

The genetic mechanisms of primary angle closure glaucoma

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REVIEW

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 plane¹² 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 $<90^\circ$ 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 worldwide⁵ 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 fluctuations⁶⁸ 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
<i>NNO1</i>	Nanophthalmos, hyperopia and ACG	11p13	Othman <i>et al</i> ⁶¹
<i>PLEKHA7</i> , <i>COL11A1</i> , <i>PCMTD1</i> and <i>ST18</i>	PACG	11p15, 1p21, 8q11.23	Vithana <i>et al</i> ⁶²
<i>COL1A1</i>	Myopia	1p21	Inamori <i>et al</i> , ⁶⁴ Zhang <i>et al</i> ⁶⁵
<i>MMP9</i>	PACG	20q13.12	Awadalla <i>et al</i> , ⁷³ Cong <i>et al</i> , ⁶⁹ Wang <i>et al</i> , ⁷⁰ Micheal <i>et al</i> ⁷¹
<i>MTHFR</i>	PACG, anterior segment extracellular matrix (ECM) remodeling	1p36.3	Micheal <i>et al</i> ⁷⁶
<i>MFRP</i>	PACG	11q23.3	Wang <i>et al</i> , ⁷⁷ Aung <i>et al</i> , ⁷² Shi <i>et al</i> ¹⁰³
<i>MFRP</i>	Autosomal recessive nanophthalmos, short axial length, high degree of hyperopia, high lens-to-eye-volume ratio and small corneal diameter	11q23.3	Sundin <i>et al</i> ⁷⁹
<i>CHX10</i>	PACG	14q24.3	Aung <i>et al</i> ⁷²
<i>HGF</i>	PACG and hyperopia	7q21.1	Awadalla <i>et al</i> , ⁸⁶ Jiang <i>et al</i> ⁸⁵
<i>RSPO1</i> , <i>C3orf26</i> , <i>LAMA2</i> , <i>GJD2</i> , <i>ZNRF3</i> , <i>CD55</i> , <i>MIP</i> , <i>ALPPL2</i> and <i>ZC3H11B</i>	Axial length regulation	1p34.3, 3q12.1, 6q22.33, 15q14, 22q12.1, 1q32, 12q13, 2q37, 1q41	Cheng <i>et al</i> ⁸⁷
<i>PRSS56</i>	ACG, posterior microphthalmia	2q37.1	Nair <i>et al</i> ⁹³
<i>ABCC5</i>	PACG, ACD regulation	3q27	Nongpiur <i>et al</i> ⁹⁴
<i>MYOC</i>	ACG	1q24.3	Faucher <i>et al</i> , ⁹⁸ Dai <i>et al</i> ¹⁰⁰
<i>CYP11B</i>	PACG	2p22.2	Chakrabarti <i>et al</i> , ¹⁰¹ Dai <i>et al</i> ¹⁰⁰
<i>eNOS</i>	PACG, ACD regulation	7q36	Ayub <i>et al</i> , ¹⁰²
<i>HSP70</i>	PACG	19q13.42	Ayub <i>et al</i> , ¹⁰² Shi <i>et al</i> ¹⁰³
<i>SPARC</i>	PACG, IOP regulation	5q33.1	Yan <i>et al</i> , ¹⁰⁹ Chua <i>et al</i> , ¹⁰⁴ Haddadin <i>et al</i> ¹¹⁰
<i>CALCRL</i>	Acute PACG	2q32.1	Cao <i>et al</i> ¹¹¹
<i>NEB</i>	Canine PACG		Ahram <i>et al</i> 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 *ALPL2* 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 cohort⁹⁷ 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 in 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.

References

- 1 King A, Azuara-Blanco A, Tuulonen A. Glaucoma. *BMJ* 2013; **346**: f3518.
- 2 Kwon YH, Fingert JH, Kuehn MH, Alward WL. Primary open-angle glaucoma. *N Engl J Med* 2009; **360**(11): 1113–1124.
- 3 Bonomi L. Epidemiology of angle-closure glaucoma. *Acta Ophthalmol Scand Suppl* 2002; **236**: 11–13.
