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Significance of the lncRNAs MALAT1 and ANRIL in occurrence and development of glaucoma

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Abstract

Background: Primary open-angle glaucoma (POAG) is the commonest form of glaucoma which is estimated to cause bilaterally blind within 11.1 million people by 2020. Therefore, the primary objectives of this study were to investigate the clinical significance of single-nucleotide polymorphisms (SNPs) in the lncRNAs MALAT1 and ANRIL in a Chinese Han POAG cohort.

Methods: Three hundred and forty-six glaucoma patients and 263 healthy controls were recruited, and totally 14 SNPs in MALAT1 and ANRIL were genotyped between the two populations.

Results: The MALAT1 SNPs rs619586 (A>G), rs3200401 (C>T), and rs664589 (C>G) were associated with POAG risk, and the ANRIL SNPs rs2383207 (A>G), rs564398 (A>G), rs2157719 (A>G), rs7865618 (G>A), and rs4977574 (A>G) were associated with POAG ($p < 0.05$). The MALAT1 haplotypes ACG and ATC, comprised rs619586, rs3200401, and rs664589, increased POAG risk, and the ANRIL haplotype AAGAA, made up of rs2383207, rs7865618, rs4977574, rs564398, and rs2157719, show a significantly increased risk of POAG. In addition, rs619586 (A>G) of MALAT1 and rs564398/rs2157719 of ANRIL were associated with a smaller vertical cup-to-disc ratio, while rs619586 of MALAT1 and rs2383207/rs4977574 of ANRIL were associated with higher intraocular pressure in the POAG population.

Conclusion: Single-nucleotide polymorphisms and haplotypes in ANRIL and MALAT1 were associated with POAG onset in our study population, which provide more possibilities to POAG diagnosis and treatment.

KEYWORDS
Chinese population, LncRNA ANRIL, LncRNA MALAT1, primary open-angle glaucoma, single-nucleotide polymorphism

Guoqiang Huang and Dong Liang contributed equally.

1 | INTRODUCTION

Glaucoma is the second leading cause of blindness worldwide,[1] with clinical features, including optic atrophy, visual field defects, and irreversible blindness. Primary open-angle glaucoma (POAG) is a common type of primary glaucoma,[2] and multiple genetic loci, including MYOC, OPTN, and WDR36, have been reported to be associated with POAG onset.[3,4] However, the reported genetic variants explained no more than 10% of glaucoma cases,[3,5] and the underlying mechanism of POAG remains still unclear.

Recent studies have suggested a correlation between lncRNAs variants and POAG; here, we focus on the lncRNAs MALAT1 and lncRNA ANRIL. Of note, ANRIL, also known as CDKN2B-AS, has been reported to be associated with occurrence and progression of cardiovascular diseases,[6] cancers,[7] diabetes,[8] glaucoma,[9] and endometriosis.[10] Specifically, ANRIL was reported to protect human trabecular meshwork cells in a glaucoma experimental model by down-regulating miR-7.[11] ANRIL knockdown can alleviate retinopathy in diabetic rats by repressing inflammation and apoptosis through the NF-κB signaling pathway.[12] Yin et al.[13] reported that ANRIL promotes cisplatin resistance in retinoblastoma cells by inhibiting apoptosis, supporting proliferation, and increasing expression of drug resistance-related proteins by altering the expression of miR-328 and ABCG2. Single-nucleotide polymorphisms (SNPs) in ANRIL have been found to correlate with visual disease. For example, the G allele at rs2157719 was associated with a smaller cup-to-disc ratio and lower POAG risk, while the A allele at rs2157719 was predictive of a larger cup-to-disc ratio and lower intraocular pressure (IOP) in POAG patients from the United States.[14] However, it is not clear whether these associations exist in the Chinese populations.

MALATI is a highly conserved lncRNA amongst mammals located at 11q13, and its expression is significantly up-regulated in lung cancer, liver cancer, renal cell carcinoma, bladder cancer, and osteosarcoma.[15] MALAT1 knockout reduced retinal inflammation in diabetic rats and increased the survival of retinal endothelial cells, thereby reducing retinal blood vessel damage and improving retinal function.[16] MALAT1 also affected development of retinal neurodegenerative disease by modifying cyclic AMP response element (CRE)-binding protein (CREB) signaling to promote Müller cell activity.[17] Michalik et al.,[18] demonstrated that ablation of MALAT1 inhibited proliferation of endothelial cells and blocked neonatal retinal vascularization. Although MALAT1 is correlated with visual diseases, it is not clear whether MALAT1 SNPs are associated with POAG.

