15 Recent Advances in our Understanding of the Genetic Basis of Primary Angle-Closure Glaucoma

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Abstract

The etiology of primary angle-closure glaucoma (PACG) is multifactorial but much is still to be investigated. Environmental or inducible factors are not evidently identified. Gene variants confirmed in association with PACG account for less than 5% of PACG heritability. Considerably smaller number of genes were mapped and less gene variants known to associate with PACG than primary open-angle glaucoma (POAG), another major form of glaucoma. But PACG loci are clearly distinctive from the associated gene variants of POAG. The genetic components of PACG include large ethnic differences in prevalence, familial trends of occurrence, the heritability of phenotype and susceptible genes which are identified principally by candidate gene investigations, familial linkage analyses, and genome-wide association studies (GWAS). The only PACG endophenotype with known genetic association is anterior chamber depth. More PACG genes will be mapped by GWAS and whole-genome sequencing with family analysis. Genotype-phenotype correlation studies on big cohorts with longitudinal follow up for the establishment of pharmacogenomics database and genetic biomarkers will be key areas of attention for PACG.

Keywords

PACG · Heritability · Ethnicity · Genes Phenotypes

15.1 Introduction

Primary angle-closure glaucoma (PACG) is a complex disease with multifactorial etiology, which involves complicated anatomical, physiological and genetic mechanisms [1]. Narrow to closed anterior chamber angle, pupillary block, and plateau iris are essential anatomical features in PACG. The former is a pre-requisite of obstruction to aqueous outflow in the trabecular mesh-

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work. Pupillary block is usually a triggering factor for acute angle-closure attack [2]. The plateau iris is a common cause of persistent occludable angle after iridotomy [3]. PACG is also linked to other anatomical abnormalities, such as shortened axial length, shallowed anterior chamber depth, and increased lens volume as seen in cataract. Environmental risk factors for PACG are not readily quantifiable, except that aging plays an important role. Angle-closure glaucoma (ACG) can be secondary to ocular diseases like chronic uveitis and rubeosis iridis that lead to synechial angle closure. ACG can also develop with some congenital conditions, mainly nanophthalmos and Axenfeld Rieger Syndrome, which are resulted from angle dysgenesis [4–6]. Therefore, there has to be differentiation of primary and secondary forms of ACG for treatment plan since the pathology is so different. The genetic basis for such complex disease mechanisms is understandably complicated [7]. However, in comparison with primary open-angle glaucoma (POAG), another major glaucoma form, there is currently no gene known to cause PACG directly [8]. The number of genes confirmed to have an association with PACG is also limited.

Albeit such complex mechanistic background with unknown environmental risk, the genetic basis of PACG is evidently attributed to ethnic diversities in prevalence, familial linkage, and phenotype heritability [9, 10]. Genes with strong and clear susceptibility for PACG have been mapped by candidate gene approach, family linkage analysis, and genome-wide association study (GWAS) [8, 11].

15.2 Genetic Epidemiology of PACG

PACG prevalence is known to be diversified among different ethnic populations, in general lower in Caucasians and higher in Asian populations [7]. Its occurrence was noticeably high in the Inuit population including Eskimos in the Arctic regions. Almost 5% of the Eskimos populations over 40 years old in Greenland and Alaska have PACG, about 40 times higher than Europeans [12, 13]. In a systemic review of PACG studies in Europeans published during 1948–2011, PACG prevalence for people over 40 years old was 0.4% (95% confidence interval [CI]: 0.3%–0.5%), with female to male ratio 3.25 to 1 [14]. PACG occurs more in Asians than Europeans. In a meta-analysis and review of 50 population-based studies, PACG is the highest in Asia at 1.09% (95% CI: 0.43–2.32%) against 0.60% (95% CI: 0.16–1.48%) in Africa, 0.42% (95% CI: 0.13–0.98%) in Europe, and 0.26% (95% CI: 0.03–0.96%) in North America [15]. When two big Indian studies were included in the meta-analysis, PACG prevalence in Asia was decreased to 0.73% (95% CI: 0.18–1.96%) [16]. It is notable in this study that in contrast to POAG, in which the prevalence is essentially similar among different Asian populations, PACG at age between 40 and 80 years occurs more in East Asia (Mongolia, China, Korea, and Japan) at 1.07% (95% CI: 0.28–2.74%), than South Central Asia (India, Iran, Nepal, and Sri Lanka) at 0.69% (95% CI: 0.13–2.07%) or South East Asia (Singapore, Myanmar, and Thailand) at 0.64% (95% CI: 0.19–1.49%). People in East Asia are 5.55 times (95% CI: 1.52–14.73) more likely than people in South East Asia to develop PACG after adjustment for gender and age [16]. Overall in Asia, males aged between 40 and 80 years have a higher likelihood to have POAG (odds ratio [OR]: 1.37, 95% CI: 1.17–1.59) than females, but less to have PACG (OR: 0.54, 95% CI: 0.41–0.71). For this age range, people of urbanized habitation have less PACG at 0.73% than rural living people at 0.94%. Notably, the trend was reversed for POAG, 2.24% against 1.53%. In a recent study in Eastern India, with 7408 people living in rural areas and 7248 in cities, PACG is also higher in rural living at 1.03% (95% CI: 0.99–1.07%) than in city dwellers at 0.97% (95% CI: 0.94–1.00%) [17].

