

## Correlations of Primary Angle Closure Glaucoma Susceptibility Gene and Ocular Biometry

Haihong Shi and Huaijin Guan\*

Eye Institute, Affiliated Hospital of Nantong University, Nantong, PR China

\*Corresponding author: Dr. Huaijin Guan, Eye Institute, Affiliated Hospital of Nantong University, China, 20 Xisi Road, Nantong 226001 Jiangsu, PR China, Tel: +8613809088972 ; E-mail: [guanhjeye@163.com](mailto:guanhjeye@163.com)

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### Abstract

Specific anatomic features are risk factors for primary angle closure glaucoma (PACG), a dominant type of glaucoma in Asia. Some tissue remodeling genes have been reported associated with PACG. A Genome-wide association study identified three new susceptibility loci for PACG. However, the exact mechanism of these genes in PACG pathogenesis is still unclear. This commentary summarized the correlations of PACG susceptibility genes and ocular biometry and may help to understand the pathology of PACG better.

**Keywords:** Primary angle closure glaucoma (PACG); Single nucleotide polymorphism (SNP); Ocular biometry

### Commentary

Glaucoma is the leading cause of irreversible blindness worldwide. Primary glaucoma is classified as primary open-angle glaucoma (POAG) and primary angle closure glaucoma (PACG), according to the anterior segment anatomy. It has been reported that the proportion of all cases suffered from blindness is three times higher in PACG than in POAG [1]. There was a clear race disparity in PACG. Asian populations are at higher risk of developing PACG than other ethnic groups [2]. It was estimated that China has half the world's cases of PACG [3].

Eyes with PACG usually possess characteristic anatomical features such as a smaller corneal diameter, a steeper corneal curvature, a shallower anterior chamber, a thicker and more anteriorly positioned lens, and a shortened eyeball, often accompanied by hyperopic refraction error [4]. There is strong evidence that these biometric parameters and PACG itself have large genetic predisposition [5-7]. Candidate gene association studies have found that association of single nucleotide polymorphisms (SNP) in genes related to eye development or tissue remodeling including membrane frizzled-related protein (MFRP)[8], extracellular matrix metalloprotease-9 (MMP-9) [9-11], heat shock protein 70 (HSP70) [8,12], endothelial nitric synthase (eNOS) [12,13] and methylenetetrahydrofolate reductase (MTHFR) [14] with susceptibility to PACG. However, the above findings were controversial among different ethnic groups even in the same ethnic groups and the exact mechanism is unknown. Recently, a genome-wide association study (GWAS) identified three new susceptibility loci for PACG, including rs11024102 in PLEKHA7, rs3753841 in COL11A1, and rs1015213 in PCMTD1-ST18 [15]. Nevertheless, the molecular mechanism of these genes in PACG pathogenesis is still under investigation.

Extracellular matrix (ECM) remodeling is likely to be an important determinant for the short axial length in hyperopic eyes [10]. MMP9 is important in ECM remodeling and may regulate the growth of sclera coats [16]. However, MMP9 rs17576 was found to be associated with

susceptibility to PACG in Taiwanese, no differences in AL between the genotypes [11]. Similarly, Cong et al. found that MMP9 rs2250889 was associated with PACG in Southern China, but the patients in their study have regular AL and no obvious microphthalmia [10]. Awadalla found that MMP9 rs17576 and MMP9 rs3918249 were associated with PACG in Australian, but they did not test the relationship between these SNPs and AL or refractive status [17]. We interpreted that PACG is different from nanophthalmos and hyperopic for a clinical manifestation and these genes may not directly involved in this blindness-causing disease. A Singapore study found that the mean AL of PAC was 23.02 mm compared to 23.85 mm in normal subjects [18]. We can see that the AL of PACG is shorter than that of normal populations but not as short as nanophthalmic eyes.

Although HSP70, eNOS and MTHFR does not regulate tissue remodeling directly, they regulate the expression of MMPs and is thought to be associated with PACG in Pakistani population [8,12,14]. However, the above results have not been confirmed in different populations and the relationship between ocular biometry and polymorphisms have not been studied. In a population-based study, Shi et al. found that eNOS rs11771443 variation was associated with deeper ACD but not associated with PAC, AL and DS in Han Chinese [19]. eNOS has been hypothesized to be involved in glaucoma pathogenesis by affecting the blood flow to the optic nerve thus dysfunctioning retinal ganglion cells [20]. However, optic nerve injury in PACG has been attributed primary to elevated intraocular pressure (IOP) caused by anatomic changes in the anterior and posterior globe, in contrast with the molecular and biochemical abnormalities suspected in POAG [21]. eNOS also has been hypothesized to be involved in IOP modulation through affecting the outflow resistance or affecting the tone of the ciliary muscle [22]. Since the increased IOP in PACG is caused by obstruction of the iridocorneal angle but have nothing to do with aqueous humor outflow facility, we speculate that the variation of rs11771443 might increase NO production in anterior segment endothelia, and result in relaxation of ciliary muscle and thus increase the depth of anterior chamber. These results suggested that the above genes may not be causative in PACG and the possible mechanism in which these genes might contribute to PACG needs to be further studied.

Three well-known loci identified by a GWAS may explain in part some aspects of the PACG pathogenesis. Some studies conformed the results of GWAS [23], but the mechanism of these genes in PACG is still unclear. Shi et al. did not find any association between these three genes with ACD, AL and DS [24]. Day et al. conducted a genotype-phenotype analysis of these three SNPs with the ocular biometry of 988 European people [25]. They found that the A allele of rs1015213 was nominally associated with narrower ACD ( $p=0.046$ ), but not associated with AL and corneal keratometry. As to rs11024102 and rs1015213, the genotype was not associated with ocular biometry, including AL, ACD and corneal keratometry. In addition, Nongpiur Me [26] and Xinghuai Sun [27] also reported that these loci were not associated with ACD and AL. Wei et al. found no association between these three loci and diseases severity or progression [28]. They suggested that disease-causing genes may be different from disease modifying genes and other genetic factors modulated the clinical progression in PACG independent of initial susceptibility may exist. Quigley et al. postulated that dynamic process related to iris and choroid is more likely affecting the pathogenesis than static anatomic differences [29]. Liang et al. observed that primary angle closure suspects had similar shallower anterior chamber and thicker lens to PAC and PACG [30], but only a few of them developed to PAC and PACG. Recently, a GWAS meta-analysis identified nine AL loci, five of them were also associated with refraction in 18 independent cohorts [31]. Nevertheless, those three loci identified in GWAS on PACG were not associated with AL in this meta-analysis. Above results suggests that these three genes may be really involved in developing PACG but other risk factors other than shallow ACD, short AL and hyperopic error could still be great attributors to the pathogenesis of PACG.

In summary, although a number of genetic loci have been identified to this complex multifactorial disease, the mechanism of these genes in PACG pathogenesis is still unclear. Lack of association with ACD, AL and DS in most studies indicates that other factors may involve in the pathogenesis of PACG.

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