- 4 Cedrone C, Mancino R, Cerulli A, Cesareo M, Nucci C. Epidemiology of primary glaucoma: prevalence, incidence, and blinding effects. *Prog Brain Res* 2008; **173**: 3–14.
- 5 Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol* 2006; **90**(3): 262–267.
- 6 Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol* 2002; **86**(2): 238–242.
- 7 Foster PJ, Johnson GJ. Glaucoma in China: how big is the problem? *Br J Ophthalmol* 2001; **85**(11): 1277–1282.
- 8 Salmon JF. Predisposing factors for chronic angle-closure glaucoma. *Prog Retin Eye Res* 1999; **18**(1): 121–132.
- 9 Ritch R. The treatment of angle-closure glaucoma. *Ann Ophthalmol* 1979; **11**(9): 1373–1375.
- 10 Nazm N, Gandhi M, Dubey S, Pegu J. Angle closure glaucoma. *Ophthalmology* 2009; **116**(12): 2478 author reply 2478–2479.
- 11 Sihota R. An Indian perspective on primary angle closure and glaucoma. *Indian J Ophthalmol* 2011; **59**(Suppl1): S76–S81.
- 12 Kumar RS, Tantisevi V, Wong MH, Laohapojanart K, Chansanti O, Quek DT et al. Plateau iris in Asian subjects with primary angle closure glaucoma. *Arch Ophthalmol* 2009; **127**(10): 1269–1272.
- 13 Kumar RS, Baskaran M, Chew PT, Friedman DS, Handa S, Lavanya R et al. Prevalence of plateau iris in primary angle closure suspects an ultrasound biomicroscopy study. *Ophthalmology* 2008; **115**(3): 430–434.
- 14 Congdon N, Wang F, Tielsch JM. Issues in the epidemiology and population-based screening of primary angle-closure glaucoma. *Surv Ophthalmol* 1992; **36**(6): 411–423.
- 15 Holmin C. Signs of activity and progression in chronic glaucoma. *Acta Ophthalmol Suppl* 1982; **153**: 1–40.
- 16 Weiss DI. Variations of primary angle closure glaucoma: precise diagnosis and treatment. *Ann Ophthalmol* 1976; **8**(1): 79–84.
- 17 Fernsebner W. Early diagnosis of acute angle-closure glaucoma. *Am J Nurs* 1975; **75**(7): 1154–1155.
- 18 Pollack IP. Chronic angle-closure glaucoma; diagnosis and treatment in patients with angles that appear open. *Archives of ophthalmology* 1971; **85**(6): 676–689.
- 19 Gorin G. The value of gonioscopy in the diagnosis and treatment of angle closure glaucoma. *Bibl Ophthalmol* 1957; **12**(47): 125–131.
- 20 Chen XY, Cai Y. Epidemiology and classification of primary angle-closure glaucoma today. *Zhonghua Yan Ke Za Zhi* 2011; **47**(10): 949–952.
- 21 Ge J. Scientific controversy to push the progress of glaucoma practice—inspiration by the debate on the classification of primary angle closure glaucoma. *Zhonghua Yan Ke Za Zhi* 2006; **42**(11): 964–966.
- 22 Zhao JL. How to face the new classification of primary angle closure glaucoma. *Zhonghua Yan Ke Za Zhi* 2006; **42**(11): 961–963.
- 23 Murphy MB, Spaeth GL. Iridectomy in primary angle-closure glaucoma. Classification and differential diagnosis of glaucoma associated with narrowness of the angle. *Arch Ophthalmol* 1974; **91**(2): 114–122.
- 24 Foster PJ, Aung T, Nolan WP, Machin D, Baasanhu J, Khaw PT et al. Defining "occludable" angles in population surveys: drainage angle width, peripheral anterior synechia, and glaucomatous optic neuropathy in east Asian people. *Br J Ophthalmol* 2004; **88**(4): 486–490.
- 25 Lowe RF. Primary angle closure glaucoma: geographic and racial variations. *Trans Ophthalmol Soc N Z* 1973; **25**: 81–84.
