841 analyzed based on Asian and Caucasian ethnicities (GG vs. AA)

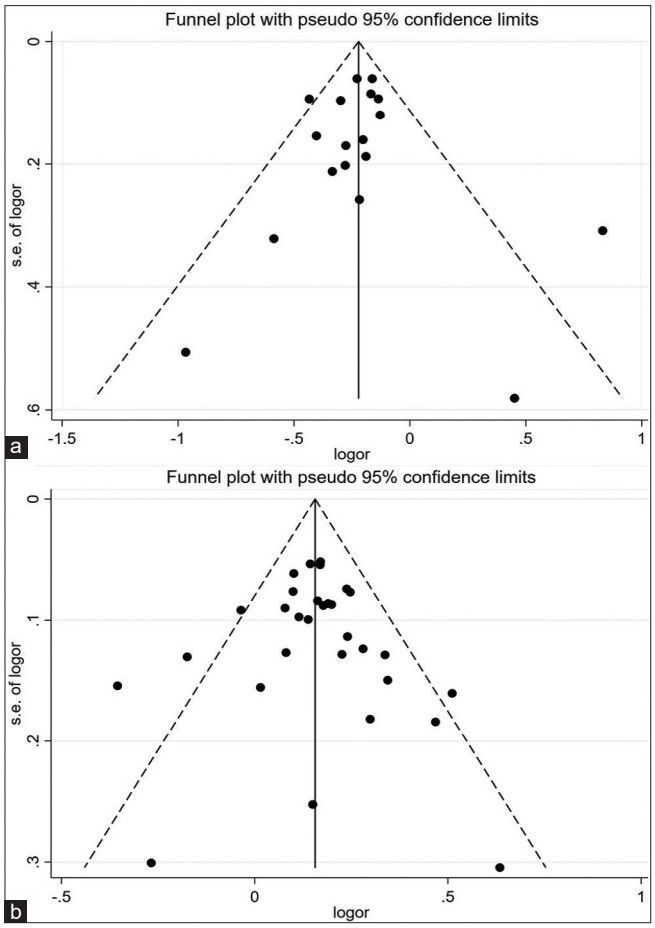

Figure 5: (a) The results of sensitivity analysis from CHAT rs1258267 (G vs. A). (b) The results of sensitivity analysis from COL11A1 rs3753841 (G vs. A)

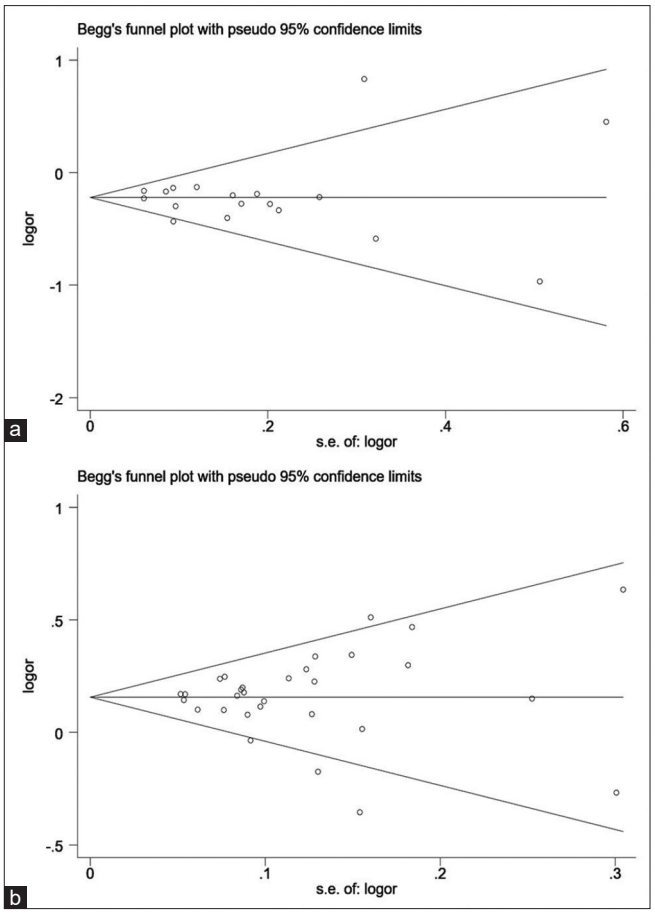

Figure 6: (a) Funnel plot from CHAT rs1258267. (b) Funnel plot from COL11A1 rs3753841

