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Genetic Associations of Primary Angle-Closure Disease

A Systematic Review and Meta-analysis

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Topic: Systematic review and meta-analysis of the genetic associations of primary angle-closure disease (PACD).

Clinical Relevance: To confirm the genetic biomarkers for PACD, including primary angle-closure glaucoma (PACG) and related phenotypes.

Methods: We searched in the MEDLINE and EMBASE databases for genetic studies of PACG or other PACD published from the start dates of the databases to May 11, 2015. We estimated the summary odds ratios (ORs) and 95% confidence intervals (CIs) for each polymorphism in PACG, primary angle-closure suspect (PACS), and primary angle-closure (PAC) using fixed- or random-effect models. We also performed sensitivity analysis to test the robustness of the results.

Results: Our literature search yielded 6463 reports. Among them, we identified 24 studies that fulfilled the eligibility criteria for meta-analysis, involving 28 polymorphisms in 11 genes/loci. We affirmed the association of PACG and combined PACS/PAC/PACG with 10 polymorphisms in 8 genes/loci, including *COL11A1* (rs3753841-G; OR, 1.22; $P = 0.00046$), *HGF* (rs17427817-C, OR, 2.02, $P = 6.9E-07$; rs5745718-A, OR, 2.11, $P = 9.9E-07$), *HSP70* (rs1043618, GG+GC; OR, 0.52; $P = 0.0010$), *MFRP* (rs2510143-C, OR, 0.66, $P = 0.012$; rs3814762-G, OR, 1.40; $P = 0.0090$), *MMP9* (rs3918249-C; OR, 1.35; $P = 0.034$), *NOS3* (rs7830-A; OR, 0.80; $P = 0.036$), *PLEKHA7* (rs11024102-G; OR, 1.24; $P = 8.3E-05$), and *PCMTD1-ST18* (rs1015213-A; OR, 1.59; $P = 0.00013$). Sensitivity analysis indicated that the results were robust.

Conclusions: In this study, we confirmed multiple polymorphisms in 8 genes/loci as genetic biomarkers for PACD, among which 3 were identified in a genome-wide association study (*COL11A1*, *PLEKHA7,* and *PCMTD1-ST18*), and 5 were identified in candidate gene studies (*HGF*, *HSP70*, *MFRP*, *MMP9*, and *NOS3*). *Ophthalmology 2016;■:1–11 © 2016 by the American Academy of Ophthalmology.*

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Glaucoma is a leading cause of irreversible blindness worldwide, estimated to affect 60.6 to 79.6 million people during 2010 to 2020.[1] Among all patients with glaucoma, approximately 26% have angle-closure glaucoma (ACG), which accounts for approximately half of the cases blinded from glaucoma.[2] Angle-closure glaucoma is characterized by acute or progressive elevation in intraocular pressure (IOP) resulting from appositional or synechial closure of the anterior chamber angle.[2,3] Angle closure can develop through primary (i.e., pupillary block) and secondary mechanisms (e.g., plateau iris, lens-related, inflammatory, and fibrovascular conditions) at multiple anatomic levels (i.e., the iris, ciliary body, lens, and vitreoretinal levels).[2,4] There are different degrees and types of angle closure, which range from irido-trabecular contact (ITC) with normal IOP to total peripheral anterior synechiae (PAS) with elevated IOP and glaucomatous changes. Therefore, primary angle-closure disease (PACD) can be categorized into primary angle-closure suspect (PACS), primary angle-closure (PAC), and primary angle-closure glaucoma (PACG).[5]

Primary angle-closure glaucoma is a multifactorial disease. Major risk factors include age, female gender, ocular biometric features, and ethnicity (e.g., African and Chinese). Shallow anterior chamber depth, thicker lens with increased anterior curvature, short axial length, small corneal diameter, and short radius of curvature also are known factors related to PACG.[2] There is also evidence for a genetic basis of PACG. First, reported prevalence of PACG varied among different ethnicities, such as 0.4% in white subjects,[6] 1.4% in Chinese,[7,8] and 2% to 8% in Eskimos[9,10]; second, PACG is more prevalent in first-degree relatives of patients[11]; and third, the heritabilities for a shallow anterior

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chamber and narrow angle (both are key features of PACG) are approximately 93%[12] and 49%,[13] respectively.

In regard to the genetics of PACD, 2 genome-wide association studies (GWAS) identified 4 susceptibility loci for PACG: *PLEKHA7*, *COL11A1*, *PCMTD1-ST18*,[14] and *ABCC5*.[15] In addition, more than 50 candidate genes have been assessed for association with PACG, PAC, or PACS in the past decade. However, the association profiles (including allele frequency, statistical significance, and odds ratio [OR]) of individual genes vary across different study cohorts. We conducted a systematic review and meta-analysis to evaluate the effects of all reported gene variants for PACG and other PACD.

Methods

Search Methods for Identifying Studies

We conducted the literature search in the EMBASE and MEDLINE databases via the Ovid platform. We adopted sensitive search strategies using the Boolean logic and search terms with controlled vocabularies (i.e., Medical Subject Heading terms): ("polymorphism(s)" OR "mutation" OR "genotype(s)" OR "genetic(s)" OR "gene(s)" OR "allele(s)" OR "DNA") AND ("glaucoma" OR "angle closure") (Table 1, available at www.aaojournal.org). In addition, we manually screened the references of the research articles, reviews, and meta-analyses identified during the initial review to reduce the chance of omitting relevant studies. No language filter was applied in the literature search. The latest search was performed on May 11, 2015.

