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Evaluation of *MYRF* as a candidate gene for primary angle closure glaucoma

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Purpose: Primary angle-closure glaucoma (PACG) is a leading cause of blindness. Despite tremendous human effort and financial input, no definitive causative gene has been identified either through genome-wide association or Mendelian family studies. In the current study, novel candidate genes for PACG were investigated by studying the variants of nanophthalmos-associated genes.

Methods: A case-control study was conducted that included 45 PACG patients and 12 normal controls with short axial length (AL, less than 23.5 mm but more than 20.5 mm). Whole-exome sequencing (WES) was performed to screen the variants in previously identified nanophthalmos-associated genes, as well as other risk genes.

Results: The age range of the 45 PACG patients was 24 to 80 years, with an average AL of 21.87±0.65 mm (range: 20.54–23.45 mm) in the right eye and 21.89±0.64 mm (range 20.60–23.23 mm) in the left eye. Four novel myelin regulatory factor (*MYRF*) gene missense variants (p.G117S, p.H1057R, p.H230R, and p.R316C) were identified in four out of the 45 enrolled PACG patients, respectively. No *MYRF* or other nanophthalmos-associated gene variants were detected in the 12 normal controls.

Conclusions: An appropriate approach was adopted to investigate the genetics of PACG through nanophthalmos-associated genes. A genetic variant, *MYRF*, was identified in four out of 45 PACG patients, which might be a novel candidate gene for PACG.

(The first two authors contributed equally to this work.)

Primary angle-closure glaucoma (PACG) is characterized by elevated intraocular pressure (IOP) due to the appositional obstruction of trabecular meshwork or synechia contact between the peripheral iris and trabecular meshwork [1]. In 2013, the number of people between 40 and 80 years old with PACG was estimated to be 20.17 million worldwide [2]. About 76.70% of PACG patients live in Asia, especially in China [2].

Significant racial differences and familial clustering suggest a strong genetic basis for PACG [2]. Although nine genes/loci, including collagen type XI alpha 1 chain (*COL11A1*) and ATP binding cassette subfamily C member 5 (*ABCC5*), have been identified using genome-wide association studies (GWAS), they only explain up to 2% of the genetic variance in PACG [3-5]. A meta-analysis also identified five additional genetic susceptibility genes for PACG in candidate gene studies, such as membrane-type frizzled-related protein (*MFRP*) and matrix metallopeptidase 9 (*MMP9*) genes [6]. Furthermore, the identification of eight PACG-associated single nucleotide polymorphisms (SNPs) using anterior segment imaging parameters provided only a marginal improvement in PACG detection [7]. The poor correlation between the genes and pathogenesis of PACG indicates that it is a heterogeneous disease with a complex etiology. The occurrence of PACG can hardly be attributed to variants within a single gene, thereby leading to the consideration that other latent factors might play important roles. Considering the heterogeneity and complexity of PACG, the lack of phenotype stratification, and a "pure" target population make existing studies limited, thereby hindering the identification of genes or genetic risk factors for PACG. A strategic change in dividing PACG based on phenotype into different subtypes might be helpful to investigate the pathogenesis of PACG.

As a complex disease, PACG involves several inheritable traits, including hyperopic refraction, small cornea,

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shallow anterior chamber, narrow iridocorneal angle, thickened lens with increased curvatures, and increased choroidal thickness. Nanophthalmos patients could present with all the phenotypes of PACG and are associated with a relatively large lens and an extremely small eye volume [8]. Several studies have reported the association of PACG with nanophthalmos-associated genes [9,10]. Zhang et al. investigated the association of the serine protease 56 (*PRSS56*) gene with PACG and high hyperopia [11], while Vithana et al. investigated the association of the *MFRP* gene with PACG [12]. However, no statistical difference in the distribution of variants between PACG cases and healthy controls was identified. Moreover, the rare missense variants of the *PRSS56* and *MFRP* genes were detected in only 2.65% and 1.90% of the PACG patients, respectively. The heterogeneity of the study population probably limits the identification of pathogenic variants and undermines interpretations. A strategic approach that explores all the genetic factors of PACG, rather than exploring a single or a few factors, as commonly performed in previous studies, might significantly increase the likelihood of identifying major functional components. Following this theoretical rationalization, nanophthalmos can lead to the identification of genetic factors for PACG, which might be an appropriate approach. The hypomorphic alleles of nanophthalmos genes might have moderate effects on the biometry of PACG and might also increase its risk.

