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

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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,\(^5,5\) and the underlying mechanism of POAG remains still unclear.

Recent studies have suggested a correlation between IncRNAs variants and POAG; here, we focus on the IncRNAs MALAT1 and IncRNA ANRIL. Of note, ANRIL, also known as CDKN2B-AS, has been reported to be associated with occurrence and progression of cardiovascular diseases, cancers, diabetes, glaucoma, and endometriosis.\(^6\) 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.

MALAT1 is a highly conserved IncRNA 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\(^10–36\) and ANRIL\(^14,37–45\) 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 \(\chi^2\) 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 \(\chi^2\) 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
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 rs645489 (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 was associated with 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 IncRNAs MALAT1 and ANRIL with primary open-angle glaucoma (POAG) onset

| Gene   | SNP     | Genotype | Cases | Controls | OR (95% CI) | p Value | pHWE Value |
|--------|---------|----------|-------|----------|-------------|---------|------------|
| MALAT1 | rs591291| CC       | 133   | 92       | 0.89 (0.70, 1.12) | 0.310   | 0.988      |
|        |         | CT       | 163   | 127      | 0.86 (0.62, 1.20)  | 0.381   |            |
|        |         | TT       | 50    | 44       | 0.84 (0.54, 1.31)  | 0.441   |            |
|        | rs619586| AA       | 216   | 115      |             |         | 0.974      |
|        |         | AG       | 115   | 118      |             |         |            |
|        |         | GG       | 15    | 30       |             |         |            |
| ANRIL  | rs2383207| AA       | 189   | 124      | 0.75 (0.59, 0.97)  | 0.027   | 0.538      |
|        |         | AG       | 133   | 110      | 0.74 (0.54, 1.02)  | 0.067   |            |
|        |         | GG       | 24    | 29       | 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.
DISCUSSION

Glaucoma, characterized by visual field defects, death of retinal ganglion cells, and gradual degeneration of the optic nerve, affected 79.6 million population worldwide in 2020. 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. Similarly, it is also hypothesized that protein-coding genes containing significant SNPs may possess response elements that affect the expression of MALAT1. The gene variants associated with these SNPs could influence the expression of ANRIL and MALAT1, which will affect their role in cell cycle progression. 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.

### 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 |
|-----------|------|---------|-------------|---------|
| MALAT11   |      |         |             |         |
| 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   |
| ANRIL2    |      |         |             |         |
| 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 **MALAT1** rs619586-rs3200401-rs664589; **ANRIL** rs2383207-rs7865618-rs4977574-rs564398-rs2157719. The bold means a significantly results with a p value < 0.05.

### 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 | pHWE Value |
|--------|----------|-------------|-------------|-------------|---------|------------|
| MALAT1 | rs619586 | AA          | 124         | 92          | 0.83 (0.68, 1.0) | 0.040 |
|        |          | AG          | 54          | 61          |         | 0.040 |
|        |          | GG          | 6           | 9           |         | 0.296 |
|        | rs3200401| CC          | 76          | 72          | 0.64 (0.41, 0.99) | 0.040 |
|        |          | CT          | 81          | 70          | 0.57 (0.20, 1.64) | 0.296 |
|        |          | TT          | 27          | 20          |         | 0.642 |
|        | rs664589 | CC          | 112         | 121         | 0.69 (1.13, 2.53) | 0.010 |
|        |          | CG          | 65          | 37          | 1.90 (1.20, 3.02) | 0.010 |
|        |          | GG          | 7           | 4           | 1.56 (0.45, 5.43) | 0.480 |
| ANRIL  | rs2383207| AA          | 93          | 96          | 1.47 (1.04, 2.08) | 0.030 |
|        |          | AG          | 73          | 60          | 1.42 (0.93, 2.18) | 0.100 |
|        |          | GG          | 18          | 6           | 2.82 (1.09, 7.28) | 0.026 |

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

The 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. 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.

Components of the cytoskeleton, including vimentin and tropomyosin-1α, were also influenced by TGF-β1/TGF-β2 in human trabecular meshwork cells. 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. 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). 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. 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. Specifically, ANRIL activated TGF-β signaling in oral squamous cell carcinoma, prostate cancer, and esophageal squamous

### TABLE 4 (Continued)

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

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<sup>1</sup> | 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<sup>2</sup> | 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 <sup>1</sup>MALAT1 rs619586-rs664589; <sup>2</sup>ANRIL rs2383207-rs564398-rs2157719. The bold means a significantly results with a p value < 0.05.
Table 6  Association of single-nucleotide polymorphisms (SNPs) in IncRNAs 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. MALAT1 expression was increased in TGF-β1-treated retinal pigment epithelial (RPE) cells, and in TGF-β2-treated lens epithelial cells. Taken together, these data suggest that ANRIL and MALAT1 may affect POAG, by interacting with TGF-β2 to regulate the trabecular meshwork.

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, and the effect of p53 codon 72 polymorphisms and missense mutations on survival of breast cancer patients differed between African-American and Caucasians women, 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, and functional polymorphism of the lncRNA TUG1 was associated with ischemic stroke risk. The mature MALAT1 transcript is highly stable in organisms, 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, and lung adenocarcinoma patients carrying the T allele of rs3200401 in the promoter region of MALAT1 survived longer than those carrying the C allele. 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 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.

### 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 | pHWE 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)
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 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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