Association of Single-Nucleotide Polymorphisms in *ABCC5* Gene with Primary Angle Closure Glaucoma and the Ocular Biometric Parameters in a Northern Chinese Population

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Keywords

ABCC5 · PACG · ACD · AL · Single-nucleotide polymorphisms

Abstract

Background: The rs1401999 gene in *ABCC5* gene was the first locus confirmed by a genome-wide association study (GWAS) to be associated with both anterior chamber depth (ACD) and primary angle closure glaucoma (PACG); however, this locus was of obvious heterogeneity among different populations in the GWAS, and the conclusion has not been further verified by other studies. Therefore, this study was carried out to investigate whether the single-nucleotide polymorphisms (SNPs) in *ABCC5* gene are associated with PACG and the ocular biometric parameters ACD and axial length (AL) in samples from northern China. **Methods:** Case-control association study included 500 PACG patients and 720 unrelated controls from northern China, and genotyping was performed for ten SNPs in *ABCC5* gene using an improved multiplex ligation detection reaction technique. The association between these SNPs and risk of PACG was estimated by PLINK using a logistic regression model, while the association between genotypes and ocular biometric parameters was performed by SPSS using generalized estima-

tion equation. **Results:** An SNP rs4148568 ($p = 0.046$) and a haplotype TCGGAG ($p = 0.0364$) in *ABCC5* were associated with PACG, and rs4148568 was nominally associated with AL ($\beta = 0.092$, $p = 0.08$). **Conclusions:** The SNP rs4148568 and a haplotype TCGGAG in *ABCC5* contribute to PACG in northern Chinese people. In addition, rs4148568 might be associated with the AL, the variant allele of which may have effect of making the AL longer. Further studies are needed to elucidate the exact mechanism of *ABCC5* in the progress of PACG.

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Introduction

Primary angle closure glaucoma (PACG) is a major subtype of glaucoma in Asia and also the most common cause of bilateral glaucoma blindness worldwide [1, 2]. PACG is a multifactorial disease and has been proven to have a strong genetic basis. To date, two genome-wide association studies (GWASs) on PACG have been conducted, and 8 genetic loci showed strong associations with

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PACG [3, 4]: rs11024102 in *PLEKHA7*, rs3753841 in *COL11A1*, rs1015213 located between *PCMTD1* and *ST18*, rs3816415 in *EPDR1*, rs1258267 in *CHAT*, rs736893 in *GLIS3*, rs7494379 in *FERMT2*, and rs3739821 mapping between *DPM2* and *FAM102A*. Besides, another GWAS on anterior chamber depth (ACD), a locus, rs1401999 in the *ABCC5* gene, was also found to be associated with PACG [5]. These discoveries based on the GWAS are reliable since they were replicated in a large sample in the replication stage; however, the conclusions were inconsistent from those of other researchers who have validated the results of GWAS by Vithana et al. [3] in different cohorts and different regions [6–8].

Beyond that, some researchers tried to find out whether the 3 susceptibility loci identified by the first GWAS on PACG were associated with ocular biometric parameters [9–11], among which Day et al. [9] confirmed an association of the locus rs1015213 with ACD in a European cohort [9], while no association was found in other studies [10, 11]. Validation in additional independent cohorts and analysis of the relationship between these genes and ocular biometric parameters will help to determine the contributions of these genes in the development of PACG. In our previous study, we have evaluated the association of the 8 susceptibility loci which were reported by the GWAS with PACG as well as ocular biometric parameters ACD and axial length (AL), and no correlation was found between these loci and ocular biometric parameters [12]. The rs1401999 in *ABCC5* gene was the first locus confirmed by the GWAS to be associated with both ACD and PACG; however, this locus was of obvious heterogeneity among different populations in the GWAS, and the conclusion has not been further verified by other studies. Therefore, this case-control study was designed to investigate whether the gene variants in *ABCC5* gene are associated with PACG and the ocular biometric parameters ACD and AL in a northern Chinese cohort.

Materials and Methods

Subjects

This study was conducted in accordance with the tenets of the Declaration of Helsinki; ethical approval was obtained from the Ningxia People's Hospital; and written informed consent was obtained from each individual prior to the study. A total of 1,220 unrelated Chinese individuals were recruited from the northern regions of China, including 500 PACG patients and 720 unaffected controls. The detailed ophthalmic examinations for every participant, and the inclusion and exclusion criteria as well as the protocol of genetic DNA extraction were identical to those in our previous study [13].

