Genetics

A Common Variant in *MIR182* Is Associated With Primary Open-Angle Glaucoma in the NEIGHBORHOOD Consortium

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PURPOSE. Noncoding microRNAs (miRNAs) have been implicated in the pathogenesis of glaucoma. We aimed to identify common variants in miRNA coding genes (*MIR*) associated with primary open-angle glaucoma (POAG).

METHODS. Using the NEIGHBORHOOD data set (3853 cases/33,480 controls with European ancestry), we first assessed the relation between 85 variants in 76 *MIR* genes and overall POAG. Subtype-specific analyses were performed in high-tension glaucoma (HTG) and normal-tension glaucoma subsets. Second, we examined the expression of miR-182, which was associated with POAG, in postmortem human ocular tissues (ciliary body, cornea, retina, and trabecular meshwork [TM]), using miRNA sequencing (miRNA-Seq) and droplet digital PCR (ddPCR). Third, miR-182 expression was also examined in human aqueous humor (AH) by using miRNA-Seq. Fourth, exosomes secreted from primary human TM cells were examined for miR-182 expression by using miRNA-Seq. Fifth, using ddPCR we compared miR-182 expression in AH between five HTG cases and five controls.

RESULTS. Only rs76481776 in *MIR182* gene was associated with POAG after adjustment for multiple comparisons (odds ratio [OR] = 1.23, 95% confidence interval [CI]: 1.11–1.42, P = 0.0002). Subtype analysis indicated that the association was primarily in the HTG subset (OR = 1.26, 95% CI: 1.08–1.47, P = 0.004). The risk allele T has been associated with elevated miR-182 expression in vitro. Data from ddPCR and miRNA-Seq confirmed miR-182 expression in all examined ocular tissues and TM-derived exosomes. Interestingly, miR-182 expression in AH was 2-fold higher in HTG patients than nonglaucoma controls (P = 0.03) without controlling for medication treatment.

CONCLUSIONS. Our integrative study is the first to associate rs76481776 with POAG via elevated miR-182 expression.

Keywords: miR-182, POAG, genetic association, NEIGHBORHOOD, exosome

Glaucoma, a heterogeneous group of disorders with many different subtypes, is a leading cause of irreversible blindness affecting more than 60 million individuals worldwide.[1-3] Primary open-angle glaucoma (POAG) is the most common type and has a complex inheritance pattern.[3] It is defined by a characteristic pattern of progressive retinal ganglion cell death, optic nerve head excavation, and visual field loss. Known risk factors for POAG include advanced age, elevated intraocular pressure (IOP), family history of glaucoma, African ancestry, and genetic factors.[3] Family-based linkage studies and case-control association studies have identified a large number of genomic loci with mutations and genetic variants associated with POAG or glaucoma-related ocular phenotypes, such as elevated IOP, increased cup-to-disc ratio, and reduced central cornea thickness (see reviews[1,4,5]).

Besides the genetic factors, microRNAs (miRNAs) also play important roles in the pathogenesis of POAG. These miRNAs are encoded by *MIR* RNA genes. For example, miR-183 targets integrin-β1 and affects trabecular meshwork (TM) physiology.[6] Regulated by TGF-β2, miR-29b modulates the expression of extracellular matrix genes, which function in the aqueous outflow pathway.[7,8] Induced miR-24 expression in the TM by cyclic mechanic stress downregulates FURIN and TGF-β1, of which higher expression levels lead to elevated IOP.[9] A number of miRNAs, such as miR-204, miR-200c, miR-182, and miR-183, are differentially expressed in human TM cells in stress-induced senescence or replicative senescence.[10,11] miR-200c inhibits the contraction of TM cells and reduces IOP in living rats, while inhibition of miR-200c in rats leads to a robust IOP increase.[12] To further understand the role of miRNAs in POAG, it will be necessary to identify the genetic factors that regulate miRNA expression in ocular tissues.

Sequence alterations in *MIR* genes encoding miRNAs have been previously associated with many human disorders.[13] Mutations of miRNA genes have been identified in a number of diseases, such as keratoconus with congenital cataract (*MIR184*) and progressive hearing loss (*MIR96*).[14-16] Variants in the seed region of miR-125a impact not only its mediated translational suppression, but also its biogenesis—processing from pri–miR-125a to pre–miR-125a.[17] Variants in several *MIR* genes have been associated with uveitis in Chinese populations.[18,19] To determine the role of *MIR* genes in POAG, we performed a candidate variant association analysis with common single nucleotide polymorphisms (SNPs) within *MIR* genes in a large POAG consortium case-control data set with European ancestry. Association analysis was followed by gene expression and differential expression analysis in human ocular tissues and aqueous humor samples.