In Chinese, a meta-analysis of 11 population-based studies conducted in different parts of China during January 1990 to July 2010 involving 35,968 adult Chinese reported a pooled PACG prevalence of 1.4% (95% CI: 1.0–1.7%), with women more likely to have PACG than men (OR: 1.75; 95% CI: 1.20–2.56; $P = 0.004$) [18].

In a recent meta-analysis of 30 cross-sectional studies reported between 1995 and 2016 from various regions of China, PACG prevalence was 1.40% (95% CI: 1.17–1.68%) for Chinese aged between 45 and 89 years [19]. There was also less PACG male patients than females (OR: 0.53; 95% CI: 0.46–0.60) [19]. PACG prevalence was reportedly 0.5% (95% CI: 0.3–0.7%) in a rural population aged over 40 years in the Handan of northern China [20]. In the same population, the prevalence of primary angle closure was higher at 1.5% (95% CI: 1.2–1.8%) and even higher for primary angle-closure suspects at 10.4% (95% CI: 9.6–11.2%). Moreover, females are more likely to develop PACG than males with an OR ranging from 1.75 to 1.89 ($P < 0.05$) [18–20]. Occurrence of POAG was similar, with an overall prevalence at 1.02% (95% CI: 0.67–1.57%) [21].

Ethnic differences in the prevalence of PACG and gender bias in disease susceptibility indicated the presence of genetic influences. In terms of environmental influence, rural living poses a higher risk than urbanized inhabitation.

15.3 Sporadic and Familial PACG

Sporadic PACG is usually late-onset with disease incidence increases with age. Familial history is also long known to be a risk factor across all populations [7, 22, 23]. In Greenland Eskimos, who are Inuit by race, family history poses more than three times risk of PACG [12]. A high heritability of narrow angle of about 60% has been revealed in a study of 100 Chinese probands with 327 first-degree relatives [24]. Among the 515 sibling pairs, a high probability of 50% was detected for narrow angle, with a sevenfold increase in likelihood of narrow angle when compared with the general population.

In 303 South Indian sibling pairs, primary angle closure (PAC)/PACG was found in 11.4% of PAC/PACG siblings but only in 4.9% of primary angle-closure suspects (PACS) siblings ($P = 0.07$) and even none in open-angle (OA) siblings ($P = 0.002$). There was more angle closure in PACS (35.0%) and PAC/PACG siblings (36.7%) than in OA siblings (3.7%; $P < 0.001$). Multivariable analysis after adjustment for age and gender revealed a 13.6-fold of higher likelihood of having angle closure if one has angle-closure siblings than with OA siblings (95% CI: 4.1–45.0; $P < 0.001$) [25]. In a recent study also in southern India of 636 sibling pairs (482 PACS and 154 PAC/PACG), the occurrence of PAC/PACG among siblings of PAC/PACG was 8.4%, which was higher than the 3.5% of PAC/PACG among siblings of PACS [26]. In Central Asia, familial segregation of angle closure was also reported in an Iranian study, with siblings of PACG patients at higher risk [27].

