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REVIEW

The genetic mechanisms of primary angle closure glaucoma

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Abstract

Primary Angle Closure Glaucoma (PACG) is one of the most common types of glaucoma affecting over 15 million individuals worldwide. Family history and ethnicity are strongly associated with the development of the disease, suggesting that one or more genetic factors contribute to PACG. Although strictly heritable disease-causing mutations have not been identified, a number of recent association studies have pointed out genetic factors that appear to contribute to an individual's risk to develop PACG. In addition, genetic factors have been identified that modify PACG endophenotypes for example, axial length. Herein we review the current literature on this important topic.

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Introduction

The two most common types of clinically characterized glaucoma in humans include primary open-angle (POAG) and angle closure glaucoma (PACG).[1] Both types of glaucoma are characterized by progressive and irreversible destruction of optic nerve axons and degeneration of the retinal ganglion cells (RGCs), frequently in association with increased intraocular pressure (IOP).[2] There are 15.7 million cases of PACG reported worldwide.[3,4] The number of PACG cases is projected to reach 21 million by 2020, and it is estimated that 5.3 million bilaterally will be blind from this condition.[5] The proportion of all cases suffering from significant loss of vision is three times higher in PACG than POAG,[6,7] as considerable damage can occur before symptoms become apparent. The absence of symptoms makes the condition difficult to detect and results in a large proportion of cases being undiagnosed and untreated, which significantly increases the risk for blindness in affected individuals.

Etiology and classification criteria

PACG is characterized by apposition of the peripheral iris against the trabecular meshwork resulting in obstruction of aqueous outflow by closure of an already narrow angle of the anterior chamber.[8] Whether this structural alteration solely results in angle closure depends on (1) the baseline position of the iris, (2) the size of the pressure differential, and (3) iris–lens channel resistance.[9,10] The PACG eye typically displays a shallow anterior chamber, increased thickness of the lens, hyperopic refractive error, and short axial length.

In the human eye, the two most commonly identified mechanisms of PACG are pupillary block and plateau iris. In pupillary block, the iris dilates and moves posteriorly at the pupillary margin, which increases resistance to the flow of aqueous humor into the anterior chamber.[11] This in turn creates a relative pressure gradient between the posterior and anterior chambers, and causes the iris to move forward and contact the trabecular meshwork, which results in aqueous blockage at (i) the pupillary margin and (ii) the trabecular meshwork. Repeated episodes of pupillary block may produce intermittent symptoms of acutely elevated IOP and lead to the development of peripheral anterior synechiae.

Plateau iris occurs when the ciliary body is positioned anteriorly or rotated forward causing the anterior displacement of the peripheral iris in relation to the trabecular meshwork, thus leading to an occluded iridocorneal angle. The condition is characterized by a relatively deep central anterior chamber and a centrally flat iris plane[12] causing either persistent angle closure or angle closure and elevated IOP upon pupillary dilation despite a patent laser iridotomy. Recent studies have shown that plateau iris, once thought to be a rare cause of angle closure, may be present in up to a third of cases of PACG.[13]

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The identification of genetic loci associated with PACG has suffered in part from the loose and indiscriminant use of the term PACG to indicate disease. This is problematic as the term is frequently used without specifying the presence of optic neuropathy, and it does not denote a quantifiable risk of vision loss.[14] Furthermore, the diagnosis of the disease has been primarily based on the detection of presenting symptoms despite their absence in the chronic form of the disease.[15–19] In an effort to address these issues, several attempts at classifying the subtypes of PACG have been made over the years.[20–23] In epidemiological studies of PACG the presence of an 'occludable angle' is frequently used as a measure to estimate glaucoma, as it is an important disease predisposing trait. An occludable angle is equated to PACG if the posterior trabecular meshwork is seen in $<90°$ of the angle circumference.[24]

PACG risk factors

There are a number of predisposing factors that have been extensively studied in an attempt to explain the observed geographic and racial variations in the prevalence of PACG. Among the demographic risk factors, such as age and sex, race is the most prominent disease risk factor.[25] PACG and POAG have dissimilar incidence rates in different populations. On average, PACG is three times more common in Asian populations compared to European-derived populations.[26–28] In Europeans, POAG contributes to ~62%, while PACG accounts for only 6% of all reported glaucoma incidences.[25] On the other hand, PACG is particularly prevalent in Eskimos as well as in Chinese and Asian Indians.[29] Chinese PACG patients account for 47.5% of the total number of PACG cases worldwide[5] and it is likely that PACG is responsible for the vast majority (91%) of bilateral glaucoma blindness in that country.[7,30,31] It is also estimated that 28 million people in China have an occludable drainage angle.