Therefore, in this study, we explored the association of MALAT1 and ANRIL SNPs with POAG, with the goal of developing novel diagnostic indicators for POAG.

2 | MATERIALS AND METHODS

2.1 | Research subjects

Three hundred and forty-six glaucoma patients and 263 healthy controls were recruited at Meizhou People's Hospital between March, 2019 and April, 2020. All patients gave informed consent, and approval was granted for the study by the ethics committee of Meizhou People's Hospital.

All subjects, both cases and controls, were of Han ethnicity and completed an ophthalmologic examination. This examination includes visual acuity, intraocular pressure (IOP) (by Goldman applanation tonometry), visual field (by computerized perimetry), anterior chamber angles (by gonioscopy), vertical cup-to-disc ratio (VCDR), and central corneal thickness (CCT) (both by optical coherence tomography). Also, a questionnaire regarding demographic, clinical, and lifestyle variables was performed on all subjects. The diagnosis of POAG was performed based on structural and functional changes in the optic disc and visual field measurements or an open angle by gonioscopy.[19] Patients with congenital glaucoma or any other forms of secondary glaucoma, such as epidermal exfoliation syndrome or a history of ocular trauma, were excluded from this investigation. The healthy control group was recruited from people attending routine physical examination in Meizhou People's Hospital and was all in good ocular health.

2.2 | Genotyping of SNPs

Genomic DNAs were extracted from venous blood samples of each participant, which were anticoagulated with ethylenediaminetetraacetic acid (EDTA), by applying approach of phenol-chloroform extraction and ethanol precipitation. Then, DNA was amplified with the aid of a PCR kit (Takara), and SNPs in MALAT1[20–36] and ANRIL[14,37–49] were genotyped using the single-base end extension (SNaPshot) method, a genetic analyzer (model: ABI3130), and Genemapper software from ABI.

2.3 | Statistical analyses

All statistical analyses were performed using SPSS 13.0 (SPSS Inc.). Hardy-Weinberg equilibrium (HWE) of each SNP was analyzed with χ^2 test in the healthy control group. The differences in clinical features and genotype frequencies of the SNPs were compared between the case group and the control group using a χ^2 test for categorical variables and a *t*-test for continuous variables. Associations between genotypes and alleles and the risk of POAG were estimated by odds ratios (ORs) and 95% confidence intervals (CIs). A p value <0.05 was considered statistically significant. The corrections for multiple comparisons were conducted by using the Bonferroni method.

3 | RESULTS

3.1 | Baseline clinical features of POAG patients

Comparing the 346 POAG patients with the 263 healthy controls, we found no difference in gender ratio, mean age, or hypertension incidence (all $p > 0.05$) (Table 1). The POAG patients, with an

TABLE 1 Baseline clinical features of POAG patients and healthy controls

Characteristics	Case	Control	t/χ^2	*p* Value
Number	346	263		
Age (years)	62.07 ± 11.43	58.45 ± 10.49	1.795	0.073
Gender (Female/Male)	171/175	139/124	0.703	0.402
Smokers	34.23%	36.95%	0.505	0.477
Hypertension	42.81%	48.54%	2.095	0.148
Follow-up period (years)	7.64 ± 3.28	NA		
VCDR	0.83 ± 0.08	0.36 ± 0.05	**83.65**	**<0.001**
IOP (mmHg)	25.74 ± 4.79	15.62 ± 2.51	**31.16**	**<0.001**
CCT (μm)	549 ± 37	515 ± 16	**13.94**	**<0.001**

Note: The bold means a significantly results with a p value < 0.05.

Abbreviations: CCT, central corneal thickness; IOP, intraocular pressure; NA, not applicable; POAG, primary open-angle glaucoma; VCDR, vertical cup-to-disc ratio.

average disease course of 7.64 ± 3.28 years, had a mean VCDR of 0.83 ± 0.08, mean IOP of 25.74 ± 4.79 mmHg, and mean CCT of 549 ± 37 μm, which were higher than those in Control group (all $p < 0.05$).

3.2 | Association between SNPs and haplotype in MALAT1 and ANRIL with POAG

According to Table 2, allele G at rs619586 (A>G) in MALAT1 reduced the risk of POAG compared with allele A, regardless of whether an allelic model (OR = 0.52, 95% CI = 0.40–0.67), a dominant model (OR = 0.47, 95% CI = 0.34–0.65), or a recessive model (OR = 0.35, 95% CI = 0.19–0.67) was used. Patients carrying allele T at rs3200401 (C>T) or allele G at rs664589 (C>G) were more susceptible to POAG than those carrying allele C at rs3200401 and rs664589, when an allelic model (T vs. C; G vs. C) or a dominant model (CT+TT vs. CC; CG+GG vs. CC) was considered.

