Evaluation of the Association Between Common Genetic Variants Near the *ABCA1* Gene and Primary Angle Closure Glaucoma in a Han Chinese Population

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Purpose. Recently, three large genome-wide association studies have identified multiple variants associated with primary open angle glaucoma (POAG) near the *ABCA1* gene. Considering that POAG and primary angle closure glaucoma (PACG) share many similar clinical manifestations, the present study was conducted to investigate whether these genetic variants were also associated with PACG in a Han Chinese population.

Methods. A case-control association study of 1122 cases (PACG/PAC) and 1311 normal, matched controls was undertaken. Seven single-nucleotide polymorphisms (SNPs) near the *ABCA1* gene, including rs2422493, rs2487042, rs2472496, rs2472493, rs2487032, rs2472459, and rs2472519, were genotyped. Genotype and allele frequencies were assessed using χ^2 tests. Linkage disequilibrium (LD) structure was analyzed by computer software.

Results. Among the SNPs genotyped, no association was observed between these SNPs and PACG. However, we discovered that two haplotypes, CATTTAC (corrected $P = 0.048$) and CGCCCGC (corrected $P = 0.048$), remained significantly associated with PACG/PAC after Bonferroni correction. Subjects with the CATTTAC haplotype have a 1.71-fold increased possibility of having PACG/PAC, whereas subjects with the CGCCCGC haplotype have 0.47-fold decreased possibility of developing PACG.

Conclusions. Our findings suggest that the genetic backgrounds of PACG and POAG might be different. However, whether or not *ABCA1* plays a role in the development of PACG is still not made certain by this study. Thus, further research is needed to find the role of *ABCA1* in the progress of PACG.

Keywords: *ABCA1*, primary angle closure glaucoma, primary open angle glaucoma, single-nucleotide polymorphism

Glaucoma represents a heterogeneous group of optic neuropathies characterized by irreversible and progressive visual field loss and damage to the optic nerve head.[1,2] It is the second leading worldwide cause of blindness.[3] Glaucoma can be classified as either primary glaucoma or secondary glaucoma, according to its cause. Primary glaucoma is divided into primary congenital glaucoma (PCG), primary open-angle glaucoma (POAG), and primary angle-closure glaucoma (PACG).[4] POAG and PACG are the two most common clinical types of glaucoma for adults and juveniles and show different incidence rates in different populations.[5] The prevalence of POAG is highest in Africa.[6] However, PACG is more prevalent in

Table 1. Demographic Features of All Subjects in This Study

Subjects	Number	% of Females	Mean ± SD Age*	Mean ± SD IOP, mm Hg		Cup-to-Disc Ratio	
				OD	OS	OD	OS
Cases	1122	57.1	63.0 ± 11.0	34.8 ± 16.4	32.9 ± 16.1	0.59 ± 0.26	0.57 ± 0.25
Controls	1311	65.8	72.7 ± 16.0	14.6 ± 2.8	14.5 ± 3.1	0.33 ± 0.11	0.34 ± 0.12

* Ages of cases and controls at which blood samples were drawn.

Chinese, Eskimo, Asian Indian, and Mongolian populations,[5] affecting approximately 0.75% of adult Asians, of whom 60% are female.[6] In the Chinese population, the occurrence of PACG is 3 times higher than that of POAG.[7]

POAG includes high-tension and normal-tension groups. High-tension POAG is characterized by an obstruction of the aqueous humor pathway, degeneration in the trabecular meshwork, optic disc cupping, and visual field loss.[5] PACG is characterized by a shallow anterior chamber, increased thickness of the lens, complete or partial chamber angle closure, hyperopic refractive error, and shortened axial length.[8] Common clinical manifestations such as elevated IOP, progressive and irreversible destruction of the optic nerve, and degeneration of retinal ganglion cells[5] are shared between these two types of glaucoma.