- 26 Foster PJ, Baasanhu J, Alsbirk PH, Munkhbayer D, Uranchimeg D, Johnson GJ. Glaucoma in Mongolia. A population-based survey in Hovsgol province, northern Mongolia. *Arch Ophthalmol* 1996; **114**(10): 1235–1241.
- 27 Foster PJ, Oen FT, Machin D, Ng TP, Devereux JG, Johnson GJ et al. The prevalence of glaucoma in Chinese residents of Singapore: a cross-sectional population survey of the Tanjong Pagar district. *Arch Ophthalmol* 2000; **118**(8): 1105–1111.
- 28 Dandona L, Dandona R, Mandal P, Srinivas M, John RK, McCarty CA et al. Angle-closure glaucoma in an urban population in southern India. The Andhra Pradesh eye disease study. *Ophthalmology* 2000; **107**(9): 1710–1716.
- 29 Coleman AL. Glaucoma. *Lancet* 1999; **354**(9192): 1803–1810.
- 30 Sun XH. Glaucoma surgery in China: problems and solutions. *Zhonghua Yan Ke Za Zhi* 2009; **45**(1): 5–7.
- 31 Quigley HA, Congdon NG, Friedman DS. Glaucoma in China (and worldwide): changes in established thinking will decrease preventable blindness. *Br J Ophthalmol* 2001; **85**(11): 1271–1272.
- 32 Foster PJ, Alsbirk PH, Baasanhu J, Munkhbayer D, Uranchimeg D, Johnson GJ. Anterior chamber depth in Mongolians: variation with age, sex, and method of measurement. *Am J Ophthalmol* 1997; **124**(1): 53–60.
- 33 Vajaranant TS, Nayak S, Wilensky JT, Joslin CE. Gender and glaucoma: what we know and what we need to know. *Curr Opin Ophthalmol* 2010; **21**(2): 91–99.
- 34 Thylefors B, Negrel AD, Pararajasegaram R, Dadzie KY. Global data on blindness. *Bull World Health Organ* 1995; **73**(1): 115–121.
- 35 Tarongoy P, Ho CL, Walton DS. Angle-closure glaucoma: the role of the lens in the pathogenesis, prevention, and treatment. *Surv Ophthalmol* 2009; **54**(2): 211–225.

- 36 Alsbirk PH. Limbal and axial chamber depth variations. A population study in Eskimos. *Acta Ophthalmol (Copenh)* 1986; **64**(6): 593–600.
- 37 Lowe RF. A history of primary angle closure glaucoma. *Surv Ophthalmol* 1995; **40**(2): 163–170.
- 38 Nongpiur ME, Ku JY, Aung T. Angle closure glaucoma: a mechanistic review. *Curr Opin Ophthalmol* 2011; **22**(2): 96–101.
- 39 Foster PJ, Devereux JG, Alsbirk PH, Lee PS, Uranchimeg D, Machin D *et al*. Detection of gonioscopically occludable angles and primary angle closure glaucoma by estimation of limbal chamber depth in Asians: modified grading scheme. *Br J Ophthalmol* 2000; **84**(2): 186–192.
- 40 Bonomi L, Marchini G, Marraffa M, Bernardi P, De Franco I, Perfetti S *et al*. Epidemiology of angle-closure glaucoma: prevalence, clinical types, and association with peripheral anterior chamber depth in the Egna-Neumarket Glaucoma Study. *Ophthalmology* 2000; **107**(5): 998–1003.
- 41 Devereux JG, Foster PJ, Baasanhu J, Uranchimeg D, Lee PS, Erdenbeleg T *et al*. Anterior chamber depth measurement as a screening tool for primary angle-closure glaucoma in an East Asian population. *Arch Ophthalmol* 2000; **118**(2): 257–263.
- 42 Salmon JF, Mermoud A, Ivey A, Swanevelder SA, Hoffman M. The prevalence of primary angle closure glaucoma and open angle glaucoma in Mamre, western Cape, South Africa. *Arch Ophthalmol* 1993; **111**(9): 1263–1269.