As for ANRIL, the G alleles of rs2383207, rs564398, and rs2157719 (all A>G) all decreased the risk of POAG compared to the A alleles (allelic model: OR = 0.75, 95% CI = 0.59–0.97; OR = 0.63, 95% CI = 0.47–0.83; OR = 0.49, 95% CI = 0.39–0.62). Conversely, patients with mutant alleles of rs7865618 (G>A) or rs4977574 (A>G) had a higher susceptibility to POAG, which was found in all three models (allelic model: OR = 3.08, 95% CI = 2.31–4.12, OR = 1.74, 95% CI = 1.38–2.18; dominant model: OR = 3.53, 95% CI = 1.66–7.49, OR = 2.09, 95% CI = 1.45–3.03; recessive model: OR = 3.79, 95% CI = 2.67–5.38, OR = 2.09, 95% CI = 1.41–3.08).

In addition, the ACG and ATC haplotypes of rs619586, rs3200401, and rs664589 in MALAT1 were associated with increased susceptibility to POAG (OR = 2.13, 95% CI = 1.08–4.22, OR = 1.90, 95% CI = 1.23–2.93), while the GCC haplotype was associated with lower risk of POAG onset (OR = 0.40, 95% CI = 0.26–0.61) (Table 3). The AAGAA haplotype of rs2383207, rs7865618, rs4977574, rs564398, and rs2157719 in rendered people more vulnerable to POAG, compared with other haplotypes (OR = 3.08, 95% CI = 1.86–5.11).

3.3 | Association of SNPs and haplotypes in MALAT1 and ANRIL with VCDR in POAG patients

The POAG patients were divided into high VCDR and low VCDR groups based on whether their VCDR was higher or lower than the mean VCDR of the population (Table 4). Allele G at rs619586 (A>G) of MALAT1, as well as at rs564398 and rs2157719 of ANRIL, were correlated with lower VCDR in POAG patients under an allelic model (G vs. A) and dominant model (AG+GG vs. AA). In contrast, patients with G at rs664589 (C>G) of MALAT1 and G at rs2383207 of ANRIL (A>G) tended to have higher VCDR in an allelic model (OR = 1.69, 95% CI = 1.13–2.53; OR = 1.47, 95% CI = 1.04–2.08). Furthermore, the GAA haplotype contributed to higher VCDR in POAG patients than other haplotypes in ANRIL (OR = 1.89, 95% CI = 1.04–3.45) (Table 5).

3.4 | Association of SNPs and haplotypes in MALAT1 and ANRIL with IOP and CCT in POAG patients

The POAG patients were divided into high IOP (>25.74 mmHg) and low IOP (≤25.74 mmHg) groups (Table 6). The frequency of allele A of rs619586 in MALAT1 was higher in POAG patients with high IOP than in patients with low IOP (allelic model: OR = 0.53, 95% CI = 0.37–0.77, dominant model: OR = 0.54, 95% CI = 0.34–0.85, recessive model: OR = 0.20, 95% CI = 0.06–0.64). In addition, rs2383207 (A>G) and rs4977574 (A>G) of ANRIL were associated with high IOP, while allele G at rs564398 was associated with low IOP (allelic model: OR = 1.65, 95% CI = 1.14–2.38, OR = 1.50, 95% CI = 1.10–2.05, OR = 0.41, 95% CI = 0.27–0.62). The AAG haplotype in ANRIL was associated with low IOP (OR = 0.29, 95% CI: 0.11–0.76), whereas GGA was associated with high IOP (OR = 2.26, 95% CI: 1.08–4.73) (Table 7).

The POAG patients were also grouped into high CCT (>549 μm) and low CCT (≤549) (Table 8). However, none MALAT1 or ANRIL SNPs or haplotype were correlated with CCT.