PACG is a complex heterogeneous disease, and the molecular mechanisms underlying PACG are still unclear. Recently, Vithana et al.[9] conducted a large, two-stage genome-wide association study in which they found three susceptibility loci: rs11024102 in *PLEKHA7*, rs3753841 in *COL11A1*, and rs1015213, located between *PCMTD1* and *ST18*. Their findings were confirmed in three independent studies in South India, China, Australia, and Nepal.[10–12] Furthermore, candidate genes were investigated to evaluate genetic susceptibility to PACG by using different enzymes and proteins, including extracellular matrix metalloprotease-9 (MMP-9),[13–15] membrane frizzled-related protein (MFRP),[16,17] methylenetetrahydrofolate reductase (MTHFR),[18] manganese superoxide dismutase (SOD2),[19] and endothelial nitric oxide synthase (ENOS).[20] However, those findings have not been replicated by independent studies and are still controversial.

Considering that POAG and PACG share many similar characteristics, several studies were conducted to investigate whether the genes associated with POAG were also associated with PACG. MYOC and CYP1B1 have long been identified as related to POAG,[21,22] and the Arg46Stop mutation in the MYOC gene and Leu432Val in the CYP1B1 gene were identified in all patients of a Chinese family with PACG.[23] Furthermore, the Arg368His mutation in the CYP1B1 gene was found in Indian PACG patients, and a similar haplotype background was noted between POAG and PACG.[24] These results indicate that PACG and POAG might have origins that are common across complex glaucoma phenotypes.

More recently, we and other investigators reported that genetic variants near the *ABCA1* gene were significantly associated with POAG through genome-wide association studies (GWAS).[4,25,26] Recent findings also suggest that coordinated *ABCA1* activity across neurons and glial cells influences neuroinflammation and neurodegeneration.[10] In the DBA/2J glaucoma mouse model, the transcriptional change of *ABCA1* is related to ganglion cell death.[27] Given that optic nerve degeneration is the most common characteristic between POAG and PACG, we hypothesized that common genetic variants near the *ABCA1* gene also may be associated with PACG. This study was conducted to investigate whether single-nucleotide polymorphisms (SNPs) near *ABCA1* were associated with PACG in a Han Chinese population.

Materials and Methods

Subjects

Approval was obtained from the Institutional Review Boards of the Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital. Written informed consent was obtained from all subjects prior to this study. This study was conducted in accordance with the tenets of the Declaration of Helsinki and its subsequent revisions.

In the present study, a total number of 2433 participants, including 1122 cases (994 cases in the discover group and 128 cases in the replication group) and 1311 matched controls (1121 cases in the discover group and 190 cases in the replication group) were recruited by the Hospital of the University of Electronic Science and Technology of China, Sichuan Provincial People's Hospital, and Eye, Ear, Nose, and Throat Hospital of Fudan University. Demographic features of the subjects are listed in Table 1. All participants were Han Chinese from southern China. Expert ophthalmologists diagnosed each case based on a cup-to-disc ratio of more than 0.7, an IOP of >21 mm Hg, presence of at least 180° of closed angle in which the trabecular meshwork was not visible on gonioscopy, and peripheral visual loss, following criteria of the International Society of Geographical and Epidemiological Ophthalmology (ISGEO).[28] Primary angle closure eye features indicating that trabecular obstruction by the peripheral iris had occurred (IOP >21 mm Hg or peripheral anterior synechiae) but without glaucomatous optic neuropathy. Acute PAC/PACG was defined as an episode with (1) a presenting IOP of >28 mm Hg on Goldmann applanation tonometry; (2) at least three signs from a list of signs (namely, conjunctival injection, corneal epithelial edema, mid-dilated nonreactive pupil, and shallow anterior chamber); and (3) at least two symptoms from a list of symptoms (e.g., ocular or periocular pain, nausea, vomiting, or a history of intermittent blurring of vision).[29]

In our study, 1122 affected Chinese participants were identified with PAC and PACG. Among the PAC/PACG patients, 454 patients were defined as having acute PAC/PACG, 453 patients were defined as having chronic PAC/PACG, and 215 patients lacked clinical information and so were not able to be separated into either acute or chronic categories. Our controls were required to have none of the above characteristics and were without any known family cases of glaucoma. Each participant went through a complete eye examination, including slit-lamp measurement of the anterior chamber, gonioscopy, best-corrected visual acuity testing, test of intraocular pressure, fundus assessment with special attention to optic disc parameters, and visual field examination.