From a molecular perspective, the mechanisms of anatomic angle closure can be categorized into the regulation of the developments in the ocular axial, the anterior chamber angle structures, including lens and lens zonules, and the retina-choroid-sclera complex [13-15]. Therefore, this study mainly included PACG patients with short axial length (AL, average: 21.87 mm in the right eye and 21.89 mm in the left eye) to reduce potential phenotypic heterogeneity.

Previously, a novel nanophthalmos gene *MYRF* [16] was identified through the de novo variants trio analysis of families with nanophthalmos. In the current study, whole-exome sequencing (WES) was performed to screen all the identified nanophthalmos-associated genes, including transmembrane protein 98 (*TMEM98*), bestrophin 1 (*BEST1*), *PRSS56*, crumbs cell polarity complex component 1 (*CRB1*), *MFRP*, and *MYRF*. Finally, *MYRF* missense variants were found in four out of the 45 recruited PACG patients with short AL (less than 23.5 mm but more than 20.5 mm).

METHODS

Subject recruitment: We consecutively recruited 45 Chinese PACG patients at Zhongshan Ophthalmic Center (ZOC), Sun Yat-sen University. Inclusion criteria were as follows: (1) at least 180° of peripheral anterior synechiae under gonioscopy; (2) elevated IOP measured by Goldmann applanation tonometry; (3) glaucomatous optic neuropathy confirmed by correlated structural and functional defects through optic nerve imaging, optical coherence tomography (OCT), and visual field tests; and (4) less than 23.5 mm but more than 20.5 mm of AL. Another 12 normal controls with short AL ranging from 20.5 mm to 23.5 mm were recruited. AL was measured by IOL Master. Subjects with uncontrolled ocular infection, severe systemic diseases, or who declined to participate were excluded. This study is strictly in accordance with the tenets of the Declaration of Helsinki, and was approved by the Ethics Committee of ZOC. All patients provided informed consent before recruitment.

Whole exome sequencing and mutational analysis: Genomic DNA was extracted from peripheral blood using an isolation kit (OSR-M104-T1, Tiangen Biotech, Beijing, China). The coding DNA was enriched using the SureSelect Human All Exon Kit (Agilent V6, Santa Clara, CA), and paired-end sequencing was performed with the Novaseq 6000 sequencer (Illumina, San Diego, CA) with an average sequencing depth of 102.53X. The sequencing reads were processed with the Burrows-Wheeler Aligner (BWA) for alignment on the human reference genome of hg19 and the Genome Analysis Toolkit (GATK) for local realignment, quality recalibration, and variant calling. The Variant Call Format (VCF) files were then analyzed using ANNOVAR software. The variants were filtered using the following criteria: (1) low-quality variants were removed by GATK recommended filters; (2) variants present in the public genetic variant databases, Genome Aggregation Database (GnomAD v2.0.1), with an allele frequency <2% were included; and (3) nonsense variants, frameshift variants, splice site, or predicted damaging missense variants by Combined Annotation Dependent Depletion (CADD), Sorting Intolerant From Tolerant (SIFT), PolyPhen2, or MutationTaster were included. Nanophthalmos genes, including autosomal dominant genes (*TMEM98*, *BEST1*, and *MYRF*) and autosomal recessive genes (*PRSS56*, *CRB1*, and *MFRP*), were screened in these patients. Only exome variants could be detected by the methods used in the current study, while other variants such as intronic, copy number variations (CNVs), and structural variants (SVs) could not be detected.

The sequencing depth in subjects in the discovery stage ranged from 86.02 to 187.65. The mapping rate of clear data ranged from 94.43% to 99.95%, and the genome coverage ranged from 97.89% to 99.60% (Appendix 1).

Table 1. Demographic characteristics of PACG cases and controls.