Thirty studies were included to demonstrate a notable increase in the risk of PACG carrying *COL11A1* rs3753841 genotypes. A 42% increased risk could be identified under GG vs. AA model (OR = 1.42, 95%CI = 1.28-1.57, *P* = 0.000) and a 32% higher risk could be indicated under GG vs. GA + AA model (OR = 1.32, 95%CI = 1.20-1.45, *P* = 0.000). We also found about 15% growth using other genetic models [shown in Table 1]. In stratified analysis by ethnicity, Fig. 4 indicates evidently increased risk in Asians under GG vs. AA model (OR = 1.46, 95%CI = 1.33-1.61, *P* = 0.000) and the results of other models were consistent [shown in Table 3]. However, in Caucasians, the results were of no statistical significance (*P* > 0.05 under five genetic models). Depending on HWE deviation, we performed some other stratified analyses. The results of the two groups were almost the same as the meta-analysis including all studies, besides GA vs. AA with no HWE deviation (OR = 1.06, 95%CI = 0.93-1.20, *P* = 0.381, Table 4).

Sensitivity analysis

Sensitivity analysis was conducted by excluding the studies with HWE deviation. We also compared the summary ORs calculated by using fixed-effect models and random-effect models, respectively, and the results were not substantially altered, indicating that our conclusion was reliable.

Publication bias

Publication bias was calculated quantitatively by Begg's test [shown in Table 5] and qualitatively by the funnel plot. In the overall analyses, publication bias for *CHAT* rs1258267 and *COL11A1* rs3753841 had not been discovered. As shown in Figs. 5 and 6, the studies were symmetrically scattered in the funnel plots.

Discussion

This meta-analysis included eight articles supplying forty-eight studies to examine whether *CHAT* rs1258267 G/A polymorphisms and *COL11A1* rs3753841 G/A polymorphisms have a possible impact on PACG susceptibility. From what has been discussed above, we may safely confirm these relationships. We found that *CHAT* rs1258267 decreased the risk of PACG and *COL11A1* rs3753841 increased this risk. These associations remained in Asians, but not in Caucasians.

CHAT had been found to encode an enzyme ChAT synthesizing the neurotransmitter Ach and Yang *et al*.[14] used anticholinergic agents to regulate pupillary block causing an increased risk of acute PACG. Under the circumstances, we could speculate that the risk of PACG is under the control of natural genetic variation in CHAT by adjusting ACh metabolism.[15] The pooled results showed the relevance

Table 4: Stratified analysis of *COL11A1* rs3753841 based on HWE deviation

Genetic models	OR (95%CI)	*P*	I^2 (%)	P_{het}
HWE (Yes)				
G vs. A	1.17 [1.11, 1.23]	0.000	43.20%	0.010
GG + GA vs. AA	1.18 [1.13, 1.24]	0.000	25.10%	0.118
GG vs. GA + AA	1.31 [1.18, 1.46]	0.000	43.00%	0.010
GA vs. AA	1.13 [1.07, 1.19]	0.000	9.10%	0.330
GG vs. AA	1.41 [1.26, 1.59]	0.000	43.90%	0.008
HWE (No)				
G vs. A	1.17 [1.07, 1.27]	0.000	0.00%	0.577
GG + GA vs. AA	1.14 [1.01, 1.28]	0.032	0.00%	0.581
GG vs. GA + AA	1.36 [1.04, 1.77]	0.000	52.10%	0.124
GA vs. AA	1.06 [0.93, 1.20]	0.381	0.00%	0.441
GG vs. AA	1.46 [1.17, 1.82]	0.000	24.30%	0.267

