

Association Study in a South Indian Population Supports rs1015213 as a Risk Factor for Primary Angle Closure

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PURPOSE. Three loci defined by single nucleotide polymorphisms (SNPs) rs11024102 in *PLEKHA7*, rs3753841 in *COL11A1*, and rs1015213 between the *PCMTD1* and *ST18* genes, recently have been associated with primary angle closure glaucoma (PACG). We explored the genetic association of these SNPs with subtypes of primary angle closure in a South Indian population.

METHODS. The study included three case definitions: primary angle closure/primary angle closure glaucoma (PAC/PACG, $N = 180$); primary angle closure suspect (PACS, $N = 171$), and a combined any-angle closure group. Controls consisted of 411 individuals from South India. Genotyping for all three SNPs was performed using the TaqMan allelic discrimination assay. Genetic association was estimated using a χ^2 test statistics and logistic regression.

RESULTS. Among the three studied SNPs, significant genetic association was identified for rs1015213 in the PAC/PACG ($P = 0.002$) and any-angle closure ($P = 0.003$) analyses. However, no significant genetic association was seen when in PACS subjects ($P = 0.052$). SNPs rs3753841 and rs11024102 showed no evidence of genetic association with angle-closure phenotypes ($P > 0.05$) in South Indian participants.

CONCLUSIONS. In our study, rs1015213 (located in the intergenic region between *PCMTD1* and *ST18*) was associated significantly with PAC/PACG, confirming prior reports of an association between this region and angle closure glaucoma. Further work with a larger sample size is necessary to confirm the importance of *COL11A1* and *PLEKHA7* in the pathogenesis of glaucoma.

Keywords: PACG, *PCMTD1-ST18*, South India

Glaucoma is the second leading cause of blindness worldwide. Clinically, it is characterized by progressive retinal ganglion cell damage and distinctive optic neuropathy¹ with or without elevated intraocular pressure.² Primary angle closure glaucoma (PACG), in which the iris abuts most of the trabecular meshwork, is less common than primary open angle glaucoma (POAG), though it accounts for nearly 50% of glaucoma-related blindness.³ In 2020, it is predicted that PACG prevalence will reach 21 million, with roughly 5 million bilaterally blind cases.⁴ In fact, it has been estimated that PACG blinds more people than POAG worldwide, mostly in Asian countries.⁵⁻⁷ Identifying risk factors for PACG is particularly relevant, as patients with PACG are likely to have progression through primary angle closure suspect (PACS) or primary angle closure (PAC) before reaching PACG. Fellow eyes of patients presenting with acute angle closure are unlikely to suffer progression to glaucoma after laser iridotomy, suggesting that iridotomy may prevent PAC progression in at least some instances.⁸

Genetic factors have been studied extensively for their role in the pathogenesis of PACG. Family history is found to be a

consistent risk factor, which suggests a strong genetic predisposition to this disease.⁹⁻¹² First degree relatives of PACG patients have been estimated to be at 6 to 9 times greater risk of suffering PACG compared to similar relatives of noncases.^{13,14} All these facts strongly suggest that genetic factors are involved in the pathogenesis of PACG. Indeed, genome wide association studies (GWAS) have identified chromosomal loci and candidate genes statistically associated with PACG.

Recently, Vithana et al. conducted a two-stage GWAS to determine the genetic determinants underlying susceptibility to PACG.¹⁵ The first (discovery) stage included 11,854 PACG cases and 9608 controls. It was followed by a second (replication) stage, comprising 1917 PACG cases and 8943 controls from five different ethnic groups. The study found a genome-wide significant association between PACG and three genetic markers: rs11024102 in *PLEKHA7*, rs3753841 in *COL11A1*, and rs1015213 located between *PCMTD1* and *ST18* on chromosome 8q. These results have implicated specific genetic loci in PACG susceptibility, though further studies are required to confirm these associations.

Furthermore, it is unclear whether these genes simply predispose individuals to iridotrabecular contact (which might be found as an isolated finding in PACS) or whether they are risk factors for later disease stages (i.e., PAC and PACG). The current study was done to replicate the findings of Vithana et al.¹⁵ in a South Indian population. Subanalyses also were conducted to determine the association of these markers in PAC patients with varying disease severity (PACS and PAC/PACG).