METHODS

Study Population

Our research adhered to the tenets of the Declaration of Helsinki and was Health Insurance Portability and Accountability Act (HIPAA)-compliant. Institutional Review Board (IRB)/Ethics Committee approval was obtained at the Medical College of Georgia and all the participating institutions involved in the NEIGHBORHOOD (National Eye Institute Glaucoma Human Genetics Collaboration Heritable Overall Operational Database) consortium. Written informed consent was obtained from all participating individuals. Our study used the NEIGHBORHOOD consortium containing eight data sets: Iowa, NEIGHBOR, MEEI, OHTS, Marshfield, Nurses' Health Study (NHS)/Health Professionals Follow-up Study (HPFS) Affymetrix, NHS/HPFS Illumina, and Women's Genome Health Study (WGHS).[20] Details of these eight data sets and the definition of POAG have been described previously.[20] NEIGHBORHOOD includes 3853 POAG cases and 33,480 controls with European ancestry from the United States. Primary open-angle glaucoma was defined as characteristic visual field defects consistent with glaucomatous optic neuropathy. Elevated IOP (>21 mm Hg) was not used as a criterion for POAG. Primary open-angle glaucoma cases were classified as either high-tension glaucoma (HTG) (maximum IOP > 21 mm Hg) or normal-tension glaucoma (NTG) (maximum IOP ≤ 21 mm Hg) when data on maximum IOP were available.[20]

Genotype imputation was done by using IMPUTE2 or MACH with the 1000Genomes Project Reference panel (March 2012), and quality control was done for each data set as previously described.[20] Principal components were computed for all participants by using EIGENSTRAT. For each data set, logistic regression analysis was performed with ProbABEL for all analyses (POAG overall, HTG, NTG, POAG among males only, and POAG among females only), with the adjustment for age, sex, and any significant eigenvectors from principal components analysis. METAL was used for a meta-analysis of the estimated genotypic probabilities for all 6,425,680 variants as previously described.[20]

Meta-analysis of MIR-Related Sequence Variants

Table Browser in the UCSC Genome Browser was used to identify a list of genomic coordinates for all known miRNA genes in the human genome, based on the GRCh37/hg19 build. Using dbSNP version 141, a list of common SNPs with minor allele frequency (MAF) > 0.01 was then created, covering all genomic regions of *MIR* genes, including precursors and seed regions of miRNAs. The MAF was calculated in the general population. A total of 253 common SNPs are located in the autosomal chromosomes (Supplementary Table S1), of which 138 SNPs have MAF greater than 0.05, meeting the minimum MAF cutoff for imputed SNPs in the NEIGHBORHOOD data set. Overlap between these 138 SNPs and the imputed SNPs in NEIGHBORHOOD analysis was examined, indicating that 85 SNPs were available in the NEIGHBORHOOD. The genetic analysis included association with POAG overall, two subtype analyses (NTG and HTG), and two stratified analyses (POAG among males, and POAG among females). Eighty-five SNPs in 76 *MIR* genes were included in the NEIGHBORHOOD meta-analysis with POAG overall in all eight data sets (Supplementary Table S2). Sex-stratified and subtype analyses for NTG and HTG were performed by using the controls from each related data set. Although this is a genome-wide analysis for *MIR*-related SNPs, only 85 statistical comparisons were performed, rendering a stringent *P* value cutoff of 5.88×10^{-4} (0.05/85) for significant associations.