Table 1. Demographic features of study participants

	Cases	Controls	<i>p</i> value
<i>n</i>	500	720	
Age (mean±SD), years	63.77±9.576	71.82±7.2	0.000 [#]
Sex, <i>n</i> (%)			
Male	147 (29.4)	332 (46.1)	0.000*
Female	353 (70.6)	388 (53.9)	
Nationality, <i>n</i> (%)			
Han	407 (81.4)	591 (82.1)	0.761*
Hui	93 (18.6)	129 (17.9)	

[#] The *p* value was tested by *t* test. * The *p* value was assessed by χ^2 test.

SNP Selection and Genotyping

A total of ten tag single-nucleotide polymorphisms (SNPs) in *ABCC5* gene were selected from HapMap Beijing Han Chinese population (International HapMap Project) utilizing the tagger program implemented in Haploview 4.2 software (Daly Lab at the Broad Institute, Cambridge, MA) via a pairwise tagging algorithm; there were rs112754234, rs9838667, rs1016752, rs4912517, rs1401999, rs6767306, rs7620781, rs6773408, rs4148568, and rs1879258. Each tag SNP had to adhere to the following criteria: r^2 threshold >0.8 and minimal allele frequency >10%. SNP genotyping was conducted by the Genesky Biotechnologies Inc (Shanghai, China) using an improved multiplex ligation detection reaction technique.

Statistical Analysis

The comparisons of demographic characteristics between cases and controls and the correlations analyses between genotypes and ocular biometric parameters were implemented by SPSS software (version 17.5; SPSS Science, Chicago, IL, USA); the genetic association analyses were performed by PLINK (version 1.07; <http://pngu.mgh.harvard.edu/~purcell/plink/>, in the public domain); the detailed statistical analysis methods were the same as our previous study [13]. The statistical power was evaluated by the Power and Sample Size Calculation (PS; version 3.1.232).

Results

This study included 500 PACG patients and 720 control subjects, as shown in Table 1; there were no significant differences in ethnicity between cases and controls. However, the cases were significantly younger (mean age 63.77 ± 9.58 years vs. 71.82 ± 7.2 years; $p = 0.000$) and included more women (70.6 vs. 53.9%; $p = 0.000$) than the control group.

Genotype frequencies of all SNPs were within the Hardy-Weinberg equilibrium (HWE) ($p > 0.05$), with the exception of rs9838667 (Table 2), which was slightly deviant in the case group ($p = 0.045$). Among the 10 SNPs, sig-

Table 2. Association between SNPs and PACG under the allelic model

SNP	CHR	BP	Minor allele	Genotype (AA/AB/BB)*		MAF		HWE- <i>p</i>		OR (95% CI)	<i>p</i> value
				case	control	case	control	case	control		
rs112754234	3	183652932	C	74/253/173	120/318/281	0.401	0.3886	0.2641	0.07076	1.124 (0.9341–1.353)	0.2158
rs9838667	3	183664678	T	83/269/148	158/349/213	0.435	0.4603	0.04509	0.5006	1.015 (0.8427–1.221)	0.8788
rs1016752	3	183665062	G	4/93/403	10/132/578	0.101	0.1058	0.8053	0.4281	0.9656 (0.7163–1.302)	0.8183
rs4912517	3	183671340	T	27/202/271	50/261/409	0.256	0.2493	0.1975	0.3716	1.152 (0.934–1.42)	0.1863
rs1401999	3	183678342	C	16/148/336	28/221/470	0.18	0.1925	1	0.7201	0.9824 (0.7767–1.243)	0.8824
rs6767306	3	183680368	A	75/256/169	123/345/252	0.406	0.4109	0.1943	0.8173	0.867 (0.7183–1.047)	0.1372
rs7620781	3	183710480	A	15/158/327	28/226/465	0.188	0.1957	0.5572	0.9061	1.017 (0.8051–1.286)	0.8853
rs6773408	3	183716609	G	43/196/261	60/279/380	0.282	0.2772	0.5073	0.4025	1.027 (0.8407–1.256)	0.7914
rs4148568	3	183723021	T	11/167/322	37/244/439	0.189	0.2208	0.05669	0.6657	0.7135 (0.5649–0.9012)	0.00461
rs1879258	3	183729664	G	41/231/228	80/318/321	0.313	0.3326	0.1184	0.9331	0.8414 (0.6911–1.024)	0.08555