15.4 Phenotype Heritability

Hereditability of anatomical and ophthalmic features in relation to both major forms of glaucoma, POAG and PACG, have been reported in different ethnic populations. Compared with the general population, PACG has greater central cornea thickness (CCT), shorter axial length (AL), shallower anterior chamber depth (ACD), bigger cup-to-disc ratio, and narrower angle width. These are independent risk factors [17]. Intraocular pressure (IOP) is one dominant risk factor for PACG. Its heritability has been estimated to range from 0.36–0.50 [24, 28]. In Greenland Eskimos, the corneoscleral size was found to be inheritable [13]. For cup-to-disc ratio, the heritability ranged from 0.48 to 0.80 [29, 30]. The variance in drainage angle width in Chinese children appeared to be largely attributable to genetic effects, with a heritability of approximately 70% [31]. The variance of optic nerve head parameters, namely disc area (DA), cup area (CA), and cup/disc area ratio (CDAR) appears to be attributable to additive genetic and unshared environmental effects. Approximately 80% of these phenotypic variances are genetically determined [32]. Genetic variants have been tested in a recent study on Chinese PACG patients, and three SNPs, rs3753841 in *COL11A1*, rs1258267 in *CHAT,* and rs736893 in *GLIS3*, were associated with PACG and also had a mild association with ACD [33]. In the same cohort, rs7290117 in *ZNRF3* was associated with axial length in PACG

patients, but not with PACG [34]. Besides, a number of genetic variants associated with the endophenotypes of glaucoma had been identified in population-based samples. A SNP rs1015213 at the *PCMTD1-ST18* locus has been associated with ACD in a European population [35]. SNP rs33912345 in *SIX6*, a POAG gene, has been associated with optic disc parameters in Europeans [36], and retinal nerve fiber layer thickness in Europeans and Chinese [36, 37]. Three SNPs (rs7126851, rs7104512, and rs10835818) in the *ELP4* gene, which neighbors and plays a crucial role in the expression of *PAX6*, were associated with disc area in Caucasians [38]. In a GWAS of optic disc parameters in population-based cohorts, SNPs at chromosomal regions 1p22 (near *CDC7*), 10q21.3-q22.1 (near *ATOH7*), and 16q12.1 were associated with optic disc area, and SNPs at 9p21 (near *CDKN2B*), 14q22.3-q23 (near *SIX1*), 11q13, 13q13, 17q23, and 22q12.1 were associated with vertical cup-to-disc ratio [39].

15.5 Mapping the PACG Genes by Candidate Gene Analysis

Many attempts have been made to map PACG genes in different ethnic populations utilizing cohorts of PACG patients and controls [9]. A candidate gene analysis has led to the identification of nine genes associated with PACG (Table 15.1). In a meta-analysis, we summarized all reported genetic associations from candidate gene analysis and affirmed five genes (*HGF*, *HSP70*, *MFRP*, *MMP9,* and *NOS3*) to be associated with primary angle-closure disease [10]. Most candidate gene association studies did not involve a big sample size. Some of the genes have not been replicated. They are statistically linked to susceptibility to PACG, not directly causative. Understanding of the functions and properties of these genes have given some clues to the disease mechanism but not the elucidation of the pathogenesis [9]. It is notable that *MTHFR* and *HGF* have been linked to the regulation of axial length, and shorter axial length is a trait of PACG.

Different investigation strategies other than direct comparison of patient and control genotypes have recently identified novel PACG genes. In an exploration of gene expressions in peripheral blood of Korean patients with acute PACG, microarray analysis of RNA extracted from mononuclear cells showed upregulation of 347 gene transcripts and downregulation of 696 transcripts by more than twofold than controls. Further molecular studies including RT-PCR have confirmed the association of PACG with thrombospondin-1 (TSP-1), transforming growth factor (TGF-β1), and prostaglandin-endoperoxide synthase (2PGE2) [54]. In a big Iranian pedigree with 8 affected individuals with PAC, confirmed PACG, and PACS, investigations by extensive family linkage analysis, segregation analysis, whole-genome sequencing, and sequence screening of other unrelated patients and controls have identified *COL18A1* mutations evident for causing the iridocorneal angle closure in these patients [53]. Future work on the structural and functional roles of type XVIII collagen, especially in the human iris and cornea, should help to reveal the pathophysiology of angle closure.

15.6 Mapping the PACG Genes by Genome-wide Association Studies

So far three major GWAS have been conducted for PACG, having identified 9 genes with specific polymorphisms associated with PACG with high statistical significance (Table 15.2). The primary cohort was mixed in ethnicities and validation has been conducted in multiple ethnic populations including Caucasians, Indians, Malays, Chinese, Koreans, and Japanese [55, 59, 61]. In a previous meta-analysis, we have assessed replication studies on the GWAS SNPs reported by Vithana E et al. [55] and Nongpiur ME et al. [59], and affirmed 3 of them, rs11024102 of *PLEKHA7*, rs3753841 of *COL11A1* rs1015213 of *PCMTD1-ST18*, to be significantly associated with PACG (Table 15.2) [10]. In subsequent replication studies, three of the associated SNPs, rs1015213 of *PCMTD1-ST18*, rs3816415 of *EPDR1*, and rs3739821 of *DRM2-FAM102A* showed consistent associations with PACS in a