miRNA Sequencing

miRNA sequencing (miRNA-Seq) was performed as previously described.[21,22] Briefly, human ocular tissues including two corneal (53-year old female and 49-year old male), two ciliary body (CB) (67-year-old male and 72-year-old female), two retinal (72-year-old female and 59-year-old female), and four trabecular meshwork (TM) samples (77-year-old male, 67-year-old female, 59-year-old female, and 61-year-old female) were obtained from 10 postmortem eyes donated by healthy individuals with no history of ocular diseases, within 24 hours of death as described previously.[23] Total RNA was extracted by using mirVana miRNA Isolation kit from Life Technologies (Carlsbad, CA, USA) according to the standard protocol. After quality and quantity check, 1 μg total RNA was used to generate the small RNA sequencing library using the TruSeq Small RNA Sample Prep kit from Illumina (San Diego, CA, USA) according to the standard protocol. Sequencing was performed with Illumina MiSeq, using the MiSeq Reagent kit v2 with 50 cycles. Sequencing reads for all 10 samples were analyzed as previously described.[22] The expression level for each miRNA was normalized as the number of sequence reads per million of total sequencing reads for each tissue with Microsoft Excel 2013 (Microsoft Corp., Seattle, WA, USA) and the R Language and Environment for Statistical Computing.[24] The expression levels of miR-182 were examined in these 10 ocular samples.

miR-182 Expression in Human Ocular Tissues

To examine the expression of miR-182 in human ocular tissues, we determined miR-182 expression in eight postmortem human ocular samples from four tissues (two CB, two corneal, 2 retinal, and two TM samples) by using droplet digital polymerase chain reaction (ddPCR). RNA from the tissues was prepared by using the same method described above.[23] Droplet digital PCR was performed by using the QX200 Droplet Digital PCR system from Bio-Rad (Hercules, CA, USA) as described previously.[25] TaqMan miRNA assay for miR-182 (Cat No. 4427975, Assay ID 002234) was obtained from Applied Biosystems (Grand Island, NY, USA). To perform the ddPCR, approximately 20 ng total RNA of each sample was reverse transcribed to cDNA with TaqMan microRNA Reverse Transcriptase kit from Applied Biosystems according to the manufacturer's instructions. Droplet digital PCR was performed by using QX200 ddPCR Supermix for Probes (no dUTP) from Bio-Rad. The amplified PCR products were quantified by using Bio-Rad QX200 droplet reader and analyzed by the QuantaSoft software. For quality control, PCR reactions with fewer than 10,000 droplets were excluded, and negative controls containing water instead of cDNA were included to ensure no contamination in all reagents.

Characterization of Exosomes and miRNAs Derived From Primary Human TM

Human TM (HTM) cells were isolated from donor eyes by using a blunt dissection technique and then the extracellular matrix digestion protocol. Cell strains were characterized as previously described.[26] Cells were grown in low-glucose Dulbecco's modified Eagle's medium, containing 1% exosome-depleted fetal bovine serum (FBS), 100 U/mL penicillin, 0.1 mg/mL streptomycin, and 0.29 mg/mL glutamine with 5% CO_2 at 37°C. Cells were serum starved overnight before exosome collection. Culture media was replaced with fresh serum-free media, and cells were allowed to condition the media for 2.5 hours. Conditioned media was centrifuged at 300g for 10 minutes at 4°C, followed by 10,000g for 40 minutes at 4°C. The resulting supernatant was then spun at 100,000g for 70 minutes at 4°C in an SW28 rotor (Beckman Coulter, Inc., Indianapolis, IN, USA), and the pellet was resuspended with PBS. This solution was spun again at 100,000g for 70 minutes at 4°C in an SW28 rotor. The supernatant was removed, and the pellet resuspended in PBS. The concentration and size distribution of the prepared vesicles were determined by using nanoparticle tracking analysis (NanoSight NS500, Malvern, Inc., Malvern, United Kingdom) as previously described.[22] Three separate measurements were performed for the isolated exosomes, and the average of these measurements was used in the analysis. Exosomal RNA was extracted with the miRCURY RNA Isolation kit (Exiqon, Woburn, MA, USA) according to the recommended procedure.[22] miRNA-Seq was performed as previously described.[21,22] After miRNA-Seq, the expression of miR-182 was examined in these exosomes.

miR-182 Expression in Aqueous Humor (AH) From Glaucoma Patients and Normal Controls

Human AH samples (~100 μL per individual) were collected at Vanderbilt University Medical Center with protocols approved by Vanderbilt University IRB. All samples were collected by a single surgeon (RWK) using consistent techniques described previously.[27] Our study for ddPCR included AH from five HTG cases and five controls. The mean age was 64.4 ± 9.7 years for controls (48, 64, 67, 71, and 72 years individually) and 73.6 ±

TABLE 1. The Number of Individuals From the NEIGHBORHOOD Data Set

	No. Cases	No. Controls
NEIGHBORHOOD	3853	33,480
High-tension glaucoma	1868	31,497
Normal-tension glaucoma	725	11,145
Male	1691	4367
Female	2160	29,111

NEIGHBORHOOD, National Eye Institute Glaucoma Human Genetics Collaboration Heritable Overall Operational Database.