SNP Selection

Among three recent GWAS of POAG, studies by both Hysi et al.[25] and Gharahkhani et al.[26] noted that rs2472493 was significantly associated and, in both supplementary materials, that rs2472496, a SNP in the same linkage disequilibrium (LD) as rs2472493, was mentioned as reaching genome-wide significance in the discovery cohort. In the meantime, we

Table 2. Association Results for PAC/PACG in the SNPs Near *ABCA1* Between All Cases and Controls

SNP (Minor Allele)	Chromosome*	Position, bp*	Case/Control *P*-HWE	Case/Control MAF	Allelic *P*†	Corrected *P*‡	OR (95% CI)§
rs2422493(T)	9	107,690,995	0.0012/0.077	0.428/0.441	0.067	0.469	0.89 (0.79-1.00)
rs2487042(A)	9	107,694,522	0.17/0.12	0.301/0.303	0.639	1	0.97 (0.85-1.11)
rs2472496(T)	9	107,695,353	0.87/0.37	0.435/0.443	0.329	1	0.94 (0.83-1.06)
rs2472493(T)	9	107,695,848	0.94/0.21	0.462/0.474	0.234	1	0.93 (0.82-1.05)
rs2487032(T)	9	107,703,934	0.76/0.28	0.470/0.475	0.503	1	0.96 (0.85-1.08)
rs2472459(A)	9	107,710,562	0.054/0.095	0.321/0.315	0.396	1	1.06 (0.93-1.21)
rs2472519(C)	9	107,715,878	0.08/0.15	0.343/0.359	0.483	1	0.96 (0.84-1.09)

P-HWE, the *P* value of the Hardy-Weinberg equilibrium (HWE) testing; MAF, the minor allele frequency.
* Genomic position and chromosome in build 37.
† Allelic *P* has been adjusted for age and sex.
‡ Corrected *P* has been adjusted using Bonferroni correction (allelic *P* ×7).
§ ORs (95% CI) were analyzed by logistic regression analysis and adjusted for age and sex, cases versus controls.

revealed that rs2487032, rs2472459, and rs2472519 located upstream of the *ABCA1* gene on 9q31.1 were associated with POAG in a Han Chinese population. In addition, rs2422493 and rs2487042 are in the same LD block with rs2472496 in the Han Chinese in Beijing (HCB) population of the HapMap database, and rs2422493 is a promoter variant encompassing a proximal regulatory region of *ABCA1*.[30] As a result, we selected rs2422493, rs2487042, rs2472496, rs2472493, rs2487032, rs2472459, and rs2472519 and genotyped these seven SNPs in a mainland Han Chinese population.

SNP Genotyping

Venous blood was withdrawn from peripheral blood samples of each subject and collected in an EDTA tube. Genomic DNA was extracted from the venous blood by serial phenol/chloroform extraction and ethanol precipitation. SNP genotyping was conducted with the dye terminator-base SNaPshot method (Applied Biosystems, Grand Island, NY, USA). SNP analysis was undertaken using the 3730 Genetic Analyzer (Applied Biosystems). Briefly, PCRs contained 50 ng of genomic DNA, 1 μL of each primer (10 pmol/μL), 1 μL of 10× buffer (Takara Bio, Inc., Shiga, Japan), 0.8 μL of deoxyribonucleotide triphosphates (2 mM; Takara Bio, Inc.), 0.4 μL of $MgCl_2$ (2.5 mM; Takara Bio, Inc.), and 0.1 μL of ExTaq polymerase (5 U/μL; Takara Bio, Inc.), with a final mixture volume of 10 μL. Then, the product was processed according to the SNaPshot protocol, using primers designed for fluorescent dideoxynucleotide termination (Supplementary Table S1). All SNPs in our study had a genotyping success rate greater than 97% and an accuracy of more than 98%, as verified by direct Sanger sequencing analysis.