- 43 Alsbirk PH. Primary angle-closure glaucoma. Oculometry, epidemiology, and genetics in a high risk population. *Acta Ophthalmol Suppl* 1976; **127**: 5–31.
- 44 Alsbirk PH. Anterior chamber of the eye. A genetic and anthropological study in Greenland Eskimos. *Hum Hered* 1975; **25**(5): 418–427.
- 45 Alsbirk PH. Anterior chamber depth, genes and environment. A population study among long-term Greenland Eskimo immigrants in Copenhagen. *Acta Ophthalmol (Copenh)* 1982; **60**(2): 223–224.
- 46 Alsbirk PH. Early detection of primary angle-closure glaucoma. Limbal and axial chamber depth screening in a high risk population (Greenland Eskimos). *Acta Ophthalmol (Copenh)* 1988; **66**(5): 556–564.
- 47 Wang YE, Li Y, Wang D, He M, Lin S. Comparison of factors associated with occludable angle between american Caucasians and ethnic chinese. *Invest Ophthalmol Vis Sci* 2013; **54**(12): 7717–7723.
- 48 Lowe RF. Causes of shallow anterior chamber in primary angle-closure glaucoma. Ultrasonic biometry of normal and angle-closure glaucoma eyes. *Am J Ophthalmol* 1969; **67**(1): 87–93.
- 49 Tomlinson A, Leighton DA. Ocular dimensions in the heredity of angle-closure glaucoma. *Br J Ophthalmol* 1973; **57**(7): 475–486.
- 50 Tiedeman JS. A physical analysis of the factors that determine the contour of the iris. *Am J Ophthalmol* 1991; **111**(3): 338–343.
- 51 Lowe RF. Primary angle-closure glaucoma. Inheritance and environment. *Br J Ophthalmol* 1972; **56**(1): 13–20.
- 52 Alsbirk PH. Anterior chamber depth and primary angle-closure glaucoma. II. A genetic study. *Acta Ophthalmol (Copenh)* 1975; **53**(3): 436–449.
- 53 Alsbirk PH. Anterior chamber depth and primary angle-closure glaucoma. I. An epidemiologic study in Greenland Eskimos. *Acta Ophthalmol (Copenh)* 1975; **53**(1): 89–104.
- 54 Hu CN. An epidemiologic study of glaucoma in Shunyi County, Beijing. *Zhonghua Yan Ke Za Zhi* 1989; **25**(2): 115–119.
- 55 He M, Wang D, Zheng Y, Zhang J, Yin Q, Huang W *et al*. Heritability of anterior chamber depth as an intermediate phenotype of angle-closure in Chinese: the Guangzhou Twin Eye Study. *Invest Ophthalmol Vis Sci* 2008; **49**(1): 81–86.
- 56 van Koolwijk LM, Despriet DD, van Duijn CM, Pardo Cortes LM, Vingerling JR, Aulchenko YS *et al*. Genetic contributions to glaucoma: heritability of intraocular pressure, retinal nerve fiber layer thickness, and optic disc morphology. *Invest Ophthalmol Vis Sci* 2007; **48**(8): 3669–3676.
- 57 Stone EM, Fingert JH, Alward WL, Nguyen TD, Polansky JR, Sunden SL *et al*. Identification of a gene that causes primary open angle glaucoma. *Science* 1997; **275**(5300): 668–670.
- 58 Rezaie T, Child A, Hitchings R, Brice G, Miller L, Coca-Prados M *et al*. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. *Science* 2002; **295**(5557): 1077–1079.
- 59 Monemi S, Spaeth G, DaSilva A, Popinchalk S, Ilitchev E, Liebmann J *et al*. Identification of a novel adult-onset primary open-angle glaucoma (POAG) gene on 5q22.1. *Hum Mol Genet* 2005; **14**(6): 725–733.
- 60 Pasutto F, Matsumoto T, Mardin CY, Sticht H, Brandstatter JH, Michels-Rautenstrauss K *et al*. Heterozygous NTF4 mutations impairing neurotrophin-4 signaling in patients with primary open-angle glaucoma. *Am J Hum Genet* 2009; **85**(4): 447–456.