In addition to geographic and population-specific patterns of PACG prevalence, the incidence of the disease increases with age.[32] The manifestations of ocular damage as a result of PACG are rarely observed in cases below the age of 40 years. Moreover, females are at greater risk of developing PACG than males.[32,33] Studies estimating global disease prevalence have shown that females represent 59% of all glaucoma cases, but 70% of all PACG cases.[5,34]

The configuration of the eye itself is perhaps the most prominent PACG risk factor. The reported anatomic risk factors for angle closure glaucoma include short axial length, small corneal diameter, shallow anterior chamber, steep curvature, and thick, relatively anteriorly positioned lens.[35–38] A small anterior segment represents a major risk factor with limbal and axial anterior chamber depth being the traits most strongly correlated with ACG.[39–41] In eyes with hyperopia or shallow anterior chamber depth, the iris is repositioned so that its anterior movement during dilation blocks the iridocorneal angle. This can lead to an acute entrapment of aqueous fluid behind the iris and a rapid increase in IOP. In a population-based study in South Africa, individuals of Southeast Asian descent with hyperopia showed increased predisposition for PACG.[42]

The association between older age, female gender, and angle closure might be explained by basis of differences in anterior segment biometry. Females and individuals of older age tend to present with smaller eyes and narrower anterior chamber depth (ACD). Eskimo women were found to have shallower ACD than men from the same population.[43] Several studies have demonstrated that individuals of Eskimo or Chinese descent present with shallower ACD than those of European descent and are therefore at greater risk for PACG.[44–47] One possible mechanism explaining the increased risk of PACG in older individuals is the steady expansion of the crystalline lens throughout life. This leads to shallowing of ACD and narrowing of the iridocorneal angle, a condition known as phacomorphic glaucoma.[48,49]

The baseline position of the iris relative to the cornea is another inherent anatomical factor that predisposes certain individuals and populations over others, to angle narrowing and subsequent outflow impediment. One model established by Tiedman to explain iris behavior predicts that the forward movement of the iris increases with a more anterior lens position and with a mid-dilated pupil, thus increasing the risk of angle occlusion.[50]

The genetics of PACG

The ethnicity and gender-specific predisposition to PACG suggests a genetic basis for the development of PACG in certain populations. There is strong evidence that glaucoma in humans is influenced by genetic factors and that it is a complex, multifactorial disease. The reported high incidence of PACG among siblings of affected patients further suggests the involvement of genetic factors in pathology of the disease.[51] Family history is one of the major risk factors for glaucoma and heritability estimates have shown that there is 3.7 times higher risk to develop the disease for the siblings than the general population.[52,53] In Eskimos, the prevalence of PACG in any first-degree relatives of affected individuals is reported to be at least 3.5 times higher than in the general population,[43] and a population-based survey in China revealed that any family history of glaucoma results in a sixfold increase in risk of PACG.[54] Significant heritability of PACG was also indicated through the study of Chinese monozygotic and dizygotic twins.[55] Previous studies in Chinese twins and nuclear families also reported high

heritability estimates for IOP, which supports the role of genetic effects in the segregation of IOP among families.[55,56] Moreover, it has been shown that the size of the anterior chamber is strongly determined by genetic components, suggesting that morphological characteristics predisposing to PACG are also heritable.[52,53]

Recent advances have indicated several genes and genetic loci[57–60] that may be causative for POAG, but evidence for genes causing PACG remains sparse. The first evidence for a genetic locus linked to familial PACG comes from the analysis of a large family with nanophthalmos, hyperopia, and angle closure glaucoma.[61] This study has led to the identification of the gene nanophthalmos 1 (*NNO1*) on chromosome 11. *NNO1* is currently the only human gene known to cause an angle closure glaucoma phenotype (Table 1).