Statistical Analysis

All statistical analyses were conducted using SPSS version 15.0 software (SPSS, Inc., Chicago, IL, USA). A standard χ^2 test was used to evaluate Hardy-Weinberg equilibrium (HWE) and the differences of allele frequencies for each SNP between the case and control groups. All results were considered statistically significant with a *P* value of <0.05. The Bonferroni correction was used to adjust *P* values for multiple testing. Logistic regression analysis was tested to calculate odds ratio (OR) and 95% confidence interval (CI) and to correct for the confounding effects of age and sex. In order to further investigate the association between *ABCA1* and PACG, we applied different statistical models, including additive 1, additive 2 and dominant and recessive models. The haplotype blocks and LD block structures were estimated by Haploview software (version 4.2; Broad Institute, Cambridge, MA, USA).[31] We used software (PS; Power and Sample Size Calculation, version 3.1.2[32]) to calculate statistical power. ORs of different haplotypes were calculated with χ^2 tests, using SPSS version 15.0 software.

Results

In this study, we enrolled a total of 1122 PAC/PACG cases (384 males and 738 females) with a mean ± SD age of 63.0 ± 11.0 years, and 1311 normal controls (562 males and 749 females) with a mean ± SD age of 72.7 ± 16.0 years. The mean ± SD maximum cup-to-disc ratios were 0.59 ± 0.26 and 0.34 ± 0.12, and mean ± SD maximum IOP values were 34.8 ± 16.4 and 14.6 ± 2.8 mm Hg for cases and controls, respectively (Table 1).

All seven SNPs were successfully genotyped, and their allele distributions were within the HWE for both case and control groups ($P > 0.05$) (Table 2), with the exception of the HWE of rs2422493, which was slightly deviant in the case ($HWE = 0.0012$). The association results between all cases and controls are listed in Table 2. All of the selected SNPs showed no differences in distribution of allele frequencies between the cases and controls in a combined group. Results of the replication and discover groups are presented separately in Supplementary Table S2.

To further investigate the association between these selected SNPs and PACG/PAC, we used different genetic models (Table 3). Rs2422493 showed significant associations in additive 1 and recessive models ($P = 0.035$; OR = 0.75; 95% CI: 0.58–0.98; and $P = 0.035$; OR = 0.78; 95% CI: 0.62–0.98, respectively) after adjusting for sex and age. For the multiple comparison correction, the *P* value for significant observation should be less than the product of [0.05/(7 SNP × the number of models)] or 0.0018, as four statistical models were applied. As a result, none of the SNPs in any model remained significantly and robustly associated with PACG after the Bonferroni correction.

In the subgroup comparisons of PAC versus controls and PACG versus controls, there were no statistically significant associations (Table 4). Among the PAC/PACG group, there were 453 chronic PAC/PACG patients, 454 acute PAC/PACG patients, and 215 patients unclassified for lack of clinical information. Clinical characteristics of the acute PAC/PACG and chronic PAC/PACG subjects are listed in Table 5. There were more females in the acute PAC/PACG group than in the chronic PAC/PACG group ($P < 0.001$). The maximum IOP before treatment of acute PAC/PACG (38.7 ± 18.9 mm Hg) was higher than that of chronic PAC/PACG (31.5 ± 13.6 mm Hg; $P < 0.001$), and the maximum cup-to-disc ratio of chronic PAC/

Table 3. Genotype Analysis of 7 SNPs by Four Statistical Models, Cases (PAC/PACG) Versus Controls