TABLE 2 Association of single-nucleotide polymorphisms (SNPs) in lncRNAs MALAT1 and ANRIL with primary open-angle glaucoma (POAG) onset

Gene	SNP	Genotype	Cases	Controls	OR (95% CI)	*p* Value	p_{HWE} Value
MALAT1	rs591291	CC	133	92			0.988
		CT	163	127			
		TT	50	44			
		T vs. C			0.89 (0.70, 1.12)	0.310	
		CT+TT vs. CC			0.86 (0.62, 1.20)	0.381	
		TT vs. CC+CT			0.84 (0.54, 1.31)	0.441	
	rs619586	AA	216	115			0.974
		AG	115	118			
		GG	15	30			
		G vs. A			**0.52 (0.40, 0.67)**	**<0.001**	
		AG+GG vs. AA			**0.47 (0.34, 0.65)**	**<0.001**	
		GG vs. AA+AG			**0.35 (0.19, 0.67)**	**0.001**	
	rs3200401	CC	148	160			0.940
		CT	151	90			
		TT	47	13			
		T vs. C			**1.94 (1.50, 2.51)**	**<0.001**	
		CT+TT vs. CC			**2.08 (1.50, 2.88)**	**<0.001**	
		TT vs. CC+CT			**3.02 (1.60, 5.71)**	**<0.001**	
	rs664589	CC	233	221			0.397
		CG	102	39			
		GG	11	3			
		G vs. C			**2.33 (1.62, 3.35)**	**<0.001**	
		CG+GG vs. CC			**2.55 (1.71, 3.80)**	**<0.001**	
		GG vs. CC+CG			2.85 (0.79, 10.31)	0.096	
	rs11227209	CC	151	134			0.755
		CG	155	106			
		GG	40	23			
		G vs. C			1.27 (0.99, 1.62)	0.060	
		CG+GG vs. CC			1.34 (0.97, 1.85)	0.073	
		GG vs. CC+CG			1.36 (0.79, 2.34)	0.258	
Gene	**SNP**	**Genotype**	**Cases**	**Controls**	**OR (95% CI)**	***p* Value**	**p_{HWE} Value**
	rs1194338	CC	120	80			0.774
		CA	167	128			
		AA	59	55			
		A vs. C			0.85 (0.67, 1.07)	0.156	
		CA+AA vs. CC			0.82 (0.58, 1.16)	0.267	
		AA vs. CC+CA			0.78 (0.52, 1.17)	0.226	
ANRIL	rs2383207	AA	189	124			0.538
		AG	133	110			
		GG	24	29			
		G vs. A			**0.75 (0.59, 0.97)**	**0.027**	
		AG+GG vs. AA			0.74 (0.54, 1.02)	0.067	
		GG vs. AA+AG			0.60 (0.34, 1.06)	0.076	

TABLE 2 (Continued)

Gene	SNP	Genotype	Cases	Controls	OR (95% CI)	*p* Value	p_{HWE} Value
	rs7865618	GG	10	25			0.941
		GA	68	113			
		AA	268	125			
		A vs. G			**3.08 (2.31, 4.12)**	**<0.001**	
		GA+AA vs. GG			**3.53 (1.66, 7.49)**	**0.001**	
		AA vs. GG+GA			**3.79 (2.67, 5.38)**	**<0.001**	
	rs4977574	AA	67	88			0.969
		AG	171	128			
		GG	108	47			
		G vs. A			**1.74 (1.38, 2.18)**	**<0.001**	
		AG+GG vs. AA			**2.09 (1.45, 3.03)**	**<0.001**	
		GG vs. AA+AG			**2.09 (1.41, 3.08)**	**<0.001**	
	rs10120688	GG	94	88			0.742
		GA	173	126			
		AA	79	49			
		A vs. G			1.24 (0.98, 1.55)	0.069	
		GA+AA vs. GG			1.35 (0.95, 1.91)	0.093	
		AA vs. GG+GA			1.29 (0.87, 1.93)	0.208	
	rs564398	AA	244	152			0.975
		AG	90	96			
		GG	12	15			
		G vs. A			**0.63 (0.47, 0.83)**	**0.001**	
		AG+GG vs. AA			**0.57 (0.41, 0.80)**	**0.001**	
		GG vs. AA+AG			0.59 (0.27, 1.29)	0.184	
	rs1063192	GG	17	21			0.957
		GA	135	106			
		AA	194	136			
		A vs. G			1.21 (0.94, 1.57)	0.143	
		GA+AA vs. GG			1.68 (0.87, 3.25)	0.121	
		AA vs. GG+GA			1.19 (0.86, 1.64)	0.285	
	rs2157719	AA	184	85			0.996
		AG	136	129			
		GG	26	49			
		G vs. A			**0.49 (0.39, 0.62)**	**<0.001**	
		AG+GG vs. AA			**0.42 (0.30, 0.59)**	**<0.001**	
		GG vs. AA+AG			**0.35 (0.21, 0.59)**	**<0.001**	
	rs3217992	CC	73	70			0.862
		CT	172	130			
		TT	101	63			
		T vs. C			1.24 (0.99, 1.56)	0.063	
		CT+TT vs. CC			1.36 (0.93, 1.98)	0.112	
		TT vs. CC+CT			1.31 (0.91, 1.89)	0.149	

Note: The bold means a significantly results with a p value < 0.05.