Eligibility Criteria

We considered a study eligible for the meta-analysis if it fulfilled the following criteria: (1) the original case-control study evaluated the genetic association of 1 or more gene polymorphisms with PACS, PAC, or PACG; (2) the study subjects were unrelated individuals recruited from explicitly defined populations; and (3) allele or genotype counts or frequencies in both the case and control groups were provided or calculable from the reported data; otherwise, the ORs and 95% confidence intervals (CIs) or standard errors (SEs) had to be available. We excluded animal studies, case reports, reviews, abstracts, conference proceedings, editorials, and studies with incomplete data.

Study Selection, Data Collection, and Risk of Bias Assessment

Two reviewers (S.S.R. and F.Y.T.) independently screened and reviewed all the records. Disagreement was resolved through discussions with a third reviewer (L.J.C.). After identifying all eligible articles, 3 groups of reviewers (group 1: S.S.R. and F.Y.T.; group 2: L.M. and S.M.T.; group 3: J.L. and H.G.) independently extracted and then cross-validated the data. Disagreement was resolved by thorough discussions among all reviewers involved in the data extraction. We adopted a customized datasheet to extract data, which included the first author, year of publication, country of study, ethnicity, definition of case and control, sample sizes in case and control groups, genes and polymorphisms, allelic and genotypic counts and frequencies, ORs and 95% CI (or SE) of the tested polymorphisms and corresponding genetic models, and results of the Hardy–Weinberg equilibrium (HWE) test in the control group. We also searched for eligible data reported in the results and supplementary materials of the 2 GWAS.[14,15] If a study had reported 2 or more independent cohorts, we recorded each cohort separately. If the allelic counts were not reported, we calculated them by using the genotype data. If the genotypic counts were missing, we estimated the counts using the allelic frequencies and the sample sizes, assuming there was no deviation from HWE unless otherwise reported.[16] If only the OR and 95% CI were reported, we estimated the SE using the equation $SE = [\beta - \ln(\text{lower limit of 95\% CI})]/1.96$, where $\beta = \ln(OR)$.[17] If HWE was not reported, we tested it from the data extracted from the control group using the chi-square test. Also, we used the Newcastle Ottawa Scale (NOS) (accessed via http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) to evaluate the quality of each case-control study[18–20] (Appendix 1, available at www.aaojournal.org). We gave 1 star to a study if it met 1 requirement in NOS from 3 dimensions (selection, comparability, and exposure). The maximum number of stars achievable in a study was 8. A study obtaining ≤6 stars was considered as high risk in introducing bias.[21]

Data Analysis

We performed a meta-analysis for each gene polymorphism if it had been reported in 2 or more studies. The genetic association was assessed using the allelic (a vs. A), dominant (aa+Aa vs. AA), recessive (aa vs. Aa+AA), homozygous (aa vs. AA), and heterozygous (Aa vs. AA) models, where "a" and "A" represent the associated allele and the reference allele, respectively. We estimated the summary outcomes using the weighted effect of a polymorphism by inverse variance in the fixed-effect model and by inverse variance and τ^2 from the DerSimonian–Laird estimator in the random-effect model.[22] We calculated the summary OR and 95% CI for each polymorphism using the fixed- or random-effects model based on the interstudy heterogeneity, which was tested using the I^2 statistic.[23] An I^2 value of <25% indicated low heterogeneity. In this case, we adopted a fixed-effect model for the meta-analysis. In the case of an I^2 value greater than 25%, which indicated a moderate to high interstudy heterogeneity, we adopted the random-effect model.[23,24] In the meta-analysis, we considered an association as statistically significant if the summary *P* value was less than 0.05. Of note, to assess the replication results of the single nucleotide polymorphisms (SNPs) identified in the PACG GWAS,[14] we first meta-analyzed the data only from replication studies and then added in the data from the initial GWAS to evaluate the overall effects. We adopted the funnel plots and the Egger's test to assess potential biases (e.g., the publication bias).[25–27] A *P* value <0.05 in the Egger's test indicated a statistically significant bias. We also conducted a sensitivity analysis to confirm the associations by sequentially omitting each of the included studies one at a time, studies that deviated from HWE, or studies of suboptimal quality. We then recalculated the summary OR and 95% CI.[28,29] We performed the statistical analyses using the R software (version 3.0.0; http://cran.r-project.org/).

A continuum of conditions compose PACD, including PAC, PACS, and PACG. According to the classification system introduced by the International Society for Geographical & Epidemiological Ophthalmology,[5] PACS is defined as >270° of ITC without PAS, IOP elevation, glaucomatous optic nerve, or visual field changes. Individuals with PAC have >270° of ITC with elevated IOP or PAS but normal disc appearance and visual field. Last, individuals with PACG have >270° of ITC with glaucomatous changes in the optic nerve or visual field. In some studies, subjects with PACG were further classified into those with a history of acute symptomatic angle-closure (also known in some literature as "acute ACG" [AACG]) and those who were asymptomatic (chronic ACG).[30] We conducted the meta-analysis first for

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