SNP ID (Minor Allele)	Genotype Counts*		Additive 1†		Additive 2†		Dominant†		Recessive†	
	Case	Control	*P*	OR(95% CI)	*P*	OR(95% CI)	*P*	OR(95% CI)	*P*	OR(95% CI)
rs2422493(T)	178/601/340	238/674/391	0.035	0.75(0.58–0.98)	0.634	0.95(0.78–1.16)	0.286	0.90(0.75–1.09)	0.035	0.78(0.62–0.98)
rs2487042(A)	92/491/537	108/576/624	0.887	0.98(0.71–1.35)	0.496	0.94(0.79–1.12)	0.524	0.95(0.80–1.12)	0.963	1.00(0.74–1.37)
rs2472496(T)	212/544/356	246/654/393	0.439	0.91(0.71–1.16)	0.137	0.86(0.71–1.05)	0.158	0.88(0.73–1.05)	0.936	0.99(0.80–1.23)
rs2472493(T)	238/552/323	279/667/347	0.280	0.87(0.68–1.12)	0.040	0.81(0.66–0.99)	0.060	0.83(0.69–1.00)	0.995	1.00(0.81–1.23)
rs2487032(T)	243/559/310	285/670/349	0.541	0.92(0.72–1.19)	0.197	0.88(0.71–1.07)	0.239	0.89(0.74–1.08)	0.902	1.01(0.82–1.25)
rs2472459(A)	103/514/504	111/598/591	0.127	1.29(0.93–1.78)	0.850	0.98(0.82–1.18)	0.803	1.02(0.86–1.21)	0.122	1.27(0.94–1.72)
rs2472519(C)	118/528/467	155/621/521	0.773	0.96(0.71–1.28)	0.277	0.90(0.75–1.09)	0.314	0.91(0.77–1.09)	0.942	1.01(0.77–1.33)

A, minor allele; B, major allele.

* Genotype counts are presented as homozygote/heterozygote/wild-type.

† OR (95% CI) were determined by logistic regression analysis, patients versus controls. ORs (95% CI) and *P* values were obtained by adjusting for age and sex. Genotype (AA/AB/BB) analyses were conducted for the additive model 1 (AA compared with BB), additive model 2 (AB compared with BB), dominant model (AA+AB compared with BB), and recessive model (AA compared with AB+BB).

Table 4. Single Nucleotide Polymorphism Allele Frequencies and Associations for 7 SNPs in Subgroup Analysis of PAC Versus Controls and PACG Versus Controls

SNP (Minor Allele)	Chromosome	Position, bp	MAF (Control)	PAC			PACG		
				MAF	*P**	OR(95% CI)*	MAF	*P**	OR(95% CI)*
rs2422493(T)	9	107,690,995	0.441	0.425	0.080	0.87(0.74–1.02)	0.430	0.143	0.90(0.78–1.04)
rs2487042(A)	9	107,694,522	0.303	0.298	0.461	0.94(0.79–1.11)	0.304	0.804	0.98(0.84–1.14)
rs2472496(T)	9	107,695,353	0.443	0.448	0.904	0.99(0.85–1.16)	0.426	0.137	0.90(0.78–1.04)
rs2472493(T)	9	107,695,848	0.474	0.477	0.779	0.98(0.83–1.15)	0.451	0.078	0.88(0.76–1.01)
rs2487032(T)	9	107,703,934	0.475	0.485	0.939	1.00(0.86–1.18)	0.458	0.195	0.91(0.79–1.05)
rs2472459(A)	9	107,710,562	0.315	0.328	0.392	1.08(0.91–1.27)	0.316	0.760	1.02(0.88–1.19)
rs2472519(C)	9	107,715,878	0.359	0.349	0.581	0.95(0.81–1.13)	0.339	0.383	0.94(0.81–1.09)

* *P* values and ORs (95% CI) have been adjusted for age and sex.