OR: Odds ratio; CI: Confidence interval; P_{het}: *P* value for heterogeneity

Table 5: Begg's test to detect publication bias

Genetic models	*Z*	*P*
rs1258267		
G vs. A	0.45	0.649
GG + GA vs. AA	0.45	0.649
GG vs. GA + AA	0.15	0.880
GA vs. AA	0.53	0.596
GG vs. AA	0.08	0.940
rs3753841		
G vs. A	0.79	0.432
GG + GA vs. AA	1.78	0.074
GG vs. GA + AA	0.18	0.858
GA vs. AA	1.18	0.239
GG vs. AA	0.14	0.887

between *CHAT* rs1258267 and PACG, and *CHAT* rs1258267 could decrease the risk of PACG. In the other words, the GG genotype of *CHAT* was the protective genotype of PACG. It was reported that ethnicity may have a pivotal role in individual susceptibility to the disease.[16] From the results of the subgroup analysis, this effect was more significant in Asians [shown in Table 2], which has been authenticated by Zhuang *et al*.[8] and Shi *et al*.[9] But no significance was found in Caucasians under five genetic models. This distinction could be ascribed to differences in ethnicity and insufficient data. The GG genotype frequencies in studies recruited in non-Asian countries such as Brazil (136 PACG cases and 213 controls), Australia (147 PACG cases and 1119 controls), and Iran (270 PACG cases and 4644 controls) were low.

COL11A1 on 1p21.1 encodes one of the two α-chains of type XI collagen.[16] Because of changes in collagen affecting TM function, alterations in the biomechanical features of the extracellular matrix (ECM) lead to decreased outflow and elevated intraocular pressure (IOP).[17] Finally, *COL11A1* in TM is responsible for regulating the aqueous outflow pathway. The *COL11A1* rs3753841 as a susceptibility locus for PACG has been identified since 2012.[5] Our meta-analysis brought into more studies in recent years with larger populations and more different ethnicities. The overall results suggested that *COL11A1* rs3753841 played a significant role in increasing PACG susceptibility. Stratified analyses showed that *COL11A1* rs3753841 had the same effect in Asians, but not in Caucasians. The Asians with the genotype GG vs. (GA + AA) even were more susceptible to PACG than the total population in our meta-analysis. A similar situation appeared when we performed stratified analyses based on HWE. People with the genotype GA vs. AA had a minor higher predisposition when the analysis was limited to the studies with no HWE deviation. According to Alsbirk *et al*.,[18] higher susceptibility in Asians might be reasonable. And it was noteworthy that the direction of effect for *COL11A1* rs3753841 in Caucasians was analogous to that of the overall results.

No significant publication bias ensured the dependability of the final results. However, some potential limitations from the following aspects should be solved. Firstly, because of pre-established standards such as lack of sufficient genotype data, some studies were excluded, particularly, which contained more relevant information about Caucasians. Meanwhile, some countries we included such as Iran have more mixed populations. Due to the rarity of the minor allele for *CHAT* rs1258267 in Europeans such as in the UK from Khor *et al*.[7] (no one with genotype GG in cases and controls), the analysis might be less persuasive for Caucasians. In addition, the analysis of the *COL11A1* rs3753841 in Caucasians was different from previous studies; hence, the role of *COL11A1* rs3753841 remained to be investigated. In addition, more factors should be considered which can influence the changes in PACG. Stratified analyses in our meta-analysis were performed just through two aspects, but sex, age, working environment, and family history may interfere with eventual results.

Conclusion

In summary, we conclude that *CHAT* rs1258267 G/A polymorphisms could cause a decreased risk of PACG susceptibility, and *COL11A1* rs3753841 G/A polymorphisms could cause an increased risk. These associations remain in Asians, but not in Caucasians. Given that there are many other factors to consider, further articles with more worldwide studies are demanded to confirm the relationship of these two genes in PACG.

Data availability statement

All data generated or analyzed during this study are included in this article and its additional files. Further inquiries can be directed to the corresponding author.

Statement of ethics

All analyses were based on previously published studies; thus, no ethical approval and patient consent are required.

Acknowledgements

The authors would like to thank the Department of Ophthalmology, Affiliated Hospital of Nantong University and Chiea Chuen Khor (Singapore National Eye Centre and Eye ACP, Duke-National University of Singapore, Singapore) for providing the basic data.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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