7.0 years for cases (64, 71, 72, 80, and 81 years individually). All 10 donors were of European descent, with three male/two female controls and five female cases. Total RNA was extracted by using the miRCURY RNA Isolation kit according to the standard procedure. To perform the ddPCR, 3 μL of 50 μL total RNA from each sample was used to perform ddPCR as described above. The absolute copies of miR-182 were measured in all 10 AH samples. Since the same volume of extracted RNA was used for all 10 AH samples, the absolute copies of miR-182 were compared between the control and POAG groups by using Student's *t*-test. No specific covariates, such as age or sex, were included in the test.

RESULTS

Genetic Association With POAG

Our study included a total of 3853 POAG cases and 33,480 controls from the NEIGHBORHOOD consortium (Table 1). Among POAG, we classified 725 cases as NTG and 1868 cases as HTG, while the remaining 1260 cases were not classifiable owing to limited available information. This consortium included 1691 male and 2160 female POAG cases as well as 4367 male and 29,111 female controls.

Eighty-five SNPs were successfully included in the NEIGHBORHOOD meta-analysis after quality control (Supplementary Table S2). Only one SNP rs76481776 located in *MIR182* gene was significantly associated POAG ($P = 0.0002$, odds ratio [OR] = 1.23, 95% confidence interval [CI]: 1.11–1.42; Table 2). This SNP was also nominally significant in the subgroup analyses of HTG ($P = 0.004$, OR = 1.26, 95% CI: 1.08–1.47), but not NTG ($P = 0.13$, OR = 1.21, 95% CI: 0.94–1.54). This SNP was also nominally significant in male POAG cases ($P = 0.007$, OR = 1.31, 95% CI: 1.08–1.60) and female POAG cases ($P = 0.005$, OR = 1.24, 95% CI: 1.07–1.45). It is noted that the stratified associations with HTG or sex were not significant after correction for multiple comparisons. The frequency of T allele was 0.05 in controls and 0.08 in POAG cases.

FIGURE 1. Expression of miR-182 in four different normal ocular tissues with miRNA sequencing (**A**) and ddPCR (**B**), including CB, cornea, retina, and TM. miRNA-Seq was done with two CB, two corneal, two retinal, and four TM samples, while ddPCR was done with two CB, two corneal, two retinal, and two TM samples.

miRNA Expression in Human Ocular Tissues

Our miRNA-Seq in normal human ocular tissue successfully identified the expression of many miRNAs, including miR-182 (Fig. 1A). miR-182 was highly expressed in all four ocular tissues tested. Our ddPCR assay successfully validated the expression of miR-182 in normal human retinal, corneal, CB, and TM tissues (Fig. 1B), with the highest expression in retina. Since the association of SNP rs76481776 appears to be specifically associated with HTG, we also examined the expression of miR-182 in human AH. We have shown previously that AH has miRNA-containing exosomes.[22] Our miRNA-Seq data from pooled nonglaucoma human AH samples indicated miR-182 expression with five reads per million sequencing reads, suggesting a relatively low expression of miR-182 in nonglaucoma human AH.

TABLE 2. Association of rs76481776 in *MIR182* in the NEIGHBORHOOD Data Set

	POAG8	NTG4	HTG6	Male7	Females8
P value	0.00020	0.13	0.0038	0.0070	0.0050
OR	1.23	1.21	1.26	1.31	1.24
95% CI	1.11–1.42	0.94–1.54	1.08–1.47	1.08–1.60	1.07–1.45
Direction	−++−++++	++++	−+++++	+++++++	+−−+−+++