- 61 Othman MI, Sullivan SA, Skuta GL, Cockrell DA, Stringham HM, Downs CA *et al*. Autosomal dominant nanophthalmos (NNO1) with high hyperopia and angle-closure glaucoma maps to chromosome 11. *Am J Hum Genet* 1998; **63**(5): 1411–1418.
- 62 Vithana EN, Khor CC, Qiao C, Nongpiur ME, George R, Chen LJ *et al*. Genome-wide association analyses identify three new susceptibility loci for primary angle closure glaucoma. *Nat Genet* 2012; **44**(10): 1142–1146.
- 63 McBrien NA, Cornell LM, Gentle A. Structural and ultrastructural changes to the sclera in a mammalian model of high myopia. *Invest Ophthalmol Vis Sci* 2001; **42**(10): 2179–2187.
- 64 Inamori Y, Ota M, Inoko H, Okada E, Nishizaki R, Shiota T *et al*. The COL1A1 gene and high myopia susceptibility in Japanese. *Hum Genet* 2007; **122**(2): 151–157.
- 65 Zhang D, Shi Y, Gong B, He F, Lu F, Lin H *et al*. An association study of the COL1A1 gene and high myopia in a Han Chinese population. *Mol Vis* 2011; **17**: 3379–3383.
- 66 Norman RE, Flanagan JG, Sigal IA, Rausch SM, Tertinegg I, Ethier CR. Finite element modeling of the human sclera: influence on optic nerve head biomechanics and connections with glaucoma. *Exp Eye Res* 2011; **93**(1): 4–12.
- 67 Downs JC, Ensor ME, Bellezza AJ, Thompson HW, Hart RT, Burgoyne CF. Posterior scleral thickness in perfusion-fixed normal and early-glaucoma monkey eyes. *Invest Ophthalmol Vis Sci* 2001; **42**(13): 3202–3208.
- 68 Huang W, Fan Q, Wang W, Zhou M, Laties AM, Zhang X. Collagen: a potential factor involved in the pathogenesis of glaucoma. *Med Sci Monit Basic Res* 2013; **19**: 237–240.
- 69 Cong Y, Guo X, Liu X, Cao D, Jia X, Xiao X *et al*. Association of the single nucleotide polymorphisms in the extracellular

- matrix metalloproteinase-9 gene with PACG in southern China. *Mol Vis* 2009; **15**: 1412–1417.
- 70 Wang IJ, Chiang TH, Shih YF, Lu SC, Lin LL, Shieh JW *et al*. The association of single nucleotide polymorphisms in the MMP-9 genes with susceptibility to acute primary angle closure glaucoma in Taiwanese patients. *Mol Vis* 2006; **12**: 1223–1232.
- 71 Micheal S, Yousaf S, Khan MI, Akhtar F, Islam F, Khan WA *et al*. Polymorphisms in matrix metalloproteinases MMP1 and MMP9 are associated with primary open-angle and angle closure glaucoma in a Pakistani population. *Mol Vis* 2013; **19**: 441–447.
- 72 Aung T, Yong VH, Lim MC, Venkataraman D, Toh JY, Chew PT *et al*. Lack of association between the rs2664538 polymorphism in the MMP-9 gene and primary angle closure glaucoma in Singaporean subjects. *J Glaucoma* 2008; **17**(4): 257–258.
- 73 Awadalla MS, Burdon KP, Kuot A, Hewitt AW, Craig JE. Matrix metalloproteinase-9 genetic variation and primary angle closure glaucoma in a Caucasian population. *Mol Vis* 2011; **17**: 1420–1424.
- 74 Robertson JV, Siwakoti A, West-Mays JA. Altered expression of transforming growth factor beta 1 and matrix metalloproteinase-9 results in elevated intraocular pressure in mice. *Mol Vis* 2013; **19**: 684–695.