TABLE 3 Association of haplotypes in lncRNAs MALAT1 and ANRIL with primary open-angle glaucoma (POAG) onset

Haplotype	Case	Control	OR (95% CI)	*p* Value
MALAT1[1]				
ACC	146	123	0.83 (0.6, 1.15)	0.260
ACG	32	12	**2.13 (1.08, 4.22)**	**0.027**
ATC	78	35	**1.90 (1.23, 2.93)**	**0.004**
GCC	39	64	**0.40 (0.26, 0.61)**	**<0.001**
GTC	21	18	0.88 (0.46, 1.69)	0.699
ANRIL[2]				
AGGAA	11	10	0.83 (0.35, 1.99)	0.676
AAAAA	60	31	1.57 (0.98, 2.5)	0.057
AAAAG	22	23	0.71 (0.39, 1.3)	0.265
AAAGA	11	10	0.83 (0.35, 1.99)	0.676
AAGAA	76	22	**3.08 (1.86, 5.11)**	**<0.001**
AAGAG	28	17	1.27 (0.68, 2.38)	0.447
GAAAA	21	15	1.07 (0.54, 2.11)	0.850
GAGAA	27	11	1.94 (0.94, 3.98)	0.067

Note: Haplotype for [1]*MALAT1* rs619586-rs3200401-rs664589; [2]*ANRIL* rs2383207-rs7865618-rs4977574-rs564398-rs2157719.

The bold means a significantly results with a p value < 0.05.

4 | DISCUSSION

Glaucoma, characterized by visual field defects, death of retinal ganglion cells, and gradual degeneration of the optic nerve,[5] affected 79.6 million population worldwide in 2020.[19] The majority of primary glaucoma cases are POAG, and elevated intraocular pressure is among the hazard factors for POAG onset and development. The trabecular meshwork, involved in drainage of aqueous humor, could induce changes in intraocular pressure.

Our results demonstrated that three SNPs (rs619586, rs3200401, and rs664589) in MALAT1 and five SNPs (rs2383207, rs7865618, rs4977574, rs564398, and rs2157719) in ANRIL were associated with POAG in a population of Chinese Han ethnicity. The hypothesis about the role of these SNPs in POAG pathogenesis is that the mutant alleles of SNPs alter a regulatory element which could influence the expression of ANRIL and its sense transcripts.[46] Similarly, it is also hypothesized that protein-coding genes containing significant SNPs may possess response elements that affect the expression of MALAT1.[50,51] The gene variants associated with these SNPs could influence the expression of ANRIL and MALAT1, which will affect their role in cell cycle progression.[52] Such a change has been widely implicated in many diseases, such as coronary artery disease, type 2 diabetes mellitus, intracranial aneurysm, lung cancer, endometriosis, and glaucoma.[53–57]

TABLE 4 Association of single-nucleotide polymorphisms (SNPs) in lncRNAs MALAT1 and ANRIL with vertical cup-to-disc ratio (VCDR) of primary open-angle glaucoma (POAG) patients

Gene	SNP		VCDR > 0.83	VCDR ≤ 0.83	OR (95% CI)	*p* Value	p_{HWE} Value
MALAT1	rs619586	AA	124	92			0.788
		AG	54	61			
		GG	6	9			
		G vs. A			**0.68 (0.47, 0.98)**	**0.040**	
		AG+GG vs. AA			**0.64 (0.41, 0.99)**	**0.040**	
		GG vs. AA+AG			0.57 (0.20, 1.64)	0.296	
	rs3200401	CC	76	72			0.642
		CT	81	70			
		TT	27	20			
		T vs. C			1.13 (0.83, 1.55)	0.450	
		CT+TT vs. CC			1.14 (0.74, 1.75)	0.550	
		TT vs. CC+CT			1.22 (0.66, 2.27)	0.527	
	rs664589	CC	112	121			0.565
		CG	65	37			
		GG	7	4			
		G vs. C			**1.69 (1.13, 2.53)**	**0.010**	
		CG+GG vs. CC			**1.90 (1.20, 3.02)**	**0.010**	
		GG vs. CC+CG			1.56 (0.45, 5.43)	0.480	
ANRIL	rs2383207	AA	93	96			0.363
		AG	73	60			
		GG	18	6			
		G vs. A			**1.47 (1.04, 2.08)**	**0.030**	
		AG+GG vs. AA			1.42 (0.93, 2.18)	0.100	
		GG vs. AA+AG			**2.82 (1.09, 7.28)**	**0.026**	