In contrast, a number of genetic loci have been identified that may not be causative, but enhance an individual's risk to develop PACG (Table 1). A recent, genome-wide association study (GWAS) in an Asian population of PACG identified three PACG susceptibility loci in *PLEKHA7*, *COL11A1*, and within *PCMTD1* and *ST18*.[62] *COL11A1* is a particularly interesting gene as it encodes one of the two alpha chains of type XI collagen, which is highly expressed in the scleral tissue. Several studies provide further evidence for the potential role of collagen in glaucoma. Alterations in collagen deposition impact the biomechanical and remodeling capabilities of the sclera and could thereby result in glaucoma-predisposing axial length changes and associated refractive errors.[63] A single-nucleotide polymorphism (SNP) in the gene *COL1A1* is associated with increased risk of myopia in a Japanese and Chinese Han populations[64,65] and it is conceivable that other genetic variants result in conformational changes to the anterior segment that predispose toward the development of the disease. However, differences in collagen composition of the sclera may be correlated with suboptimal optic nerve head biomechanics, resulting in increased susceptibility to axonal damage in glaucomatous eyes.[66,67]

The extracellular composition of the sclera is influenced and modified as a result of intraocular pressure fluctuations[68] and PACG-associated variants have also

Table 1 A review of genes identified in linkage or association with PACG and/or PACG predisposing traits

Gene	*Phenotype*	*Location*	*Authors*
NNO1	Nanophthalmos, hyperopia and ACG	11p13	Othman *et al*[61]
PLEKHA7, COL11A1, PCMTD1 and *ST18*	PACG	11p15, 1p21, 8q11.23	Vithana *et al*[62]
COL1A1	Myopia	1p21	Inamori *et al*,[64] Zhang *et al*[65]
MMP9	PACG	20q13.12	Awadalla *et al*,[73] Cong *et al*,[69] Wang *et al*,[70] Micheal *et al*[71]
MTHFR	PACG, anterior segment extracellular matrix (ECM) remodeling	1p36.3	Micheal *et al*[76]
MFRP	PACG	11q23.3	Wang *et al*,[77] Aung *et al*,[72] Shi *et al*[103]
MFRP	Autosomal recessive nanophthalmos, short axial length, high degree of hyperopia, high lens-to-eye-volume ratio and small corneal diameter	11q23.3	Sundin *et al*[79]
CHX10	PACG	14q24.3	Aung *et al*[72]
HGF	PACG and hyperopia	7q21.1	Awadalla *et al*,[86] Jiang *et al*[85]
RSPO1, C3orf26, LAMA2, GJD2, ZNRF3, CD55, MIP, ALPPL2 and *ZC3H11B*	Axial length regulation	1p34.3, 3q12.1, 6q22.33, 15q14, 22q12.1, 1q32, 12q13, 2q37, 1q41	Cheng *et al*[87]
PRSS56	ACG, posterior microphthalmia	2q37.1	Nair *et al*[93]
ABCC5	PACG, ACD regulation	3q27	Nongpiur *et al*[94]
MYOC	ACG	1q24.3	Faucher *et al*,[98] Dai *et al*[100]
CYP1B1	PACG	2p22.2	Chakrabarti *et al*,[101] Dai *et al*[100]
eNOS	PACG, ACD regulation	7q36	Ayub *et al*,[102]
HSP70	PACG	19q13.42	Ayub *et al*,[102] Shi *et al*[103]
SPARC	PACG, IOP regulation	5q33.1	Yan *et al*,[109] Chua *et al*,[104] Haddadin *et al*[110]
CALCRL	Acute PACG	2q32.1	Cao *et al*[111]
NEB	Canine PACG		Ahram *et al*[118]

been identified in the matrix metalloproteinase-9 (*MMP9*) gene, which encodes an enzyme participating in tissue remodeling. These studies include a GWAS of PACG in a Southern-Chinese population that implicated the SNP rs2250880 in *MMP9 in* association with the disease.[69] A different SNP (rs17576) within the same gene was identified in association with increasing risk for PACG in studies of acute PACG in a Taiwanese as well as a Pakistani patient cohort.[70,71] The same variant, however, was not found to display a statistically significant association with PACG in Singaporean patients.[72] In addition, two risk variants (rs3818249 and rs17576) in the *MMP9* were identified in association with PACG in an Australian Caucasian population, which further supports the role of *MMP9* in conferring risk for PACG.[73] It was suggested that variants in *MMP9* affect protein function by impairing its ability to remodel extracellular matrices. It has also been shown that *MMP9* among several other MMPs are present in the aqueous humor and may be involved in mechanisms of IOP regulation.[74,75]