- 75 Schlotzer-Schrehardt U, Lommatzsch J, Kuchle M, Konstas AG, Naumann GO. Matrix metalloproteinases and their inhibitors in aqueous humor of patients with pseudoexfoliation syndrome/glaucoma and primary open-angle glaucoma. *Invest Ophthalmol Vis Sci* 2003; **44**(3): 1117–1125.
- 76 Micheal S, Qamar R, Akhtar F, Khan MI, Khan WA, Ahmed A. MTHFR gene C677T and A1298C polymorphisms and homocysteine levels in primary open angle and primary closed angle glaucoma. *Mol Vis* 2009; **15**: 2268–2278.
- 77 Wang IJ, Lin S, Chiang TH, Chen ZT, Lin LL, Hung PT *et al*. The association of membrane frizzled-related protein (MFRP) gene with acute angle-closure glaucoma—a pilot study. *Mol Vis* 2008; **14**: 1673–1679.
- 78 Kimbrough RL, Trempe CS, Brockhurst RJ, Simmons RJ. Angle-closure glaucoma in nanophthalmos. *Am J Ophthalmol* 1979; **88**(3 Pt 2): 572–579.
- 79 Sundin OH, Leppert GS, Silva ED, Yang JM, Dharmaraj S, Maumenee IH *et al*. Extreme hyperopia is the result of null mutations in MFRP, which encodes a Frizzled-related protein. *Proc Natl Acad Sci USA* 2005; **102**(27): 9553–9558.
- 80 Kruman II, Culmsee C, Chan SL, Kruman Y, Guo Z, Penix L *et al*. Homocysteine elicits a DNA damage response in neurons that promotes apoptosis and hypersensitivity to excitotoxicity. *J Neurosci* 2000; **20**(18): 6920–6926.
- 81 Dun Y, Thangaraju M, Prasad P, Ganapathy V, Smith SB. Prevention of excitotoxicity in primary retinal ganglion cells by (+)-pentazocine, a sigma receptor-1 specific ligand. *Invest Ophthalmol Vis Sci* 2007; **48**(10): 4785–4794.
- 82 Martin PM, Ola MS, Agarwal N, Ganapathy V, Smith SB. The sigma receptor ligand (+)-pentazocine prevents apoptotic retinal ganglion cell death induced in vitro by homocysteine and glutamate. *Brain Res Mol Brain Res* 2004; **123**(1-2): 66–75.
- 83 Nilforoushan N, Aghapour S, Raoofian R, Saeed Rad S, Greene WK, Fakhraie G *et al*. Lack of association between the C677T single nucleotide polymorphism of the MTHFR gene and glaucoma in Iranian patients. *Acta medica Iranica* 2012; **50**(3): 208–212.
- 84 Gupta S, Bhaskar PK, Bhardwaj R, Chandra A, Chaudhry VN, Chaudhry P *et al*. MTHFR C677T predisposes to POAG but not to PACG in a North Indian population: a case control study. *PLoS One* 2014; **9**(7): e103063.
- 85 Jiang Z, Liang K, Ding B, Tan W, Wang J, Lu Y *et al*. Hepatocyte growth factor genetic variations and primary angle-closure glaucoma in the Han Chinese population. *PLoS One* 2013; **8**(4): e60950.
- 86 Awadalla MS, Thapa SS, Burdon KP, Hewitt AW, Craig JE. The association of hepatocyte growth factor (HGF) gene with primary angle closure glaucoma in the Nepalese population. *Mol Vis* 2011; **17**: 2248–2254.
- 87 Cheng CY, Schache M, Ikram MK, Young TL, Guggenheim JA, Vitart V *et al*. Nine loci for ocular axial length identified through genome-wide association studies, including shared loci with refractive error. *Am J Hum Genet* 2013; **93**(2): 264–277.
- 88 Tomaselli S, Megiorni F, Lin L, Mazzilli MC, Gerrelli D, Majore S *et al*. Human RSPO1/R-spondin1 is expressed during early ovary development and augments beta-catenin signaling. *PLoS One* 2011; **6**(1): e16366.