TABLE 4 (Continued)

Gene	SNP		VCDR > 0.83	VCDR ≤ 0.83	OR (95% CI)	*p* Value	p_{HWE} Value
	rs7865618	GG	4	6			0.078
		GA	34	34			
		AA	146	122			
		A vs. G			1.28 (0.82, 2.01)	0.270	
		GA+AA vs. GG			1.73 (0.48, 6.25)	0.400	
		AA vs. GG+GA			1.26 (0.76, 2.09)	0.371	
	rs4977574	AA	34	33			0.402
		AG	85	86			
		GG	65	43			
		G vs. A			1.24 (0.92, 1.68)	0.160	
		AG+GG vs. AA			1.13 (0.66, 1.93)	0.650	
		GG vs. AA+AG			1.51 (0.95, 2.39)	0.078	
	rs564398	AA	143	101			0.760
		AG	37	53			
		GG	4	8			
		G vs. A			**0.51 (0.34, 0.77)**	**<0.001**	
		AG+GG vs. AA			**0.47 (0.29, 0.75)**	**<0.001**	
		GG vs. AA+AG			0.43 (0.13, 1.46)	0.160	
	rs2157719	AA	109	75			0.893
		AG	65	71			
		GG	10	16			
		G vs. A			**0.64 (0.46, 0.90)**	**0.010**	
		AG+GG vs. AA			**0.59 (0.38, 0.90)**	**0.020**	
		GG vs. AA+AG			0.52 (0.23, 1.18)	0.118	

Note: The bold means a significantly results with a p value < 0.05.

TABLE 5 Association of haplotypes in lncRNAs MALAT1 and ANRIL with vertical cup-to-disc ratio (VCDR) of primary open-angle glaucoma (POAG) patients

Haplotype	Case	Control	OR (95% CI)	*p* Value
MALAT1[1]				
AC	119	106	0.97 (0.62, 1.51)	0.883
AG	32	17	1.80 (0.96, 3.37)	0.066
GC	26	33	0.64 (0.37, 1.13)	0.124
GG	7	5	1.24 (0.39, 3.99)	0.716
ANRIL[2]				
AAA	87	68	1.24 (0.81, 1.90)	0.322
AAG	26	32	0.67 (0.38, 1.18)	0.162
AGA	12	18	0.56 (0.26, 1.20)	0.130
GAA	37	19	**1.89 (1.04, 3.45)**	**0.035**
GAG	11	9	1.08 (0.44, 2.68)	0.866

Note: Haplotype for [1]*MALAT1* rs619586-rs664589; [2]*ANRIL* rs2383207-rs564398-rs2157719The bold means a significantly results with a p value < 0.05.

The progression of the cell cycle can be inhibited by the TGF-β pathway, which has been implicated in a wide variety of disorders, including glaucoma.[58]

TGF-β signaling has been shown to affect the trabecular meshwork by facilitating the deposition of extracellular matrix. In particular, TGF-β2 was found to up-regulate the MMP-2 precursor protein, and to diminish MMP-2 activity by enhancing plasminogen activator inhibitor-1 (PAI-1) expression, which promoted production of extracellular matrix by human trabecular meshwork cells.[59] Components of the cytoskeleton, including vimentin and tropomyosin-1α, were also influenced by TGF-β1/TGF-β2 in human trabecular meshwork cells.[60] Later studies suggested that isomers of versican, which were relevant to aqueous humor outflow and IOP, were up-regulated in TGF-β1/TGF-β2-treated human trabecular meshwork cells.[61] Furthermore, exposure to TGF-β2 increased the expression of connective tissue growth factor (CTGF), thrombospondin-1 (TSP-1), fibronectin, type I/II/III collagen, and PAI-1. These effects were antagonized by bone morphogenetic protein-7 (BMP-7).[62] Furthermore, gremlin, which is over-expressed in the trabecular meshwork of POAG patients, blocked the inhibitory effect of BMP-4 on TGF-β2-mediated elevation of fibronectin expression.[63] Overall, it appears that TGF-β promotes the formation of the cytoskeleton and extracellular matrix, which play pivotal roles in drainage of aqueous humor. There is some evidence that ANRIL and MALAT1 interact with TGF-β to induce disease onset.[64] Specifically, ANRIL activated TGF-β signaling in oral squamous cell carcinoma, prostate cancer, and esophageal squamous

