Genetic Variants Associated With Different Risks for High Tension Glaucoma and Normal Tension Glaucoma in a Chinese Population

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P</p>
7q31. All of these selected genes primarily point to pathways involved in optic nerve development and retinal ganglion cell (RGC) apoptosis. For instance, ATOH7 is known to have a key role in RGC formation;6 SIX1/SIX6 are transcription factors involved in eye development;7,8 and CDKN2B-AS1 codes for an antisense RNA that regulates the expression of CDKN2B, which in turn regulates cell cycle maintenance and apoptosis of RGCs.5,9 The TMCO1 gene encodes a transmembrane protein with a coiled-coil domain that may localize to the Golgi apparatus and endoplasmic reticulum or to the mitochondria in different cell types, also with a proposed role in apoptosis.4,10 The CAV1 and CAV2 are members of the caveolin gene family which regulate adult neural stem cell proliferation, and this is essential for establishing the credibility of a genetically meaningful if they are replicated across different ethnic groups and this is essential for establishing the credibility of a genotype-phenotype association. In this study, we aimed to replicate previously reported SNPs in POAG in a large sample size Han Chinese population. Genetic associations generally are more biologically meaningful if they are replicated across different ethnic groups and this is essential for establishing the credibility of a genotype-phenotype association. In this study, we aimed to replicate previously reported SNPs in POAG in a large sample size Han Chinese population and investigate their association predilection toward two major subphenotypes of POAG.

Multiple studies have confirmed or replicated these genetic associations in populations from Europe,11–14 the United States,15–17 Japan,18–21 and Africa.22–25 However, these loci have not been validated in a large sample size Han Chinese population. Genetic associations generally are more biologically meaningful if they are replicated across different ethnic groups and this is essential for establishing the credibility of a genotype-phenotype association. In this study, we aimed to replicate previously reported SNPs in POAG in a large sample size Han Chinese population and investigate their association predilection toward two major subphenotypes of POAG.

Materials and Methods

Patients

The study was approved by the ethical committee of Eye and ENT hospital, Fudan University, and all procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each individual.

The samples used in the study were collected in the Eye and ENT hospital. Each participant underwent a complete eye examination including best corrected visual acuity, slit-lamp examination of the anterior chamber, measurement of IOP, and fundus examination. Central corneal thickness (CCT), axial length (AL), gonioscopy, and visual field (VF) were examined if POAG was suspected.

Subjects with POAG were unrelated and met the following inclusion criteria22: glaucomatous optic neuropathy in at least one eye and VF loss consistent with optic nerve damage in at least one eye. Glaucomatous optic neuropathy was defined as a glaucomatous VF defect and open angles associated with a glaucomatous VF defect and open angles resulting in a notch in the neuroretinal rim, in at least one eye. Glaucomatous optic neuropathy was defined as a notch in the neuroretinal rim, in at least one eye. Glaucomatous optic neuropathy was defined as a notch in the neuroretinal rim, in at least one eye. Glaucomatous optic neuropathy was defined as a notch in the neuroretinal rim, in at least one eye. Glaucomatous optic neuropathy was defined as a notch in the neuroretinal rim, in at least one eye. Glaucomatous optic neuropathy was defined as a notch in the neuroretinal rim, in at least one eye. Glaucomatous optic neuropathy was defined as a notch in the neuroretinal rim, in at least one eye.

Exclusion criteria for POAG subjects included the diagnosis or history of any secondary glaucoma, history of ocular trauma, or significant use of systemic or ocular glauocorticoids. Patients from pedigrees with glaucoma inherited as a Mendelian trait also were excluded from this study. The POAG cases were further stratified into HTG or NTG based on maximum recorded IOP ≥21 mm Hg or ≤21 mm Hg, respectively. The examined control subjects were unrelated and met the following criteria: no known first degree relative with glaucoma, IOP less than 21 mm Hg in both eyes without treatment, and no evidence of glaucomatous optic neuropathy in either eye.

Methods

Genomic DNA was extracted from leukocytes of the peripheral blood for each participant. It was purified by the Qiagen QIAmp Blood Kit (Qiagen, Hilden, Germany). A total of 13 previously reported SNPs was chosen for validation, including rs4656461 and rs7555523 at TMCO1; rs1063192, rs523096, rs7049105, rs2157719, rs4977756, and rs10116277 at CAV1/CAV2; as well as rs53912345 and rs10483727 at SIX1/SIX6. The SNP rs4236601 in the CAV1/CAV2 region has shown a monomorphic minor allele frequency in Asian populations including those of Chinese2 and Japanese ancestry.20 Additionally, rs4236601 has failed validation in some replication studies.23,24 Thus, it was not included in this study as it is less likely to affect POAG risk to a great extent in the Han Chinese population.

The SNP genotyping was performed using iPLEX Gold chemistry on the MassARRAY system (Sequenom, Inc., San Diego, CA, USA) by means of matrix assisted laser desorption ionization time-of-flight mass spectrometry method (MALDI-TOF) according to the manufacturer’s instructions. Genotype calling was performed in real time with MassARRAY RT software version 3.0.0.4 and analyzed using the MassARRAY Typer software version 3.4 (Sequenom, Inc., ). Each SNP with call rate greater than 95% was analyzed in the next step. Genotype and allele frequencies were calculated for each SNP. All genotyping results were screened for deviations from Hardy–Weinberg equilibrium (HWE; P > 0.01). Association analyses were conducted using PLINK (1.07). Logistic regression was used to calculate odds ratios (OR) with 95% confidence intervals (CI) and adjusted for age and sex. Each SNP was assessed for association with each quantitative trait, including age at diagnosis, CCT, IOP, AL, and VCDR, using linear regression under an additive genetic model. Continuous variables were expressed as mean ± SD and compared across groups using a Student’s t-test. Correction for multiple comparisons was done using a Bonferroni correction, generating a required P value of 0.004 to account for testing 13 SNPs. The analysis of CCT and AL was performed using the averaged data from both eyes. The analysis of IOP and VCDR was performed using the greater values between eyes. The IOP with correction for CCT was calculated using the Kohlhaas method,26 as ΔIOP = (−0.0425 × CCT) + 23.28.