Parameter	PACG	Control	P
Number	45	12	
Age, years (Mean ± SEM)	56.47±12.52	53.58±13.31	0.62
AL/OD, mm (Mean ± SEM)	21.87±0.65	21.66±0.70	0.35
AL/OS, mm (Mean ± SEM)	21.89±0.64	22.01±0.65	0.57

Age represents age at recruitment

RESULTS

In this study, the average age of PACG patients was 56.47±12.51 years old and that of normal controls was 58.58±13.31 years old (p>0.05). The average AL in the right eye was 21.87±0.65 mm in the PACG group and 21.66±0.70 mm in the control group (p>0.05), whereas for the left eye, the average was 21.89±0.64 mm for the PACG group and 22.01±0.65 mm for the control group (p>0.05; Table 1).

Four of the 45 PACG patients were identified with novel *MYRF* missense variants (Table 2). Three heterozygous missense variants (NM_001127392: c.349G>A, p.G117S; c.689A>G, p.H230R and c.946C>T, p.R316C) and one homozygous missense variant (NM_001127392: c.3170A>G, p.H1057R) in the *MYRF* gene were identified in the PACG patients with short AL, which were confirmed by Sanger sequencing (Figure 1). The frequencies of p.G117S, p.H1057R, p.H230R, and p.R316C in GnomAD ($8.49*10^{-6}$; $6.98*10^{-5}$; $1.15*10^{-5}$; $3.90*10^{-5}$, respectively) were all less than 2% (Table 3). All of these *MYRF* missense variants were predicted to be "damaging" by in silico prediction using SIFT and CADD (Table 3). Moreover, these variants were all located in conserved domains among various species (Figure 2). On the other hand, the three heterozygous variants in the nanophthalmos-associated gene (*CRB1*, c.2585C>G p.T862S; *BEST1*, c.274C>G, p.R92G; *MFRP*, c.496C>G, p.P166A) were also identified in the PACG patients with short AL (Appendix 2). Among these, the variant c.496C>G in the *MFRP* gene has been reported previously [17]. The frequencies of these variants in 1000G, GnomAD, and the exome aggregation consortium (ExAC) were less than 2% and predicted to be "damaging" by the in silico prediction (Table 3). Importantly, none of the variants in the nanophthalmos-associated genes were detected in the 12 control subjects.

DISCUSSION

In the current study, four novel *MYRF* missense variants (NM_001127392: c.349G>A, p.G117S; c.689A>G, p.H230R; c.946C>T, p.R316C; and c.3170A>G, p.H1057R) were detected in 8.9% of PACG patients with short AL. In addition, another three nanophthalmos-associated gene variants (*CRB1*, c.2585C>G, p.T862S; *BEST1,* c.274C>G, p.R92G; *MFRP,* c.496C>G, p.P166A) were detected in this study. No variants in nanophthalmos-associated genes were detected in the 12 controls.

Although the molecular function of *MYRF* in PACG is not yet known, several *MYRF* variants have been confirmed to be associated with nanophthalmos/high hyperopia as reported in our previous study [16], as well as by Garnai et al. [18] and Xiao et al. [19], suggesting the important role of *MYRF* in the regulation of AL. Recently, we reported the functional role of *Myrf* in the retina and zonule using mouse models, which indicated the underlying function of *MYRF* in eye development [20,21]. In addition, Sun et al. [22] indicated that PACG was frequently associated with *MYRF*-associated high-hyperopia. However, nanophthalmos genes, including *MYRF*, are primarily involved in the intra-uterus and early post-birth period ocular development, while genetic and environmental factors contributing to refractive (myopic)

Table 2. Clinical data and genetic findings of four patients with *MYRF* variant.

Case number	Age (years)	Gender	Axial length (AL), mm		Lens thickness, mm		Refraction, D		Variant
			OD	OS	OD	OS	OD	OS	
1	59	Male	20.54	20.71	5.33	5.62	−1.75	3	c.349G>A, p.G117S
3	31	Male	20.8	20.6	-	-	-	-	c.3170A>G, p.H1057R
9	64	Male	23.45	23.23	4.78	4.73	0.5	0.75	c.689A>G, p.H230R
36	70	Female	21.51	21.73	5.5	5.46	1	0.5	c.946C>T, p.R316C

Age represents age at recruitment. Refraction was measured before surgery with phakic.