Symbols ± refer to the direction of effect of the reference allele (A1) where + indicates a variant is associated in the positive direction, − indicates it is associated in the negative direction. Order of data sets in POAG8 and Females8: Iowa, NEIGHBOR, MEEI, OHTS, Marshfield, NHS/HPFS Affymetrix, NHS/HPFS Illumina, and WGHS; order of data sets for NTG4: NEIGHBOR, MEEI, NHS/HPFS Affymetrix, NHS/HPFS Illumina; order of data sets for HTG6: OHTS, NEIGHBOR, MEEI, NHS/HPFS Affymetrix, NHS/HPFS Illumina, WGHS; order of data sets for Male7: Iowa, NEIGHBOR, MEEI, OHTS, Marshfield, NHS/HPFS Affymetrix, NHS/HPFS Illumina. NEIGHBORHOOD, National Eye Institute Glaucoma Human Genetics Collaboration Heritable Overall Operational Database.
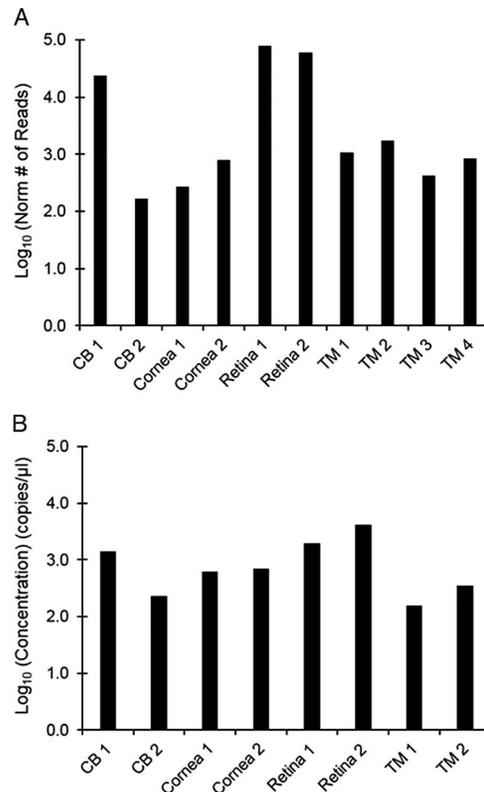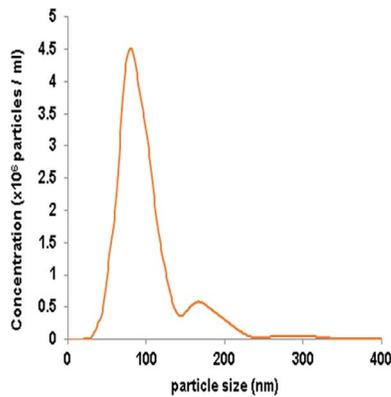
FIGURE 2. Nanoparticle tracking analysis (size and concentration) of exosomes derived from primary human nonglaucoma trabecular meshwork cells, using NanoSight NS500 system. The exosome sample was resuspended in 1X PBS and diluted by 1:500 with PBS. Three separate measurements were performed to calculate the mean, which were used to derive this figure.

miR-182 Expression in HTM-Derived Exosomes

Because of the critical role of TM in aqueous outflow pathway, we isolated and characterized the exosomes from human primary nonglaucoma TM cells by using nanoparticle tracking analysis (Fig. 2). The data shown in Figure 2 were the average of three separate measurements of HTM-derived exosomes. The diameter (the most abundant peak) was 82 nm and the concentration of isolated exosomes was 2.87×10^8 particles/mL with 1:500 dilution, therefore with an original concentration of 1.44×10^{11} particles/mL. After extracting RNA from these exosomes, our miRNA-Seq data indicated the expression of miR-182 in the HTM-derived exosomes as four read counts per million sequencing reads, suggesting a relatively low expression level in exosomes from nonglaucoma HTM cells.

Differential Expression Analysis in Glaucoma

Using five nonglaucoma and five glaucoma AH samples, we checked the differential expression of miR-182 using ddPCR. We have found that although the relative expression of miR-182 in human AH was low, the absolute expression of miR-182 in AH from patients with HTG was significantly elevated by 2-fold ($P = 0.03$; Fig. 3).

DISCUSSION

For the first time, using the comprehensive NEIGHBORHOOD data set, we have identified a significant association of rs76481776 in *MIR182* gene with POAG, especially with the HTG subset. We have confirmed the expression of miR-182 in several normal human ocular tissues including AH, as well as miRNA-containing exosomes derived from human primary TM cells. Our study also indicated the significantly elevated expression of miR-182 in AH samples from HTG patients compared to those from unaffected controls. Both genetic association and differential expression data indicated the potential contribution of miR-182 in the pathogenesis of POAG.