In addition, several PACG-associated risk conferring variants have been identified in the membrane-type frizzled related protein (*MFRP*) gene, methylenetetrahydrofolate reductase (*MTHFR*) gene, and retinal homeobox gene *CHX10*.[76,77] *MFRP* and *CHX10* are thought to be involved in the regulation of eye size and axial length of the eye.[72,77] Mutations in *MFRP* to cause autosomal recessive nanophthalmos, which is characterized by short axial length, a high degree of hyperopia, a high lens-to-eye-volume ratio, as well as a small corneal diameter.[78,79] One function of *MTHFR* appears to be the remodeling of connective tissue and the extracellular matrix (ECM) of the anterior segment.[76] On the other hand, the combined genotype of two *MTHFR* polymorphisms (C677T and A1298C) was associated with PACG, but also correlated with high homocysteine serum levels in patients in a Punjabi study.[76] Elevated plasma levels of the sulfur-containing amino-acid homocysteine can elicit a DNA damage response in neurons and promote apoptosis and vulnerability to excitotoxicity.[80] Furthermore, homocysteine may directly induce retinopathy through damage specifically to RGC, but not to other retinal neurons and photoreceptors.[81,82] It must be cautioned that data with regard to the association of *MTHFR* variants with PACG is conflicting, which may suggest that the presence of polymorphism of this gene vary in different ethnic populations.[76,83] For example, a recent case-control study in a north Indian population did not provide evidence for an association of *MTHFR* variant C677T with PACG. Rather this study found that this variant is associated with POAG.[84] This may suggest that the pathogenic effect of *MTHFR* mutations is primarily related to homocysteine toxicity leading to RGC loss, which is a characteristic feature of all types of glaucoma.

Another gene with possible function in axial length regulation is hepatocyte growth factor (*HGF*). Variants in this gene have been reported in association with PACG and hyperopia in the Nepalese and Han Chinese populations, two conditions sharing the features of reduced axial length and shallow AC depth.[85,86] A recent meta-analysis of genome-wide associations for ocular axial length was conducted in patients of European and Asian ethnicity displaying refractive errors, which along with hyperopia and myopia is majorly determined by axial length. Nine genome-wide significant loci for axial length were identified including *RSPO1*, *C3orf26*, *LAMA2*, *GJD2*, *ZNRF3*, *CD55*, *MIP*, *and ALPPL2 and ZC3H11B*.[87] Variation in gene expression was observed for these loci in a minus-lens-induced myopia mouse model and human ocular tissues. Furthermore, *RSPO1* and *ZNRF3* have been previously described to influence Wnt signaling, a pathway implicated in the regulation of eyeball size.[88–91] Members of the R-Spondin family, which includes *RSPO1*, appear to act as potent activators of the Wnt/β-catenin signaling pathway by inhibiting the cell-surface transmembrane ZNRF3.[89,92] Associations to genes implicated in axial length regulation have also been identified in animal-based genetic studies. A novel serine protease-encoding gene (*PRSS56*) was identified in association with reduced axial length in a mouse model with an ACG-like phenotype.[93] Variations in *PRSS56* were also found to cause significant reduction in the ocular axial length of individuals with posterior microphthalmia in the same study. In a recent GWA study of ACD and PACG in an Asian cohort, variants in the ATP-binding cassette, sub-family C (CFTR/MRP), and member 5 encoding gene (*ABCC5*) were found to influence ACD and increase the risk of PACG development.[94] *ABCC5* has been shown to participate in tissue defense and cellular signal transduction mechanisms.[95] The findings of this study support the role of ACD-modifying variants in mediating risk to PACG. Collectively, data from these studies suggest that multiple genes contribute to the regulation of ocular axial length and AC depth, which ultimately determines the potential risk for developing ACG.

Investigation of associations between PACG and the open angle glaucoma genes myocilin (*MYOC*), optineurin (*OPTN*), WDR 36 and cytochrome P450 (*CYP1B1*) in middle-eastern patients failed to identify risk-conferring variants.[96] Similarly, no risk-conferring associations to *MYOC* were identified in a Chinese PACG cohort[97] despite reports of *MYOC* association in a study of PACG in a Quebec population.[98,99] On the basis of these results, it is unlikely that *MYOC* is a major contributor to the development of the PACG, contrary to its positive association with POAG.

On the other hand, a positive association to *CYP1B1*, a gene implicated in the development of congenital glaucoma, was identified in studies of PACG in patients of Chinese, Indian, and Canadian origin.[100,101] Likewise, variants in the endothelial nitric oxide synthase (*eNOS*) and heat-shock protein 70 (*HSP70*) have been identified in association with PACG in a Pakistani population.[102] A weak association of *HSP70* with PACG was additionally identified a Han Chinese population.[103] In this study, *eNOS* was found to display a positive association with anterior chamber depth regulation, thus hinting at its possible role in the pathogenesis of PACG.