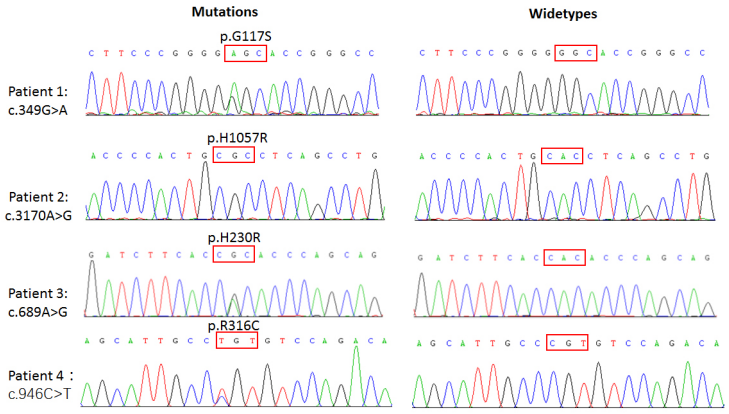

Figure 1. Identification of *MYRF* variants (c.349G>A, p.G117S; c.3170A>G, p.H1057R; c.689A>G, p.H230R; c.946C>T, p.R316C) in PACG patients by Sanger sequencing.

Table 3. The Allele Frequencies and *silico* prediction for the variants found in patients.

Gene	variant	GnomAD, ALL	GnomAD, EAS	GERP++_RS	CADD	SIFT	Polyphen-2	MutationTaser
MYRF	c.349G>A, p.G117S (het)	$8.49*10^{-6}$	$1.11*10^{-5}$	C (4.44)	D (17.09)	D	B	N
MYRF	c.3170A>G, p.H1057R (hom)	$6.98*10^{-5}$	$9.66*10^{-4}$	C (4.26)	D (15.63)	D	PD	D
MYRF	c.689A>G, p.H230R (het)	$1.15*10^{-5}$	$1.52*10^{-4}$	C (4.35)	D (23.2)	D	D	D
MYRF	c.946C>T, p.R316C (het)	$3.90*10^{-5}$	$1.50*10^{-4}$	C (2.55)	D (25.1)	D	PD	D
CRB1	c.2585C>G, p.T862S (het)	$7.98*10^{-6}$	$1.09*10^{-4}$	C (5.34)	D (22.5)	D	D	D
BEST1	c.274C>G, p.R92G (het)	-	-	C (5.03)	D (32)	D	D	D
MFRP	c.496C>G, p.P166A (het)	$4.67*10^{-4}$	0.00598	C (2.06)	D (21.6)	T	D	D

het=heterozygous; hom=homozygous; ALL=all population; EAS=East Asian populations; C=conserved; D=damaging; T=tolerable; PD=possibly damaging; B=benign; n=polymorphism.

	p.G117S	p.H1057R	p.H230R	p.R316C
Homo sapiens	PKPFPGGTGPPIK	SSGTPLHLSLTLQ	VPTDLHHTQQSQM	LPLSIARVQTPPW
Macaca nemestrina	PKPFPGGAGPPIK	SSGTPLHLSLTLQ	VPTDLHHTQQSQM	LPLSIARVQTPPW
Pan paniscus	PKPFPGGTGPPIK	SSGTPLHLSLTLQ	VPTDLHHTQQSQM	LPLSIARVQTPPW
Callithrix jacchus	PKPYPGGAGPPIK	SSNTPLHLSLTLQ	VPTELHHAQQSQM	LPLSIARVQTPPW
Pan troglodytes	PKPFPGGTGPPIK	SSGTPLHLSLTLQ	VPTDLHHTQQSQM	LPLSIARVQTPPW
Pongo abelli	PKPFPGGAGPPIK	SSGTPLHLSLTLQ	VPTDLHHTQQSQM	LPLSIARVQTPPW
Cebus capucinus imitator	PKPYPGGTGPPIK	SSGTPLHLSLTLQ	VPTELHHTQQSQM	LPLSIARVQTPPW

Figure 2. Evolutionary conservation of *MYRF* variants (p.G117S; p.H1057R; p.H230R, p.R316C) across different species.

development, especially in industrialized and near-work societies, play important roles in later days [23]. These two components are combined to determine the final AL in the eye (phenotype). Therefore, the effects of genetic and environmental factors on PACG patients with short AL need to be further investigated.