METHODS

All subjects were recruited from the Pondicherry and Madurai Glaucoma Clinics of the Aravind Eye Hospital. Both clinics are located in the South Indian state of Tamil Nadu. All subjects read and signed informed consent except for illiterate subjects, who had the information leaflet read out to them and provided a thumb impression. The study complied with the tenets of the Declaration of Helsinki, and ethics approval was received from the Institutional Review Board of the Aravind Eye Hospital, Madurai, Tamil Nadu, India.

Study Subjects

All subjects, including cases and controls, underwent a comprehensive ophthalmic examination, including slit-lamp examination, gonioscopy, visual acuity, and Goldmann applanation tonometry. Fundus examination was performed to assess for optic nerve head and retinal nerve fiber layer findings consistent with glaucoma.

The case group included primary angle closure suspects (PACS, $N = 171$), or either primary angle closure or primary angle closure glaucoma (PAC/PACG, $N = 180$). These stages of angle closure were defined as described by the ISGEO classification system, though PAC and PACG were collapsed into a single category given that reliable visual fields were not available in all subjects.¹⁶ All cases had at least 2 quadrants of iridotrabecular contact (ITC), which prevented visualization of any pigmented trabecular meshwork. Subjects were characterized as having primary angle closure (PAC/PACG) if any of the following characteristics were present: peripheral anterior synechiae (PAS), elevated IOP >21 mm Hg, cup-to-disc ratio of 0.7 or greater, notching of the optic nerve, or other findings suggesting glaucomatous optic neuropathy. Angle closure patients without any of the aforementioned characteristics were classified as PACS. An “any-angle closure” group also was defined, and consisted of PACS and PAC/PACG cases.

The control group comprised of 411 ethnically matched individuals from South India, recruited between 2008 and 2012. The controls were age- and sex-matched with respect to the PAC/PACG group. However, this matching could not be achieved for the PACS group, possibly because of more individuals in lower age range and female sex biased nature of the disease (Table 1).

Patients with secondary angle closure glaucoma due to uveitis, trauma, or neovascularization, or some other optic nerve injury affecting either eye were excluded. Control subjects had no clinical signs or symptoms of PACG, no family history of glaucoma, and no other ophthalmic diseases besides cataract.

Genotyping

Genomic DNA was extracted using peripheral blood by a modification of the method described by Miller et al.,¹⁷ or from saliva using the OrageneDNA/Saliva extraction kit (DNA Genotek, Inc., Ottawa, Ontario, Canada). Extracted DNA was

stored at -20°C until use. Genotyping of each of the three single nucleotide polymorphisms (SNPs; rs11024102, rs3753841, and rs1015213) was performed using a real-time based allelic discrimination TaqMan SNP assay (Applied Biosystems, Foster City, CA). Real-time PCR was performed using 2.5 μL of TaqMan Universal PCR master mix, 0.125 μL of 40 \times primer probe, and 0.375 μL MilliQ water and 2 μL of DNA sample (20 ng/ μL). PCR cycling conditions consisted of 50 $^{\circ}\text{C}$ for 2 minutes, 95 $^{\circ}\text{C}$ for 10 minutes, and 40 cycles of amplification (95 $^{\circ}\text{C}$ denaturation for 15 seconds, 60 $^{\circ}\text{C}$ annealing/extension for 1 minute). Reactions were performed in 384-well MicroAmp Optical reaction plates using the ABI 7900 HT Fast Real-time thermo-cycler. The post assay analysis was performed using the associated SDS (Sequence Detection Systems) software version 2.3. Genotypes on the allelic discrimination plot with a quality value $\geq 96\%$ and a Ct value between 21 and 30 were included in the results.

Power Calculations and Statistical Analysis

Power calculations were performed with the statistical package QUANTO, Version 1.2.4 using the following assumptions¹⁸: an additive genetic model, per-allele odds ratios (OR) equal to those of the combined analyses from Vithana et al.,¹⁵ risk allele frequencies (RAF) equal to the Gujarati Indian in Houston (GIH) HapMap population (these were within 0.01 of CEU HapMap frequencies for all three SNPs), baseline risk of affection ranging from 1% to 5%, 1-sided P value thresholds of 0.05 (nominal significance [NomS]) and 0.0167 (experiment-wise significance [EWS]), and either 180 or 351 cases and 411 controls. The estimated power was nearly identical for baseline risks between 1% and 5% for all SNPs. Hence, we reported the mean power across all baseline risk values.