p value, OR, and CI were calculated with logistic regression model by adjusting for age and sex. CHR, chromosome; BP, base pair position; MAF, minor allele frequency; HWE-*p*, the *p* value of Hardy-Weinberg equilibrium; SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval. * A represents the minor allele, B stands for the wild allele.

nificant genetic association with PACG was identified for rs4148568 after correction for age and sex using logistic regression (Table 2) and the association remained significant after Bonferroni correction ($p = 0.046$). In linkage disequilibrium analysis, rs9838667, rs1016752, rs4912517, rs1401999, rs6767306, and rs7620781 were found to be in one linkage disequilibrium block (Fig. 1), and a haplotype TCGGAG showed a significant association with PACG ($p = 0.00567$); after 10,000 permutations, the association still survived ($p = 0.0364$; Table 3).

Since the recruited participants included two ethnicities, we also performed a subanalysis within the Hui and Han groups. After correction for age and sex using logistic regression, rs4148568 was found to be associated with PACG in the Han cohort ($p = 0.009858$), while rs4912517 was associated with PACG in the Hui cohort ($p = 0.02587$) (Table 4). However, the significances were lost after the Bonferroni correction. A meta-analysis of the two different ethnicities was then performed, in which rs4148568 still showed significant association with PACG, and the meta-analysis *p* value ($p = 0.004606$) was almost the same as that in the initial overall analysis (Table 4). In addition, rs4912517 was found to be of significant heterogeneity between Hui and Han groups ($I^2 = 71.28\%$, *p* value of *Q* test = 0.0621) (Table 4).

In the association testing between the ten SNP genotypes and ocular biometric parameters AL and ACD using generalized estimation equation (GEE) tests, we found rs4148568 was associated with the AL ($p = 0.008$), the variant allele of which may have effect of making the AL longer ($\beta = 0.092$) (Table 5); however, this association was lost after the Bonferroni correction ($p = 0.08$).

The powers of this study for these ten SNPs are therefore different because of the differences of their minor allele frequencies. Assuming an allelic odds ratio of 1.29 (derived from the GWAS by Nongpiur et al. [5], the odds ratio of rs1401999 in Beijing Chinese cohort), our sample size provides more than 75% of statistical power to detect a significant association at the α level of 0.05 with the exception of rs1016752, of which the statistical power is 53.9%.

Discussion

We explored the associations of tag SNPs in *ABCC5* gene with PACG and the ocular biometric parameters ACD and AL in a northern Chinese population in our study. The SNP rs4148568 and a haplotype TCGGAG were associated with PACG significantly, and the variant

Fig. 1. Six SNPs are presented to the one haplotype block in HapMap CHB population, which were determined by the Haploview 4.2 program. Darker shades suggest higher linkage disequilibrium. SNPs, single-nucleotide polymorphism.

Table 3. Haplotype frequencies in PACG and control cohorts

SNP	Haplotype	Freq of cases (%)	Freq of controls (%)	OR [#]	<i>p</i> value [#]	<i>p</i> permutation [*]
rs9838667, rs1016752, rs4912517, rs1401999, rs6767306, rs7620781	TGGCGA	0.09962	0.1019	0.99	0.949	1
	TCGCGA	0.078	0.08422	1.03	0.86	1
	TCGGAG	0.00497	0.02335	0.241	0.00567	0.0364
	GCGGAG	0.4009	0.3852	0.945	0.558	0.993
	TCTGGG	0.2413	0.2382	1.12	0.309	0.8881
	GCGGGG	0.156	0.1481	1.06	0.645	0.998

PACG, primary angle closure glaucoma; SNP, single-nucleotide polymorphism; OR, odds ratio. [#] OR and *p* value were calculated with logistic regression model by adjusting for age and sex. ^{*} A total of 10,000 permutations were performed.