- 89 Hao HX, Xie Y, Zhang Y, Charlat O, Oster E, Avello M *et al*. ZNRF3 promotes Wnt receptor turnover in an R-spondin-sensitive manner. *Nature* 2012; **485**(7397): 195–200.
- 90 Fuhrmann S. Wnt signaling in eye organogenesis. *Organogenesis* 2008; **4**(2): 60–67.
- 91 Nakagawa S. Role of Wnt signaling in eye organogenesis. *Seikagaku* 2004; **76**(12): 1573–1576.
- 92 Binnerts ME, Kim KA, Bright JM, Patel SM, Tran K, Zhou M *et al*. R-Spondin1 regulates Wnt signaling by inhibiting internalization of LRP6. *Proc Natl Acad Sci USA* 2007; **104**(37): 14700–14705.
- 93 Nair KS, Hmani-Aifa M, Ali Z, Kearney AL, Ben Salem S, Macalinao DG *et al*. Alteration of the serine protease PRSS56 causes angle-closure glaucoma in mice and posterior microphthalmia in humans and mice. *Nat Genet* 2011; **43**(6): 579–584.
- 94 Nongpiur ME, Khor CC, Jia H, Cornes BK, Chen LJ, Qiao C *et al*. ABC5, a gene that influences the anterior chamber depth, is associated with primary angle closure glaucoma. *PLoS Genet* 2014; **10**(3): e1004089.
- 95 Jedlitschky G, Burchell B, Keppler D. The multidrug resistance protein 5 functions as an ATP-dependent export pump for cyclic nucleotides. *J Biol Chem* 2000; **275**(39): 30069–30074.
- 96 Abu-Amero KK, Morales J, Osman MN, Bosley TM. Nuclear and mitochondrial analysis of patients with primary angle-closure glaucoma. *Invest Ophthalmol Vis Sci* 2007; **48**(12): 5591–5596.
- 97 Aung T, Yong VH, Chew PT, Seah SK, Gazzard G, Foster PJ *et al*. Molecular analysis of the myocilin gene in Chinese subjects with chronic primary-angle closure glaucoma. *Invest Ophthalmol Vis Sci* 2005; **46**(4): 1303–1306.
- 98 Faucher M, Anctil JL, Rodrigue MA, Duchesne A, Bergeron D, Blondeau P *et al*. Founder TIGR/myocilin mutations for glaucoma in the Quebec population. *Hum Mol Genet* 2002; **11**(18): 2077–2090.
- 99 Vincent AL, Billingsley G, Buys Y, Levin AV, Priston M, Trope G *et al*. Digenic inheritance of early-onset glaucoma: CYP1B1, a potential modifier gene. *Am J Hum Genet* 2002; **70**(2): 448–460.
- 100 Dai X, Nie S, Ke T, Liu J, Wang Q, Liu M. Two variants in MYOC and CYP1B1 genes in a Chinese family with

- primary angle-closure glaucoma. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2008; **25**(5): 493–496.
- 101 Chakrabarti S, Devi KR, Komatireddy S, Kaur K, Parikh RS, Mandal AK *et al*. Glaucoma-associated CYP1B1 mutations share similar haplotype backgrounds in POAG and PACG phenotypes. *Invest Ophthalmol Vis Sci* 2007; **48**(12): 5439–5444.
- 102 Ayub H, Khan MI, Micheal S, Akhtar F, Ajmal M, Shafique S *et al*. Association of eNOS and HSP70 gene polymorphisms with glaucoma in Pakistani cohorts. *Mol Vis* 2010; **16**: 18–25.
- 103 Shi H, Zhu R, Hu N, Shi J, Zhang J, Jiang L *et al*. Association of frizzled-related protein (MFRP) and heat shock protein 70 (HSP70) single nucleotide polymorphisms with primary angle closure in a Han Chinese population: Jiangsu Eye Study. *Mol Vis* 2013; **19**: 128–134.
- 104 Chua J, Seet LF, Jiang Y, Su R, Htoon HM, Charlton A *et al*. Increased SPARC expression in primary angle closure glaucoma iris. *Mol Vis* 2008; **14**: 1886–1892.