Table 5. Clinical Characteristics of Acute PAC/PACG and Chronic PAC/PACG

Characteristic	Acute PAC/PACG	Chronic PAC/PACG	Uncategorized Patients†
Total *n*	454	453	215
% of females*	74.6	56.5	66.5
Mean ± SD age	62.8 ± 11.0	63.0 ± 11.0	61.0 ± 11.0
Mean ± SD maximum IOP*	38.7 ± 18.9	31.5 ± 13.6	33.4 ± 14.3
Mean ± SD maximum cup-to-disc ratio*	0.52 ± 0.24	0.67 ± 0.25	0.59 ± 0.26

* Differences were statistically significant ($P < 0.05$) between acute PAC/PACG and chronic PAC/PACG.

† Uncategorized Patients, who lacked clinical information, were therefore not able to be separated into either acute or chronic PAC/PACG categories.

PACG (0.67 ± 0.25) was higher than that of the acute PAC/PACG group (0.52 ± 0.24; $P < 0.001$).

In the next analysis, we evaluated the association between acute and chronic PAC/PACG cases and controls. Rs2422493 ($P = 0.059$; OR = 0.85; 95% CI: 0.73–1.00) showed marginal associations between acute PAC/PACG cases and controls. None of the SNPs near the *ABCA1* gene showed statistically significant differences between chronic and acute PAC/PACG cases and controls (Table 6).

The LD plot of these seven SNPs was examined with Haploview software (Fig.). The LD structures of rs2422493, rs2487042, rs2472496, rs2472493, rs2472459, and rs2472519 are mostly consistent with those of the CHB HapMap samples (Supplementary Fig. S1), as there is no genotype data for rs2487032 in the Han Chinese in Beijing population of the HapMap database. The r^2 and D′ values for all pairs of SNPs were calculated, and the haplotypes were estimated with Haploview software (Table 7). Three haplotypes, CATTTAC, TGCCCGT, and CGCCCGC, which were generated from these seven SNPs, proved to be significantly different between the cases and controls ($P = 0.004$; OR = 1.71; 95% CI: 1.18-2.27; and $P = 0.012$; OR = 1.60; 95% CI: 1.11-2.32; and $P = 0.004$; OR = 0.47; 95% CI: 0.28-0.79, respectively). After the Bonferroni correction [*P* value × the number of haplotypes], two haplotypes, CATTTAC (corrected $P = 0.048$) and CGCCCGC (corrected $P = 0.048$), remained significantly associated with PAC/PACG. Haplotype analysis results of replication and discover groups are presented in Supplementary Table S3.

Discussion

Previously, five SNPs: rs2472496, rs2472493, rs2487032, rs2472459, and rs2472519, located upstream of the *ABCA1* gene on 9q31.1, were identified as being associated with POAG.[4,25,26] Hysi et al.[26] discovered by GWAS and meta-analysis of 18 population cohorts, that rs2472493 was associated with elevated IOP and POAG. Meanwhile, Gharah-

Table 6. Single Nucleotide Polymorphism Allele Frequencies and Associations for 7 SNPs in Subgroup Analyses of Acute PACG Versus Controls and Chronic PACG Versus Controls

				Acute PAC/PACG			Chronic PAC/PACG		
SNP (Minor Allele)	Chromosome	Position, bp	MAF (Control)	MAF	*P**	OR(95% CI)*	MAF	*P**	OR(95% CI)*
rs2422493(T)	9	107,690,995	0.441	0.415	0.059	0.85(0.73–1.00)	0.438	0.446	0.94(0.80–1.10)
rs2487042(A)	9	107,694,522	0.303	0.289	0.242	0.90(0.76–1.07)	0.322	0.500	1.06(0.89–1.26)
rs2472496(T)	9	107,695,353	0.443	0.428	0.222	0.90(0.77–1.06)	0.460	0.716	1.03(0.88–1.21)
rs2472493(T)	9	107,695,848	0.474	0.463	0.371	0.93(0.79–1.09)	0.479	0.811	0.98(0.84–1.15)
rs2487032(T)	9	107,703,934	0.475	0.475	0.842	0.98(0.84–1.16)	0.479	0.768	0.98(0.83–1.14)
rs2472459(A)	9	107,710,562	0.315	0.329	0.380	1.08(0.91–1.28)	0.331	0.301	1.09(0.92–1.29)
rs2472519(C)	9	107,715,878	0.359	0.344	0.493	0.94(0.78–1.12)	0.358	0.991	1.00(0.85–1.18)