allele of rs4148568 was simultaneously found to be nominally correlated with a longer AL. *ABCC5*, known as multidrug-resistant protein 5 (*MRP5*), has been reported to play a role in tissue defense and cellular signal transduction [14, 15]. It is expressed in most human tissues, including cornea, ciliary body, lens and retinal pigment epithelial cells, and retina [5, 16, 17]. Nongpiur et al. [5] found that *ABCC5* gene was associated with ACD and weakly associated with the AL, and the rs1401999 locus, which is located in the intronic region, was associated with an increase in the risk of PACG. Tang et al. [18]

evaluated the association of some exons in *ABCC5* and its 3 adjacent and strongly linked genes with PACG in order to find out any coding variants associated with PACG in this region; unfortunately, no significant association was found between the target loci and PACG. Nevertheless, in our study, the notable association between *ABCC5* and PACG was indeed confirmed. Interestingly, the original positive association between rs1401999 and PACG was not replicated, while another locus rs4148568 and a haplotype TCGGAG containing the wild allele G of the rs1401999 locus were verified to be associated with PACG.

Table 4. Association between SNPs and PACG in different ethnicities and results of meta-analysis

SNP	<i>p</i> value		OR (95% CI)		<i>p</i> meta	OR-meta	<i>I</i> ²	<i>p</i> het
	Hui	Han	Hui	Han				
rs112754234	0.2575	0.4786	1.267 (0.841–1.91)	1.078 (0.8753–1.329)	0.2536	1.1144	0	0.4914
rs9838667	0.438	0.837	1.18 (0.7771–1.79)	0.9784 (0.7944–1.205)	0.8701	1.0157	0	0.4311
rs1016752	0.7834	0.9614	0.9198 (0.5067–1.67)	0.9915 (0.7012–1.402)	0.8573	0.9729	0	0.831
rs4912517	0.02587	0.8354	1.665 (1.063–2.607)	1.026 (0.807–1.304)	0.3376	1.2575	71.28	0.0621
rs1401999	0.3464	0.7118	0.7747 (0.4554–1.318)	1.051 (0.8075–1.368)	0.9309	0.9896	1.59	0.3134
rs6767306	0.4599	0.1847	0.8465 (0.5441–1.317)	0.8681 (0.7043–1.07)	0.1299	0.8641	0	0.9195
rs7620781	0.4787	0.5208	0.8268 (0.4886–1.399)	1.09 (0.8381–1.417)	0.7957	1.0315	0	0.3569
rs6773408	0.3776	0.4181	0.8192 (0.526–1.276)	1.098 (0.8758–1.376)	0.748	1.0335	24.98	0.2483
rs4148568	0.241	0.009858	0.7284 (0.4289–1.237)	0.7091 (0.5461–0.9206)	0.004606	0.7128	0	0.929
rs1879258	0.9713	0.05553	0.9918 (0.6323–1.556)	0.8064 (0.6469–1.005)	0.08269	0.8393	0	0.4184

OR, odds ratio; CI, confidence interval; *I*², measures heterogeneity; *p* het, *p* value for heterogeneity; *p* value, OR, and CI were calculated with logistic regression model by adjusting for age and sex. SNPs, single-nucleotide polymorphisms; PACG, primary angle closure glaucoma; OR-meta, OR obtained by meta-analysis; *p* meta, *p* value obtained by meta-analysis; if the *I*² value was ≥50%, it takes the value of random-effects; otherwise, a fixed-effects *q* model was adopted.

Table 5. Association between SNPs, and AL and ACD

SNP	Minor allele	AL (22.92±0.891; 20.01–25.51)*			ACD (2.74±0.474; 0.67–4.51)*		
		<i>B</i>	95% CI	<i>p</i> value	<i>B</i>	95% CI	<i>p</i> value
rs112754234	C	0.015	−0.066–0.096	0.714	0.022	−0.017–0.062	0.267
rs9838667	T	−0.033	−0.107–0.04	0.373	0.001	−0.037–0.04	0.944
rs1016752	G	−0.062	−0.187–0.064	0.337	−0.022	−0.083–0.039	0.485
rs4912517	T	−0.008	−0.096–0.079	0.85	0.006	−0.037–0.05	0.774
rs1401999	C	−0.065	−0.159–0.03	0.178	−0.022	−0.072–0.028	0.384
rs6767306	A	0.037	−0.044–0.118	0.37	−0.004	−0.045–0.038	0.856
rs7620781	A	−0.062	−0.157–0.034	0.207	−0.012	−0.061–0.037	0.629
rs6773408	G	−0.061	−0.145–0.023	0.156	−0.019	−0.061–0.023	0.379
rs4148568	T	0.092	0.024–0.160	0.008	0.002	−0.048–0.052	0.925
rs1879258	G	0.05	−0.033–0.132	0.239	0.004	−0.04–0.049	0.844