Table 15.1 Candidate genes mapped for primary angle-closure glaucoma

Chromosomal location	Gene	Associated variant	Study population and sample size	Year of report	References
1p36.22	*MTHFR* Methylenetetrahydrofolate reductase	C677T, A1298C	Pakistanis 122 PACG, 143 controls	2009	[40]
		rs1537514 CC genotype	Chinese 232 PACG 306 controls	2016	[41]
2p22.2	*CYP1B1* Cytochrome P450 1B1	(−13 T > C, R48G, A119S, V432L, D449D, and N453S) C-C-G-G-T-A	Indian 90 PACG, 200 controls	2007	[42]
2q32.1	*CALCRL* Calcitonin receptor-like receptor	*CALCRL* gene (AATACAGAT)	Australian Caucasians 107 PACG, 288 controls	2012	[43]
		Haplotype T (rs840617) C (rs6759535) T (rs1157699)	Southern Chinese 207 PACG, 205 controls	2009	[44]
4p16.3	*HGF* Hepatocyte growth factor	rs5745718, rs12536657, rs12540393 and rs17427817	Nepalese 106 PACG, 204 controls	2011	[45]
7q36	eNOS Endothelial nitric oxide synthase	27 bp insertion VNTR intron 4 polymorphism	Pakistanis 111PACG, 166 controls	2010	[46]
		rs3793342 and rs7830 Sex age matched. Bonferroni correction	Australian Caucasians 129 PACG, 288 controls	2013	[47]
		No association	Nepalese 106 PACG, 204 controls	2013	[47]
11q23.3	*MFRP* Membrane type frizzled-related protein	Q175X, 492delC, and I182T, 1143insC	Nanophthalmos Amish-Mennonite kindred, 26 Caucasian kindreds	2005	[4]
		rs3814762	Chinese 232 PACG, 306 controls	2013	[48]
19q13.42	*HSP70* Heat shock protein	rs1043618	Chinese 232 PACG, 306 controls	2013	[48]
		rs1043618 G + 190C	Pakistanis 111PACG, 166 controls	2010	[46]
20q13.12	*MMP9* Matrix metalloproteinase 9	rs3918249, rs17576	Australian Caucasians 107 PACG, 288 controls	2011	[49]
		rs2664538	Taiwan Chinese 78 PACG, 86 controls	2006	[50]
		rs2250889	Southern Chinese 211 PACG, 205 controls	2009	[51]
		rs17576	Pakistanis 82 PACG, 118 controls	2013	[52]
21q22.3	*COL18A1* Collagen XVIIIa1	c.550G > A E184 K	Iranian (Genome-wide SNP genotyping, linkage analysis, segregation analysis, and whole exome sequencing were adopted in this study)	2018	[53]

Table 15.2 PACG susceptible genes identified by Genome-Wide Association Studies

Genes	SNPs	GWAS	GWAS significance	References	Study population	Evaluation significance	References	Meta-analysis significance	References
PLEKHA7	rs11024102	3771 PACG 18,551 controls	OR = 1.23 $P = 3.10 \times 10^{-12}$	[55]	Chinese 1397 PACS 943 controls	Insignificant	[56]	OR = 1.24; $P = 8.3 \times 10^{-5}$	[10]
	rs11024102				Indian 180 PAC/PACG 411 controls	Insignificant	[57]		
COL11A1	rs3753841	3771 PACG 18,551 controls	OR = 1.19 $P = 9.53 \times 10^{-9}$	[55]	Chinese 1397 PACS 943 controls	Insignificant	[56]	OR = 1.22; $P = 4.6 \times 10^{-4}$	[10]
	rs3753841				Australian 232 PACG 288 controls Nepalese 106 PACG 204 controls	$P = 0.009$	[58]		
	rs3753841				Indian 180 PAC/PACG 411 controls	Insignificant	[57]		
	rs1031820				Chinese 232 PACG 306 controls	$P = 0.047$	[41]		
PCMTD1-ST18	rs1015213	3771 PACG 18,551 controls	OR = 1.50 $P = 5.36 \times 10^{-9}$	[55]	Chinese 1397 PACS 943 controls	OR = 2.36 $P = 0.002$	[56]	OR = 1.59; $P = 1.3 \times 10^{-4}$	[10]
	rs1015213				Australian 232 PACG 288 controls Nepalese 106 PACG 204 controls	$P = 0.004$	[58]		
	rs1015213				Indian 180 PAC/PACG 411 controls	$P = 0.002$	[57]		