- 105 Brekken RA, Sage EH. SPARC, a matricellular protein: at the crossroads of cell-matrix. *Matrix Biol* 2000; **19**(7): 569–580.
- 106 Brekken RA, Sage EH. SPARC, a matricellular protein: at the crossroads of cell-matrix communication. *Matrix Biol* 2001; **19**(8): 816–827.
- 107 Bornstein P, Sage EH. Matricellular proteins: extracellular modulators of cell function. *Curr Opin Cell Biol* 2002; **14**(5): 608–616.
- 108 Pang IH, Hellberg PE, Fleenor DL, Jacobson N, Clark AF. Expression of matrix metalloproteinases and their inhibitors in human trabecular meshwork cells. *Invest Ophthalmol Vis Sci* 2003; **44**(8): 3485–3493.
- 109 Yan Q, Clark JI, Sage EH. Expression and characterization of SPARC in human lens and in the aqueous and vitreous humors. *Exp Eye Res* 2000; **71**(1): 81–90.
- 110 Haddadin RI, Oh DJ, Kang MH, Filippopoulos T, Gupta M, Hart L *et al*. SPARC-null mice exhibit lower intraocular pressures. *Invest Ophthalmol Vis Sci* 2009; **50**(8): 3771–3777.
- 111 Cao D, Liu X, Guo X, Cong Y, Huang J, Mao Z. Investigation of the association between CALCRL polymorphisms and primary angle closure glaucoma. *Mol Vis* 2009; **15**: 2202–2208.
- 112 Yousufzai SY, Ali N, Abdel-Latif AA. Effects of adrenomedullin on cyclic AMP formation and on relaxation in iris sphincter smooth muscle. *Invest Ophthalmol Vis Sci* 1999; **40**(13): 3245–3253.
- 113 Abu-Amero KK, Gonzalez AM, Osman EA, Larruga JM, Cabrera VM, Al-Obeidan SA. Susceptibility to primary angle closure glaucoma in Saudi Arabia: the possible role of mitochondrial DNA ancestry informative haplogroups. *Mol Vis* 2011; **17**: 2171–2176.
- 114 Abu-Amero KK, Gonzalez AM, Osman EA, Larruga JM, Cabrera VM, Al-Obeidan SA. Mitochondrial DNA lineages of African origin confer susceptibility to primary open-angle glaucoma in Saudi patients. *Mol Vis* 2011; **17**: 1468–1472.
- 115 Collins DW, Gudiseva HV, Trachtman BT, Jerrehian M, Gorry T, Merritt WT 3rd *et al*. Mitochondrial sequence variation in African-American primary open-angle glaucoma patients. *PLoS One* 2013; **8**(10): e76627.
- 116 Ahram DF, Cook AC, Kecova H, Grozdanic SD, Kuehn MH. Identification of genetic loci associated with primary angle-closure glaucoma in the basset hound. *Mol Vis* 2014; **20**: 497–510.
- 117 Ahonen SJ, Pietila E, Mellersh CS, Tiira K, Hansen L, Johnson GS *et al*. Genome-wide association study identifies a novel canine glaucoma locus. *PLoS One* 2013; **8**(8): e70903.
- 118 Ahram DF, Grozdanic SD, Kecova H, Henkes A, Collin RW, Kuehn MH. Variants in nebulin (NEB) are linked to the development of familial primary angle closure glaucoma in basset hounds. *PLoS One* 2015; **10**(5): e0126660.
- 119 Seah SK, Foster PJ, Chew PT, Jap A, Oen F, Fam HB *et al*. Incidence of acute primary angle-closure glaucoma in Singapore. An island-wide survey. *Arch Ophthalmol* 1997; **115**(11): 1436–1440.
- 120 Teikari JM, O'Donnell J, Nurminen M, Raivio I. Acute closed angle glaucoma and sunshine. *J Epidemiol Community Health* 1991; **45**(4): 291–293.
- 121 Subak-Sharpe I, Low S, Nolan W, Foster PJ. Pharmacological and environmental factors in primary angle-closure glaucoma. *Br Med Bull* 2010; **93**: 125–143.