Using 351 cases, the power to detect a per-allele OR of 1.5 with a population risk allele frequency of 0.09 for rs1015213 (*PCMTD1-ST18*) was 0.79 for nominal significance and 0.62 for experiment-wise significance. For rs3753841 (*COL11A1*, RAF = 0.35, OR = 1.20), the estimated power was 0.53 for NomS and 0.34 for EWS. The statistical power to detect an association signal at rs11024102 (*PLEKHA7*, RAF = 0.28, OR = 1.22) was 0.55 at NomS and 0.27 at EWS. When using 180 cases from the PACG/PAC group only and 411 controls, the power to detect an association for rs1015213 was 0.64 at NomS and 0.45 at EWS. For rs3753841 and rs11024102, the power for NomS was approximately 0.40, and between 0.23 and 0.25 for EWS.

All statistical analyses were performed using STATA software version 11.0 (STATA Corporation, College Station, TX). Categorical variables were expressed as frequencies (percentages). Continuous variables were expressed as mean \pm SD and compared across groups using Student's t -test. For each SNP, genotype and allele frequency were calculated. Genotype frequencies of all the three SNPs were consistent with Hardy-Weinberg's expectations among controls ($P > 0.05$). A χ^2 test was used to evaluate genotypic association. Logistic regression was used to calculate ORs with 95% confidence intervals (CI) for allelic association tests. For logistic regression association analyses, a one-sided P value less than 0.05 was considered NomS and a 1-sided Bonferroni-adjusted P value of 0.05/3 (0.0167) was used for EWS.

RESULTS

The study included a total of 180 PAC/PACG cases (76 males and 104 females) with a mean age 55.6 ± 7.8 years, and 171 PACS cases (43 males and 128 females) with a mean age 51.5 ± 7.2 years. The control group contained 411 subjects (165 males and 246 females) with a mean age of 56.9 ± 7.9 years.

TABLE 1. Demographic Features of Cases and Control Group

Group Variables	Cases			Controls, N = 411
	PACS, N = 171	PAC/PACG, N = 180	Any-Angle Closure Group, N = 351	
Sex				
Male	43	76	119	165
Female	128	104	232	246
P value, χ^2 test	0.001	0.636	0.076	
Age, y				
Mean \pm SD	51.46 \pm 7.17	55.63 \pm 7.75	53.60 \pm 7.75	56.89 \pm 7.93
Range	30-67	40-9	30-69	40-69
P value, <i>t</i> -test	<0.001	0.076	<0.001	

P value comparison among the cases and control group was determined by *t*-test. P values ≤ 0.05 were considered significant; value > 0.05 indicates age-matched group. All groups were age- and sex-matched except PACS possibly because of more individuals in lower age range.

TABLE 2. Genotype and Allele Frequencies of rs1015213 Among Different Cases and Control Groups

rs1015213 (PCMTD1-ST18)		Genotype				Allele				
Group	N	CC	CT	TT	P Value	C	T	P Value	OR (95% CI)	
PACS	Cases	171	117 (68.4%)	51 (29.8%)	3 (1.7%)	0.109	285 (83.3%)	57 (16.6%)	0.052	1.34 (0.92-1.92)
	Control	411	313 (76.1%)	89 (21.7%)	9 (2.2%)		715 (87%)	107 (13%)		
PAC/PACG	Cases	180	118 (65.5%)	54 (30%)	8 (4.5%)	0.021	290 (80.5%)	70 (19.5%)	0.002	1.61 (1.14-2.27)
	Control	411	313 (76.1%)	89 (21.7%)	9 (2.2%)		715 (87%)	107 (13%)		
Any-angle closure group	Cases	351	235 (67%)	105 (29.9%)	11 (3.1%)	0.019	575 (81.9%)	127 (18.1%)	0.003	1.48 (1.10-1.97)
	Control	411	313 (76.1%)	89 (21.7%)	9 (2.2%)		715 (87%)	107 (13%)		

P values ≤ 0.05 were considered nominally significant, and P values < 0.0167 were considered experiment-wise significant.

The any-angle closure group consisted of all 351 cases (119 men and 232 women) from the PAC/PACG and PACS groups. All subjects were of South Indian origin. Study sample characteristics are shown in Table 1.