ABCC5	rs1401999	4276 PACG 18,801 controls	OR = 1.13 $P = 0.00046$	[59]					
	rs939336				Chinese 422 PACG 400 controls	OR = 1.46 $P = 0.013$	[60]		
	rs1132776				Chinese 422 PACG 400 controls	$P = 0.007$, OR = 1.51	[60]		
EPDR1	rs3816415	10,503 PACG 29,567 controls	OR = 1.24 $P = 3.49 \times 10^{-15}$	[61]	Chinese 1397 PACS 943 controls	OR = 1.49 $P < 0.001$	[56]		
GLS3	rs736893	10,503 PACG 29,567 controls	OR = 1.18 $P = 1.15 \times 10^{-14}$	[61]	Chinese 1397 PACS 943 controls	Insignificant	[56]		
FERMT2	rs7494379	10,503 PACG 29,567 controls	OR = 1.13 $P = 6.32 \times 10^{-11}$	[61]	Chinese 1397 PACS 943 controls	Insignificant	[56]		
DRM2-FAM102A	rs3739821	10,503 PACG 29,567 controls	OR = 1.15 $P = 6.77 \times 10^{-12}$	[61]	Chinese 1397 PACS 943 controls	OR = 1.40 $P = 0.002$	[56]		
CHAT	rs1258267	10,503 PACG 29,567 controls	OR = 1.22 $P = 3.73 \times 10^{-16}$	[61]	Chinese 1397 PACS 943 controls	Insignificant	[56]		

Chinese cohort [56]. Two SNPs of high GWAS significance, rs11024102 of *PLEKHA7* and rs3753841 of *COL11A1*, were not replicated in a South Indian cohort [57]. The latter, *COL11A1* rs3753841, however, was replicated in a combined cohort of Australian Caucasians and Nepalese patients and controls but not in each individual cohort [62]. Three other GWAS significant SNPs, *GLS3* rs736893, *FERMT2* rs726893, and *GLS3* rs1258267 were also not associated with PACS in Chinese [56] (Table 15.2).

In a GWAS of ACD, genome-wide significant association was observed at an intronic SNP rs1401999 in the *ABCC5* gene [59]. This locus was also associated with an increased risk of PACG, suggesting a shared genetic component between PACG and its endophenotype. After testing tagging SNPs spanning the *PARL-ABCC5-HTR3D-HTR3C* region in 422 Chinese PACG patients and 400 controls all living in urban areas, we have recently revealed significant associations of PACG with 2 synonymous *ABCC5* SNPs, rs939336 (p.Cys594; OR = 1.46; 95% CI:1.08–1.97; P = 0.013;) and rs1132776 (p.Ala395; OR = 1.47; 95% CI: 1.10 to 1.95; P = 0.009) [60].

Among the GWAS associated genes, *PLEKHA7*, which encodes pleckstrin-homology-domain-containing protein 7, a junctional protein, was studied in cultured lens epithelial cells and iris tissue obtained from PACG patients, and non-pigmented ciliary epithelium (h-iNPCE) and primary trabecular meshwork cells [63]. The results revealed *PLEKHA7* to be a novel Rac1/Cdc42 GAP with a regulatory role of Rac1 and Cdc42 in the tight junction permeability of the blood-aqueous barrier. SNP rs11024102 disrupts *PLEKHA7* function, leading to deleterious effects in the blood-aqueous barrier integrity and likely aqueous humor outflow. This is thus a putative mechanism for PACG as caused by *PLEKHA7*.

15.7 Future Perspectives

Advancements in the knowledge of molecular genetics of a disease will benefit patients. Genes known to be causative of a disease can be studied for genetic markers for pre-symptomatic diagnosis and prediction of prognosis. Responses to treatment can be related to genomics. For a disease causative gene, the mechanism and disruptive pathways leading to pathogenesis can be elucidated by investigating the gene functions, properties, and interaction networks. New therapeutic agents can be tested based on the pathology. For PACG, no causative gene has been identified. A number of susceptible genes, with gene variants associated with the disease, are known. But the information is yet insufficient to establish a genetic marker or to throw light to the disease mechanism. GWAS on large samples of well-characterized patients is needed to find more PACG genes. Exome sequencing and whole-genome sequencing together with family linkage and sibling pair studies should help to identify more PACG genes and sequence variants that are responsible for the disease development.

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