Generally, variants in the *MYRF* gene cause nanophthalmos with AL <20.0 mm [16,18]; yet the AL of the PACG patients with *MYRF* variants in this study ranged from 20.5 mm to 23.5 mm. Therefore, PACG patients with *MYRF* variants might be clinically "atypical" in nanophthalmos if they are defined by the genetic factor, because their short AL might gradually increase because of environmental factors. For the detection of this type of glaucoma, a genetic diagnosis and the potential phenotypic stratification of PACG based on genetics might be helpful. Furthermore, PACG is associated with serious perioperative complications, such as choroidal effusion and malignant glaucoma, making the eye extremely overcrowded in its anterior ocular structures and pathologically thickened in its choroid and sclera. Therefore, genetic screening might be needed for nanophthalmos-associated genes.

In this study, all the frequencies of variants, including four *MYRF* variants, one *CRB1* variant, one *BEST1* variant, and one *MFRP* variant, obtained through large open databases, were less than 2%. Furthermore, all these missense variants were predicted to be "damaging" by the in silico analysis. Taken together, these findings suggest that nanophthalmos-associated genes, especially *MYRF*, might play a vital role in the pathogenesis of at least some PACG patients. People with short AL caused by variants in the *MYRF* gene or other nanophthalmos-associated genes are more susceptible to developing PACG.

Most of the *MYRF* variants, which have been previously reported, are truncating variants, while only several missense variants have been identified in nanophthalmos patients and include c.1433G>C, p.R478P [16] and c.1553C>T, p.T518M [24]. However, the variants identified in this study were all missense, and the associated phenotype was not as severe as the one reported in patients with truncating *MYRF* variants. Therefore, the pathogenicity of these *MYRF* missense variants might be slightly lower than that of the truncating *MYRF* variants; this requires further functional evidence. In particular, the variant p.H1057R found in the current study was a homozygous variant, and nanophthalmos is inherited in an autosomal dominant manner. The homozygous missense variant of the autosomal dominant gene might have more serious phenotypes than the heterozygous; yet, in this study, the phenotype was less severely associated with the *MYRF* homozygous variant.

Some limitations of this study should be considered. First, the sample size of the normal controls with short AL was very small, and we can hardly rule out *MYRF* as solely a gene for AL, yet people with short AL without no ocular diseases are rarely observed. Therefore, only 12 normal controls and 45 PACG patients with short AL were recruited during the same period. Further validation in a large multicenter clinical collection of larger trios and sporadic patients with more controls is needed in future studies. Second, the potential function of the missense variants found in this study needs to be further investigated, as the pathogenicity of the variants is still unclear even after in silico prediction. Specifically, it should be noted that the homozygous variant p.H1057R was more common in East Asian populations (allele frequency was $9.66*10^{-4}$ in GnomAD, EAS). It remains unknown whether the four *MYRF* missense variants act by haploinsufficiency or by dominant negativity. However, knockdown of the *MYRF* gene resulted in a smaller eye size in zebrafish [22], while our previous study found that the *MYRF* variant in mice caused reduced anterior chamber depth [20]. This supports the potential effect of *MYRF* on the anterior chamber development and pathology of PACG. In summary, we report that *MYRF* is a potential candidate gene for PACG, which requires further studies to be confirmed.

APPENDIX 1.

Summary of variants detected in patients by whole exome sequencing. To access the data, click or select the words "Appendix 1."

APPENDIX 2.

Clinical data and genetic findings of three patients with nanophthalmos-associated gene variants. To access the data, click or select the words "Appendix 2."

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