The genotype and allele frequencies for each of the SNPs rs1015213, rs3753841, and rs11024102 were calculated in cases and controls (Tables 2-4, respectively). The genotype and allele frequencies of each SNP were compared between controls and a case group consisting of PAC/PACG cases only, PACS cases only, or any-angle closure group. Among the three studied SNPs, significant genetic association was identified for rs1015213 when analyzing a group consisting of PAC/PACG subjects and controls ($P = 0.002$), or when analyzing the combined any-angle closure group ($P < 0.003$). However, statistically significant association was not achieved for rs1015213 when cases were defined as subjects with PACS ($P = 0.052$, Table 2). In all case groups (PACS, PAC/PACG, and any-angle closure group), the frequency of the rs1015213 T allele was higher in cases (16.6%, 19.5%, 18.1%, respectively) than among controls (13%) indicating T as a risk allele with

ORs 1.34, 1.61, and 1.48, respectively. For rs3753841, no genetic association was observed in analyses consisting of controls and PACS subjects (allelic $P = 0.213$), controls and PAC/PACG subjects (allelic $P = 0.127$), or control and cases in the any-angle closure group (allelic $P = 0.116$, Table 3). The frequency of the G allele of rs3753841 was higher in cases (47% PACS, 48% PAC/PACG, and 47.5% in the any-angle closure group) than in controls (44.3%). SNP rs11024102 also did not show statistical evidence of genetic association in analyses consisting of controls and PACS subjects (allelic $P = 0.15$), controls and PAC/PACG subjects (allelic $P = 0.105$), or controls and subjects with any-angle closure group (allelic $P = 0.079$, Table 4). The frequency of the C allele was higher in cases (34.5% PACS, 35.1% PAC/PACG, 34.8% any-angle closure group) than controls (31.4%).

DISCUSSION

Three loci defined by SNP markers rs11024102 in *PLEKHA7*, rs3753841 in *COL11A1*, and rs1015213 located in an

TABLE 3. Genotype and Allele Frequencies of rs3753841 Among Different Cases and Control Groups

rs3753841 (COL11A1)		Genotype				Allele				
Group	N	GG	GA	AA	P Value	G	A	P Value	OR (95% CI)	
PACS	Cases	164	40 (24.4%)	74 (45.1%)	50 (30.5%)	0.459	154 (47%)	174 (53%)	0.213	1.11 (0.85-1.46)
	Control	360	71 (19.7%)	177 (49.2%)	112 (31.1%)		319 (44.3%)	401 (55.7%)		
PAC/PACG	Cases	176	41 (23.2%)	87 (49.5%)	48 (27.3%)	0.520	169 (48%)	183 (52%)	0.127	1.16 (0.89-1.51)
	Control	360	71 (19.7%)	177 (49.2%)	112 (31.1%)		319 (44.3%)	401 (55.7%)		
Any-angle closure group	Cases	340	81 (23.8%)	161 (47.4%)	98 (28.8%)	0.411	323 (47.5%)	357 (52.5%)	0.116	1.14 (0.92-1.41)
	Control	360	71 (19.7%)	177 (49.2%)	112 (31.1%)		319 (44.3%)	401 (55.7%)		

P values ≤ 0.05 were considered nominally significant, and P values < 0.0167 were considered experiment-wise significant.

TABLE 4. Genotype and Allele Frequencies of rs11024102 Among Different Cases and Control Groups

rs11024102 (<i>PLEKHA7</i>)		Genotype				Allele				
Group	N	CC	CT	TT	P Value	C	T	P Value	OR (95% CI)	
PACS	Cases	171	14 (8.2%)	90 (52.6%)	67 (39.2%)	0.051	118 (34.5%)	224 (65.5%)	0.15	1.15 (0.87–1.52)
	Control	397	42 (10.6%)	165 (41.6%)	190 (47.8%)		249 (31.4%)	545 (68.6%)		
PAC/PACG	Cases	178	24 (13.5%)	77 (43.2%)	77 (43.2%)	0.461	125 (35.1%)	231 (64.8%)	0.105	1.18 (0.90–1.55)
	Control	397	42 (10.6%)	165 (41.6%)	190 (47.8%)		249 (31.4%)	545 (68.6%)		
Any-angle closure group	Cases	349	38 (10.8%)	167 (47.9%)	144 (41.3%)	0.176	243 (34.8%)	455 (65.2%)	0.079	1.17 (0.94–1.46)
	Control	397	42 (10.6%)	165 (41.6%)	190 (47.8%)		249 (31.4%)	545 (68.6%)		

The number of cases and controls for each SNP varies slightly due to random genotypic failure in allele discrimination assay. *P* values ≤ 0.05 were considered nominally significant, and *P* values < 0.0167 were considered experiment-wise significant.

intergenic region between *PCMTD1* and *ST18* have been identified as genetic risk factors for PACG.¹⁵

However, the genetic factors involved in angle closure may have differential roles depending on ethnicity, sex, environment, and severity of the disease. The involvement of genetic risk factors in disease pathogenesis can be understood better by studying their association across different ethnic groups and disease severity. In our study, we examined the association of three recently identified SNPs lying in or near *PCMTD1-ST18*, *PLEKHA7*, and *COL11A1* genes with two subtypes of primary angle closure (PAC/PACG and PACS) in a South Indian population.