Although we identified 138 *MIR*-related common SNPs, only 85 SNPs were included in our final analysis. The lack of coverage on the excluded 53 common SNPs could be due to several reasons. First, these common SNPs may not be tagged by the available genotyped SNPs on the selected Illumina/Affymetrix arrays. Second, some of these SNPs may have been removed during the quality control (MAF $\geq$ 0.05, imputation
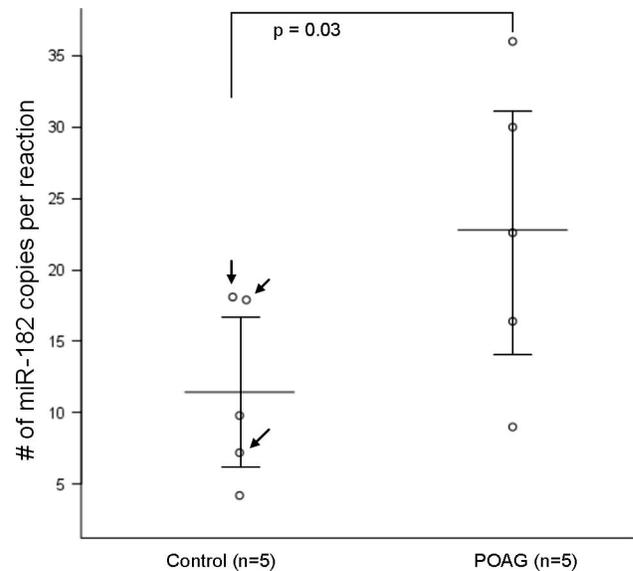

FIGURE 3. Differential expression of miR-182 in human aqueous humor samples from nonglaucoma controls ($n = 5$) and HTG patients ($n = 5$). The absolute copy numbers of miR-182 in each sample was measured by using ddPCR. All POAG patients were female, while controls included 3 males and 2 females. The males in the control group were marked with the *black arrow*.

quality score $[r^2] \geq 0.7$, presence of SNPs in at least two studies, and effect estimate $|\beta| \leq 5$) after imputation. Third, the actual observed MAF frequency in NEIGHBORHOOD data sets might be lower than 0.05. Lastly, it could be that the MAF from dbSNP141 was based on non-Caucasian populations.

Interestingly, the minor T allele of this variant rs76481776, which is associated with increased risk of POAG, has been shown to increase the expression of mature miR-182 in vitro by 30%.[28] Our genetic association suggests that elevated expression of miR-182 might underlie the increase in glaucoma risk. Our differential expression analysis with human AH confirmed the significantly 2-fold elevated expression in HTG patients. Since all of the HTG patients were treated with antiglaucoma medications at the time of AH collection, we could not rule out medication effect on the observed differentiation expression of miR-182. In addition, all five HTG cases were females, while the controls included two females and three males. Owing to the limited access to AH from HTG patients, determining the cause of elevated miR-182 expression in AH remains a challenge. As our expression data indicated, miR-182 is highly expressed in cornea, CB, and TM; it will be difficult to determine which ocular tissue directly contributes to the increased miR-182 expression in AH of glaucoma patients.

Previous research from Li and colleagues[10] has revealed that miR-182 expression is upregulated by 7- to 9-fold in primary HTM cells with stress-induced premature senescence and that miR-182 overexpression in these HTM cells may contribute to the phenotypic alterations of senescent cells. These miR-182 expression findings are consistent with our observation of elevated expression of miR-182 in POAG, suggested by both genetic association and differential AH expression. The elevated expression of miR-182 in TM cells may contribute to potential TM cellular dysfunction, such as cell contractility and/or phagocytosis ability. Additional studies are necessary to verify this hypothesis.

The specific variant rs76481776 in *MIR182* gene has been associated with several other human genetic disorders, such as late insomnia of major depression, Behçet's disease, and Vogt-Koyanagi-Harada syndrome.[18,28] Both studies[18,28] identified the

same associated risk allele T with elevated expression of miR-182 in individuals with homozygotes of T allele. Elevated miR-182 expression may reduce the expression of several circadian rhythm–related genes such as *ADCY6*, *CLOCK*, and *DISP*, which regulates the endogenous circadian clock.[28,29]