* *P* values and OR (95% CI) have been adjusted for age and sex.

khani et al.[25] discovered similar results in Australia. In addition, we performed a GWAS of POAG in 1007 cases with high-pressure glaucoma and 1009 controls, using subjects from southern China. We observed significant genome-wide associations at multiple SNPs near *ABCA1* on 9q31.1.[4] Multiple population replications indicated that the *ABCA1* gene may play a crucial role in the process of POAG. It is well known that the *ABCA1* gene encodes a membrane protein that is a member of the ATP-binding cassette A (*ABCA1*) transporter superfamily that facilitates the cellular efflux of cholesterol and phospholipid.[33] *ABCA1* is highly and specifically expressed in the ganglion cell layer of the retina.[4]

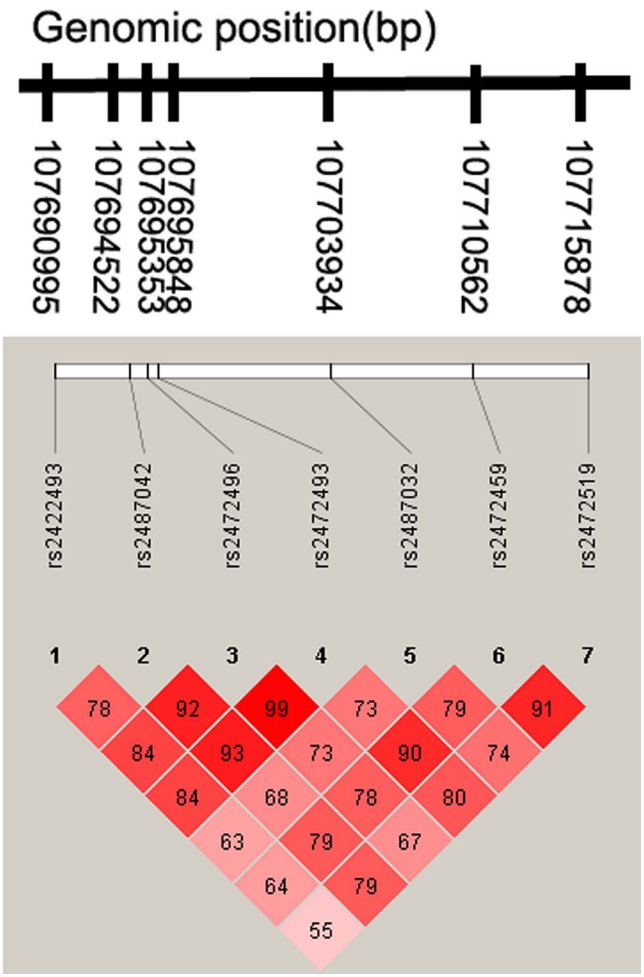

Figure. Linkage disequilibrium (LD) plot of the 7 SNPs near the *ABCA1* gene in a Han Chinese Population.This LD plot was generated using the data from all subjects in the present study. The LD plot was examined using Haploview software. The physical position of each SNP is shown above the plot, and that of *ABCA1* is 107543283 to 107690527 in build 37. Darker shades of red indicate higher LD coefficient values (D′). Numbers listed in each square represent the D′ value for pairwise analysis.