TABLE 6 Association of single-nucleotide polymorphisms (SNPs) in lncRNAs MALAT1 and ANRIL with intraocular pressure (IOP) of primary open-angle glaucoma (POAG) patients

Gene	SNP	Genotype	IOP > 25.74	IOP ≤ 25.74	OR (95% CI)	*p* Value	p_{HWE} Value
MALAT1	rs619586	AA	148	68			0.610
		AG	66	49			
		GG	4	11			
		G vs. A			**0.53 (0.37, 0.77)**	**0.001**	
		AG+GG vs. AA			**0.54 (0.34, 0.85)**	**0.006**	
		GG vs. AA+AG			**0.20 (0.06, 0.64)**	**0.003**	
	rs3200401	CC	98	50			0.632
		CT	93	58			
		TT	27	20			
		T vs. C			0.82 (0.59, 1.13)	0.225	
		CT+TT vs. CC			0.78 (0.50, 1.22)	0.286	
		TT vs. CC+CT			0.76 (0.41, 1.42)	0.396	
	rs664589	CC	153	80			0.538
		CG	61	41			
		GG	4	7			
		G vs. C			0.69 (0.47, 1.02)	0.061	
		CG+GG vs. CC			0.71 (0.45, 1.13)	0.142	
		GG vs. CC+CG			0.32 (0.09, 1.12)	0.063	
ANRIL	rs2383207	AA	107	82			0.680
		AG	93	40			
		GG	18	6			
		G vs. A			**1.65 (1.14, 2.38)**	**0.007**	
		AG+GG vs. AA			**1.85 (1.18, 2.90)**	**0.007**	
		GG vs. AA+AG			1.83 (0.71, 4.73)	0.207	
	rs7865618	GG	8	2			0.806
		GA	42	26			
		AA	168	100			
		A vs. G			0.87 (0.54, 1.39)	0.549	
		GA+AA vs. GG			0.42 (0.09, 2.01)	0.258	
		AA vs. GG+GA			0.94 (0.56, 1.59)	0.823	
	rs4977574	AA	37	30			0.371
		AG	102	69			
		GG	79	29			
		G vs. A			**1.50 (1.10, 2.05)**	**0.010**	
		AG+GG vs. AA			1.50 (0.87, 2.58)	0.142	
		GG vs. AA+AG			**1.94 (1.18, 3.19)**	**0.008**	
	rs564398	AA	172	72			0.699
		AG	41	49			
		GG	5	7			
		G vs. A			**0.41 (0.27, 0.62)**	**<0.001**	
		AG+GG vs. AA			**0.34 (0.21, 0.55)**	**<0.001**	
		GG vs. AA+AG			0.41 (0.13, 1.32)	0.119	
	rs2157719	AA	120	64			0.752
		AG	84	52			
		GG	14	12			
		G vs. A			0.82 (0.58, 1.16)	0.254	
		AG+GG vs. AA			0.82 (0.53, 1.27)	0.365	
		GG vs. AA+AG			0.66 (0.30, 1.47)	0.315	

Note: The bold means a significantly results with a p value < 0.05.

cell carcinoma.[65–67] MALAT1 expression was increased in TGF-β1-treated retinal pigment epithelial (RPE) cells,[68] and in TGF-β2-treated lens epithelial cells.[69] Taken together, these data suggest that ANRIL and MALAT1 may affect POAG, by interacting with TGF-β2 to regulate the trabecular meshwork.

TABLE 7 Association of haplotypes in lncRNAs MALAT1 and ANRIL with intraocular pressure (IOP) of primary open-angle glaucoma (POAG) patients

Haplotype	Case	Control	OR (95% CI)	*p* Value
ANRIL				
AAA	54	38	0.78 (0.48, 1.27)	0.318
AAG	7	13	**0.29 (0.11, 0.76)**	**0.008**
AGA	81	38	1.40 (0.88, 2.24)	0.158
AGG	11	13	0.47 (0.20, 1.08)	0.071
GAA	23	10	1.39 (0.64, 3.03)	0.403
GAG	3	3	0.58 (0.12, 2.92)	0.506
GGA	35	10	**2.26 (1.08, 4.73)**	**0.028**
GGG	5	3	0.98 (0.23, 4.16)	0.976

Note: The bold means a significantly results with a p value < 0.05.