In our study, we investigated separately the association of rs1015213 with early (PACS) and later (PAC/PACG) stages of angle closure glaucoma. This strategy was deliberately chosen, as the initial findings associating rs1015213 with PACG could have resulted from a genetic predisposition to iridotrabeular contact, or from a predisposition to progression to PAC/PACG from iridotrabeular contact. The genetic association of rs1015213 in the *PCMTD1-ST18* genetic locus was confirmed in our PAC/PACG group. Statistically significant association at rs1015213 was not seen when cases were defined as PACS alone; its effect size and direction (OR = 1.34 per T allele), however, was consistent with the PAC/PACG group as well as the estimates from the original GWAS (OR = 1.5 per T allele). This suggested that the locus may predispose to later stages of disease (i.e., those occurring after iridotrabeular contact already is present) to a greater extent than to milder forms of angle closure. Nevertheless, this finding also may have been the result of random sampling error and/or a higher misclassification rate in the PACS group compromising our (already limited) statistical power in subgroup analyses. The associated marker rs1015213 on chromosome 8q is positioned within an intergenic region 120 kb upstream of *PCMTD1* (NM_052937) and 130 kb downstream of *ST18* (NM_014682).¹⁵ *PCMTD1* encodes protein-L-isoaspartate O-methyltransferase domain-containing protein 1, whose function has not been well characterized. The gene *ST18* (suppression of tumorigenicity 18) encodes a Zinc finger DNA binding protein and has been known as a breast cancer tumor suppressor gene.¹⁹ Recently, a few studies also have shown it as a mediator of apoptosis and inflammation.²⁰ The association of rs1015213 provides evidence supporting *ST18* as a candidate gene for angle closure within this locus. The original GWAS showed that the linkage disequilibrium (LD) block within the location of rs1015213 extends towards *PCMTD1*, but not into *ST18*, suggesting that *PCMTD1* may be a more likely candidate gene for PACG susceptibility than *ST18*. This also is supported by the higher gene expression of *PCMTD1* in trabecular meshwork compared to *ST18* which has very limited expression in trabecular meshwork.¹⁵

The other two SNPs (rs3753841 in *COL11A1* and rs11024102 in *PLEKHA7*) were not found to be associated in our study with any of the case groups. SNP rs3753841 lies within the coding region of *COL11A1* causing a nonsynonymous (c.3968C > T) change that leads to substitution of proline to leucine at 1323 amino acid position (NM_001854.3). The rs11024102 locus contains the *PLEKHA7* gene, which encodes a pleckstrin-homology-domain-containing protein 7 involved in the stability and maintenance of adherence junction's (AJ) between the cells.^{21,22}

There was no statistical evidence for an association of rs3753841 (*COL11A1*) and rs11024102 (*PLEKHA7*) with angle closure in our study. However, these SNPs had comparatively small effect sizes in the original GWAS (per-allele OR = ~1.20) and our power to detect association at the SNPs was limited even at nominal significance levels (using 180 cases, the power was 0.4 at *P* = 0.05 and 0.24 at *P* = 0.0167). The original GWAS study included 3771 PACG cases and 18,551 controls, whereas our study contains 180 PAC/PACG cases and 411 controls. Interpopulation differences in LD patterns also may have contributed to the discrepancies between the studies. Gene- or locus-based replication study designs can be more powerful than single SNP analyses when the tested SNP is in LD with the causal variant, or when there is genetic heterogeneity. Hence, a more thorough search for potentially causal variants should be undertaken with a more highly powered study and more harmonized diagnostic criteria to confirm these loci in the South Indian population.

Overall, our study in a South Indian population replicates findings of a large GWAS implicating rs1015213 (*PCMTD1-ST18*) in the pathogenesis of PAC. On the other hand, we found no statistical evidence of association for SNPs rs3753841 (*COL11A1*) and rs11024102 (*PLEKHA7*) with angle closure phenotypes. The nonsignificant associations of *PLEKHA7* and *COL11A1* may have been influenced by a relative lack of statistical power, which could be overcome by increasing the sample size in future studies. Therefore, large studies groups will be required to confirm these associations in different ethnic groups and correctly interpret negative findings.

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