Owing to its high expression in retina, miR-182 has been previously evaluated for a role in retinal disease. Conditional knockout of miR-182 in the mouse has shown no apparent structural retinal abnormalities with either heterozygotes or homozygotes after 1 year of age.[30] Additional work indicates that miR-182, together with miR-183 and miR-96, may be necessary for cone outer segment maintenance, functional outer segment formation,[31] acute light-induced retinal degeneration in mice,[32] and postnatal functional differentiation and synaptic connectivity of photoreceptors.[33] However, miR-182's potential function in the anterior chamber tissues has not been previously evaluated. Our study suggests that expression of miR-182 is altered in glaucoma patients and that variation in expression could contribute to glaucoma development. Additional research including transgenic mouse models will be necessary to explore the specific role of miR-182 in IOP regulation and AH dynamics.

miR-182, depending on the type of cell and tissue, may affect the expression of many target genes involved in different pathways, such as DNA repair, cell cycle, phototransduction, apoptotic pathway, cell proliferation, cell migration, response to oxidative stress, and vesicle organization.[10,28,31–36] Among these target genes, sequencing variants in *CHEK2* (checkpoint kinase 2) gene have been associated with vertical cup-to-disc ratio and HTG.[37,38] Another target FOXO1 is required for proper lymphatic vascular development.[39] Variants in or near *FOXO1* have recently been associated with central cornea thickness, which is a risk factor for glaucoma.[40–42] On the other hand, FOXO1, as a direct target of FOXC1, is involved in maintaining the cellular homeostasis and resistance to oxidative stress in the eye, while *FOXC1* sequence variants have been associated with POAG.[20,43–46] Other validated target genes of miR-182 include profilin 1 (*PFN1*), metastasis suppressor 1 (*MTSS1*), microphthalmia-associated transcription factor (*MITF*), and reversion-inducing-cysteine-rick protein with Kazal motifs (*RECK*).[47–50] In human cancer TGF-β may induce miR-182 expression, which suppresses cylindromatosis expression (CYLD, an NF-κB–negative regulator), leading to prolonged NF-κB activation.[51] Interestingly, TGF-β–related pathways have been shown to play important roles in the pathogenesis of POAG and fibrosis.[52] The exact mechanism or targets associated with elevated miR-182 expression in relation to HTG remain unknown.

Our study had several limitations. First, although our NEIGHBORHOOD consortium is the largest POAG case-control data set currently available worldwide, additional genetic studies replicating the genetic association of *MIR182* variant with HTG will help confirm these findings. Since our association included only subjects with European ancestry, studies with other ethnicities will be necessary. Second, our human AH–based expression study is relatively small and is confounded by use of medications. Third, owing to the lack of genotype information from the donors, our study did not examine the correlation of miR-182 expression with different genotypes of the HTG-associated variant (rs76481776). It would be interesting to examine the miR-182 levels in AH from HTG patients with homozygous risk T alleles and controls with homozygous T alleles.

In summary, we identified a significant association between miR-182 and POAG, especially in HTG individuals. The high-level expression of miR-182 in glaucoma-associated ocular tissues and its elevated expression in AH from HTG patients and human TM-derived exosomes further support the potential contribution of miR-182 in POAG pathogenesis through regulation of AH dynamics and IOP. Further studies may identify miR-182 targets for novel therapies for POAG.

Disclosure: **Y. Liu**, None; **J. Cooke Bailey**, None; **I. Helwa**, None; **W.M. Dismuke**, None; **J. Cai**, None; **M. Drewry**, None; **M.H. Brilliant**, None; **D.L. Budenz**, None; **W.G. Christen**, None; **D.I. Chasman**, None; **J.H. Fingert**, None; **D. Gaasterland**, None; **T. Gaasterland**, None; **M.O. Gordon**, None; **R.P. Igo Jr**, None; **J.H. Kang**, None; **M.A. Kass**, None; **P. Kraft**, None; **R.K. Lee**, None; **P.

Lichter, None; **S.E. Moroi**, None; **A. Realini**, None; **J.E. Richards**, None; **R. Ritch**, None; **J.S. Schuman**, None; **W.K. Scott**, None; **K. Singh**, None; **A.J. Sit**, None; **Y.E. Song**, None; **D. Vollrath**, None; **R. Weinreb**, None; **F. Medeiros**, None; **G. Wollstein**, None; **D.J. Zack**, None; **K. Zhang**, None; **M.A. Pericak-Vance**, None; **P. Gonzalez**, None; **W.D. Stamer**, None; **J. Kuchtey**, None; **R.W. Kuchtey**, None; **R.R. Allingham**, None; **M.A. Hauser**, None; **L.R. Pasquale**, None; **J.L. Haines**, None; **J.L. Wiggs**, None

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