Additionally, a significant increase in the expression of secreted protein, acidic and rich in cysteine (*SPARC*) in the iris of PACG patients recruited at the Singapore National Eye Centre (SNEC) was noted in comparison with healthy controls, suggesting a possible role for *SPARC* in PACG.[104] SPARC is a matricellular protein, which is involved in ECM remodeling and regulation of collagen I incorporation into tissues by binding directly to various collagen fibrils.[105–107] SPARC is present in aqueous humor and is produced by trabecular meshwork endothelial cells.[108,109] *SPARC*-null mice reportedly display lower IOP than wild-type animals, which suggests a potential role for *SPARC* in regulating IOP.[110]

Furthermore, investigation of two patient cohorts of Southern Chinese origin with acute and chronic PACG has led to the identification of an association between *CALCRL* polymorphisms and acute but not chronic PACG.[111] CALCRL (calcitonin receptor like) and related receptors are a family of G-protein-coupled receptors that comprise several subtypes. The activity of this receptor is mediated by G proteins, which activate adenylyl cyclase. Overexpression of this gene has been found to result in pupillary sphincter muscle relaxation, closure of the anterior chamber angle and obstruction of the aqueous outflow leading to elevation of IOP.[112]

Heritability is also conferred through mitochondria. The analysis of this genetic material is not trivial since each cell contains several genetically heterogeneous mitochondria. Furthermore, age and stress further induce somatic mutations in the mtDNA population and these likely differ between ocular cells and those found in peripheral blood lymphocytes that are commonly used for genetic analyses. Data in support[113,114] and opposition[96,115] of mitochondrial changes in PACG have been presented, but the study size was often modest. It is hoped that the introduction of high throughput sequencing technologies will stimulate research in this area and lead to unequivocal data.

Additional insight into the genetics of PACG may also be obtained through genetic analysis of several dog breeds with a predisposition toward the disease. A recent GWA study of PACG in the Basset Hound resulted in the identification of two susceptibility loci on chromosome 14 (*COL1A2*) and chromosome 24 (*RAB22A*).[116] In addition, a GWA study of a late onset form of PACG described in a Dandie Dinmont Terrier cohort has led to the identification of a novel susceptibility locus on canine chromosome 8.[117] A recent study in a pedigree of Basset Hounds with PACG implicated variations in *NEB* (Nebulin), a large protein of the sarcomere that is highly expressed in the ciliary muscle of the eye.[118] These variations were also found to be associated with the disease in a study of unrelated Basset Hounds. These findings imply that ciliary muscle tone may be important in maintaining an open configuration of the iridocorneal angle.

Finally, as a complex disease it is likely that environmental risk factors participate in the development of PACG. Several population-based studies have reported associations of PACG attacks with sun exposure, temperature and atmospheric pressure levels. In a Singaporean study conducted to identify demographic and meteorological risk factors associated with acute PACG, a higher incidence of attacks was reported on days where the temperature was high.[119] Conversely, a Finnish study assessing the association between sun exposure and risk for acute ACG suggested that the number of hours without sunshine is positively associated with the incidence of acute closed angle glaucoma, when other meteorological variables are controlled for.[120] Acute attacks were also reported to occur more frequently in the same population group in winter and autumn than summer or spring.[120] A common factor among all these studies and environmental effects is thought to be that during adverse weather conditions people tend to stay indoors. This may increase the likelihood of a mydriatic-induced acute ACG attack due to pupillary dilation and a subsequent spike in IOP.[121] Yet, to date it is unknown whether these environmental factors are more significant in patients with certain genetic predispositions.

Conclusion

It has long been appreciated that angle closure glaucoma is associated with certain populations and families, suggesting that genetics contribute to the development of the disease. More recently, systematic investigations of large patient cohorts have revealed a number of genetic loci that are associated with PACG. The effect of each of these loci is relatively small and these studies indicate that additional genes remain to be identified. However, the conducted studies were carried out with a sufficiently large number of samples to indicate a genetic factor contributing to an overwhelming fraction of PACG probably does not exist. Rather PACG is a complex disease

with numerous genes contributing to morphologic and biochemical features placing an eye at risk.

It is likely that larger population based studies will eventually reveal additional PACG loci, but a more successful approach may lie in the study of genes regulating the development of endophenotypes, eg axial length. Such studies have already yielded convincing data that can be used to evaluate specific anatomic, functional, or ethnic aspects of PACG.

Conflict of interest

The authors declare no conflict of interest.

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