Given that optic nerve degeneration and high IOP are characteristics shared between POAG and PACG, we conducted this study using the SNaPshot method (ABI) to investigate whether *ABCA1* was also associated with PACG in a Han population. In this study, we genotyped seven SNPs located upstream of *ABCA1* (rs2422493, rs2487042, rs2472496, rs2472493, rs2487032, rs2472459, and rs2472519) in a Han Chinese cohort. As a result, five reported polymorphisms, rs2472496, 2472293, rs2487032, rs2472459, and rs2472519, showed no statistically significant association in the distribution of allele frequencies in our study, although they showed highly significant association in POAG.[4,25,26] Meanwhile, in the previous studies, minor alleles of the SNPs in the *ABCA1* gene were reported to be protective, and in this study, except for rs2472459, the minor allele of six remaining SNPs was also a protective factor, suggesting the direction of the effect in our study was the same as that in the previous studies. Although both PACG and POAG are subtypes of glaucoma, they have dissimilar clinical characteristics; thus, genetic susceptibility may be different on the same candidate gene. In the subgroup analysis, we evaluated associations among these SNPs and acute PAC/PACG, chronic PAC/PACG, and PAC and PACG, separately. None of the SNPs showed statistically significant associations between subgroups and controls. Through LD analysis, we discovered that the LD structures of rs2422493, rs2487042, rs2472496, rs2472493, rs2472459, and rs2472519 are mostly consistent with those of the CHB HapMap samples. However, we discovered that two haplotypes, CATTTAC (corrected $P = 0.048$) and CGCCCGC (corrected $P = 0.048$), remained significantly associated with PAC/PACG after the Bonferroni correction. Subjects with the CATTTAC haplotype have a 1.71-fold increased possibility of developing PAC/PACG, whereas subjects with the CGCCCGC haplotype have 0.47-fold decreased possibility.

Statistical power calculations showed that our sample size had roughly 98% power to detect an effect when the reported effect size in POAG was also true for PAC/PACG. In contrast to some other studies,[34] patients with PAC were included in this study, which could potentially dilute the observation of association with PACG. However, PAC is an early stage of PACG,[12] and it is both intriguing and important to investigate whether PAC has an association with SNPs in *ABCA1* as well. In addition, statistical power calculations showed that the sample size of PACG in this study had an approximately 80% of chance to identify the true signals of association.

Table 7. Haplotype Association With PACG on the Upstream of *ABCA1* in a Han Chinese Population

Haplotype*	Frequency	Case/Control Frequencies	χ^2	*P* Value	Corrected *P*†	OR(95% CI)‡
CGCCCGT	0.409	0.414/0.404	0.483	0.487	1	
TATTTAC	0.204	0.200/0.207	0.391	0.532	1	
TGTTTGT	0.092	0.089/0.094	0.386	0.534	1	
CGCCTGT	0.048	0.045/0.050	0.573	0.449	1	
CATTTAC	0.025	0.032/0.019	8.290	0.004	0.048	1.71(1.18–2.27)
TGCCCGT	0.024	0.030/0.019	6.344	0.012	0.144	1.60(1.11–2.32)
TATTCAC	0.021	0.019/0.022	0.333	0.564	1	
CGCTTAC	0.019	0.021/0.018	0.321	0.571	1	
CGCCCGC	0.015	0.010/0.020	8.292	0.004	0.048	0.47(0.28–0.79)
TGTTCGT	0.015	0.014/0.016	0.387	0.534	1	
TGTTTAC	0.014	0.014/0.014	0.011	0.917	1	
TATTCGT	0.014	0.015/0.012	0.949	0.330	1	

* Haplotypes were generated from SNPs rs2422493, rs2487042, rs2472496, rs2472493, rs2487032, rs2472495, and rs2472519, in that order.
† Corrected *P* has been adjusted using Bonferroni correction.
‡ The OR was calculated using SPSS version 15.0 software, if the *P* value is lower than 0.05.

In conclusion, we conducted a case-control study of 7 SNPs among 1122 PAC/PACG subjects and 1311 healthy controls. No association was observed between these SNPs and PACG, although two haplotypes were noted to be statistically significant. Our findings suggest that the genetic background of PACG may be different from that of POAG. However, whether or not *ABCA1* plays a role in PACG is still poorly understood. Thus, further research is needed to elucidate the exact mechanism of *ABCA1* in the progress of glaucoma.

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