There has been a great deal of research on the association of genotypes with disease. For example, Black women have a higher risk of advanced breast cancer than White women,[70] and the effect of p53 codon 72 polymorphisms and missense mutations on survival of breast cancer patients differed between African-American and Caucasians women,[71] indicating that disease risk is dependent on genetic background, including SNPs. SNPs can induce changes in transcription rate, genetic stability, and cellular function, making individuals predisposed to diseases. For example, rs13447455 at the promoter of CDC7 altered the structure of a DNA-protein complex in breast cancer cells,[72] and functional polymorphism of the lncRNA TUG1 was associated with ischemic stroke risk.[73] The mature MALAT1 transcript is highly stable in organisms,[74] and its stability is altered in disease state. People carrying the GG/AG genotypes of rs619586 in MALAT1 had a lower colorectal cancer risk than those carrying the AA genotype,[75] and lung adenocarcinoma patients carrying the T allele of rs3200401 in the promoter region of MALAT1 survived longer than those carrying the C allele.[76] Our study indicated that rs3200401, rs664589, rs7865618, and rs4977574 increased the risk of POAG, whereas rs619586, rs2383207, rs564398, and rs2157719 reduced the risk. The SNPs rs619586, rs2383207, and rs564398 were also associated with clinical features of POAG.

TABLE 8 Association of single-nucleotide polymorphisms (SNPs) in lncRNAs MALAT1 and ANRIL with central corneal thickness (CCT) of primary open-angle glaucoma (POAG) patients

Gene	SNP	Genotype	CCT > 549	CCT ≤ 549	OR (95% CI)	*p* Value	p_{HWE} Value
MALAT1	rs619586	AA	110	106			0.194
		AG	63	52			
		GG	4	11			
		G vs. A			0.90 (0.62, 1.30)	0.554	
		AG+GG vs. AA			1.02 (0.66, 1.58)	0.920	
		GG vs. AA+AG			0.33 (0.10, 1.06)	0.052	
	rs3200401	CC	79	69			0.639
		CT	71	80			
		TT	27	20			
		T vs. C			0.99 (0.72, 1.35)	1.000	
		CT+TT vs. CC			0.86 (0.56, 1.32)	0.475	
		TT vs. CC+CT			1.34 (0.72, 2.49)	0.354	
	rs664589	CC	113	120			0.377
		CG	59	43			
		GG	5	6			
		G vs. C			1.25 (0.85, 1.85)	0.269	
		CG+GG vs. CC			1.39 (0.88, 2.19)	0.155	
		GG vs. CC+CG			0.79 (0.24, 2.64)	0.699	
ANRIL	rs2383207	AA	89	100			1.000
		AG	73	60			
		GG	15	9			
		G vs. A			1.37 (0.97, 1.93)	0.072	
		AG+GG vs. AA			1.43 (0.93, 2.19)	0.097	
		GG vs. AA+AG			1.65 (0.70, 3.88)	0.249	

(Continues)

TABLE 8 (Continued)

Gene	SNP	Genotype	CCT > 549	CCT ≤ 549	OR (95% CI)	*p* Value	p_{HWE} Value
	rs7865618	GG	4	6			0.097
		GA	32	36			
		AA	141	127			
		A vs. G			1.30 (0.83, 2.04)	0.252	
		GA+AA vs. GG			1.59 (0.44, 5.74)	0.475	
		AA vs. GG+GA			1.30 (0.78, 2.16)	0.315	
	rs4977574	AA	30	37			0.888
		AG	86	85			
		GG	61	47			
		G vs. A			1.27 (0.94, 1.71)	0.124	
		AG+GG vs. AA			1.37 (0.80, 2.34)	0.245	
		GG vs. AA+AG			1.37 (0.87, 2.16)	0.182	
	rs564398	AA	132	112			0.377
		AG	41	49			
		GG	4	8			
		G vs. A			0.67 (0.45, 1.01)	0.056	
		AG+GG vs. AA			0.67 (0.42, 1.07)	0.090	
		GG vs. AA+AG			0.47 (0.14, 1.59)	0.209	
	rs2157719	AA	101	83			0.823
		AG	66	70			
		GG	10	16			
		G vs. A			0.74 (0.53, 1.03)	0.082	
		AG+GG vs. AA			0.73 (0.48, 1.11)	0.139	
		GG vs. AA+AG			0.57 (0.25, 1.29)	0.179	

In conclusion, SNPs in ANRIL and MALAT1 were predictive of POAG, providing an alternative approach to POAG diagnosis. However, this investigation was based on a small sample composed of a single ethnicity. It remains, therefore, unclear whether these results will hold in other populations. Stratified analyses based on family history, smoking, and other risk factors for POAG[77,78] were not concluded, so there is a risk of sampling bias. Therefore, further studies with more rigorous experimental designs are required.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article.

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