p, *p* value for association, adjusting for age and sex; SNPs, single-nucleotide polymorphisms; AL, axial length; ACD, anterior chamber depth. * The mean±SD, and the range of measured values of AL, or ACD; β, per-allele effect in ACD/AL.

Based on our result, we hold the view that the rs1401999 locus may act in the pathogenesis of PACG through synergistic action with other loci in our cohort since there was no linkage disequilibrium between rs4148568 and rs1401999, while pairwise *r*² is less than 0.1. Besides that, the obvious heterogeneity at the *ABCC5* locus among the different populations (the *I*² value of which was 60.6%) in the GWAS by Nongpiur et al. [5] maybe another consideration not to be neglected, resulting in the inconsistency about the associated locus. Hence, a comprehensive case-control association study between *ABCC5* and PACG in

different populations should be further explored to more completely understand the role of this gene. Similarly, no association was identified between rs1401999 and ACD as well as AL, but rs4148568 was found to be nominally associated with the AL in the present study, and the variant allele of rs4148568 may have effect of making the AL longer. The association of the rs4148568 locus with PACG and its possible role in the regulation of AL will provide new clues to understand the mechanism of *ABCC5* gene in PACG.

In general, binocular biometric parameters can better reflect the genetic characteristics, thus, considering the potential correlation between binocular data, we used GEE in our study since GEE is suitable for statistical analysis of correlated data [19, 20] to evaluate the association between genotypes and ocular biometric parameters. Although the association between rs4148568 and the AL was no longer significant after multiple testing corrections, as we know, the Bonferroni correction is known to be conservative for positively correlated p values [21], and the corrected p value was very close to 0.05 in our result. Hence, to some extent, we still infer that the *ABCC5* gene plays a role in the pathogenesis of glaucoma by directly or indirectly regulating the AL. Further analysis is still required to identify the veritable correlation and how they contribute to PACG.

In the subgroup analyses within two different ethnic groups, rs4912517 was nominally associated with PACG in the Hui cohort and found to be of significant heterogeneity between Hui and Han groups; in view of that the Hui sample size included in this study was small (93 cases of PACG, 129 controls), the exact association between the rs4912517 locus and PACG in Hui population is worth further exploring. The meta-analysis of the two different ethnic groups was then performed, and the results were consistent with those of the initial overall analysis. This consequence further confirms that the results of our initial analysis are reliable.

Several limitations of our study should be noted. First, the statistical power of our current sample size which is used to evaluate the association within two different ethnic groups is not strong enough. Second, many ocular biometric parameters were closely related to PACG, but in the present study, only the AL and ACD were included to assess the correlation. Therefore, more in-depth study with a large sample size is still necessary in the future.

In summary, the present case-control study validates the association between *ABCC5* and PACG; meanwhile, rs4148568 in *ABCC5* might be associated with the AL, the

variant allele of which may have effect of making the AL longer. Further research is needed to elucidate the exact mechanism of *ABCC5* in the progress of PACG.

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Statement of Ethics

This study was approved by the Ethics Committee of the People's Hospital of Ningxia Hui Autonomous Region (No. 2016-031) and met the tenets of the Declaration of Helsinki, and written informed consent was obtained from all of the subjects prior to the study.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

S.W. performed clinical examinations, carried out the technical work in the laboratory, wrote the manuscripts, and analyzed the data; W.Z. supervised the overall study, wrote the manuscripts, and analyzed the data; W.Z., M.X., W.L., S.P., Z.X., and B.C. carried out the technical work in the laboratory, including patient's requirements, and reviewed the files for clinical information; S.H. performed clinical examinations and supervised the overall study. All authors read and approved the final manuscript.

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