Results

We enrolled 1157 POAG cases and 934 normal controls were enrolled in this study. As expected, when compared to the normal population, POAG cases had elevated IOP and larger VCDR. The average age of POAG cases was 48.81 years and that of controls was 53.37 years. Of the cases 32.24% were female, while 59.74% of the controls were female. Age and sex were controlled for in all of the subsequent analyses. The case group contained 860 HTG and 297 NTG. Approximately 74.33% of POAG patients, 33.75 ± 10.60 mm Hg for HTG patients, and 18.47 ± 2.22 mm Hg for NTG patients. Demographic and other phenotypic information is provided in Tables 1 and 2.

All SNPs passed quality control and genotyping efficiency criteria (>95% with all the samples) and were in HWE in cases and controls (P > 0.01). Allele frequencies and P values for the 13 SNPs for POAG patients and control subjects are shown in Table 3. In the full case control dataset, we observed significant association of POAG with rs4656461 (P = 0.002, OR = 3.18 [1.52–6.65]) and rs7555523 (P = 0.003, OR = 3.31 [1.52–7.20]) at the TMCO1 region. rs1063192 (P = 0.047, OR = 0.85 [0.72–1.00]), rs523096 (5.833 × 10−5), OR = 0.65 [0.53–0.80], rs7049105 (0.006, OR = 0.82 [0.71–0.94]), and rs2157719 (P = 0.002, OR = 3.18 [1.52–6.65]).

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3.528 × 10^{-5}, OR = 0.64 [0.52–0.79]) at the CDKN2B-AS1 region, and rs33912345 (P = 5.503 × 10^{-4}, OR = 0.75 [0.64–0.88]) and rs10483727 (P = 0.003, OR = 0.78 [0.67–0.92]) at the SIX1/SIX6 region. Among them, rs4656461 and rs7555523 at TMCO1, rs2157719 and rs523096 at CDKN2B-AS1, and rs33912345 and rs10483727 at SIX1/SIX6 remained significant after Bonferroni correction for multiple testing. The minor alleles for SNPs at CDKN2B-AS1 and SIX1/SIX6 showed protective effects with lower frequencies in cases than controls. Low minor allele frequencies of the 2 SNPs (rs4656461 and rs7555523) at TMCO1 were detected, with both at a frequency less than 2% in cases versus 0.5% in controls (Table 3).

Next, we stratified the cases by IOP into HTG and NTG. In the HTG subgroup, we identified significant association with SNPs rs4656461 (P = 8.465 × 10^{-4}, OR = 3.70 [1.72–7.97]) and rs7555523 (P = 0.001, OR = 3.85 [1.72–8.62]) at TMCO1, rs523096 (P = 0.002, OR = 0.70 [0.56–0.87]), rs7049105 (P = 0.029, OR = 0.84 [0.72–0.98]), and rs2157719 (P = 0.002, OR = 0.70 [0.56–0.88]) at CDKN2B-AS1, as well as rs33912345 (P = 0.015, OR = 0.80 [0.68–0.96]) and rs10483727 (P = 0.046, OR = 0.84 [0.71–1.00]) at SIX1/SIX6. Only rs4656461 and rs7555523 at TMCO1 as well as rs523096 and rs2157719 at CDKN2B-AS1 survived correction for multiple testing (Table 4). In the NTG subgroup, rs523096 (P = 1.765 × 10^{-4}, OR = 0.52 [0.36–0.73]) and rs2157719 (P = 3.445 × 10^{-5}, OR = 0.47 [0.33–0.67]) at CDKN2B-AS1 as well as rs33912345 (P = 4.288 × 10^{-4}, OR = 0.64 [0.50–0.82]) and rs10483727 (P = 8.518 × 10^{-4}, OR = 0.66 [0.51–0.84]) at SIX1/SIX6 showed stronger association with lower P values than those found in the comparison of HTG and normal controls. All four SNPs survived correction for multiple testing (Table 4). The SNPs at TMCO1 did not exhibit statistical significance in the comparison of NTG versus controls.

In the case cohort, association analysis was conducted for all 13 SNPs with the 5 quantitative traits: age at diagnosis, IOP, CCT, AL, and VCDR. Only IOP showed statistically significant association with multiple SNPs in CDKN2B-AS1 (rs923096 (P = 0.001), rs2157719 (P = 0.002)), and SIX1/SIX6 (rs53912345 (P = 0.002), rs10483727 (P = 0.002)) after adjustment for age and sex (Table 5) and remained significant after Bonferroni correction. At all associated SNPs the glaucoma risk alleles were observed for age at diagnosis, CCT, VCDR, and AL.

To exclude the potential confounding effect of CCT on IOP measurement, the IOP also was analyzed after correction for CCT, using the same method as Kohlhass. The mean uncorrected IOP (30.10 ± 11.36 mm Hg) and corrected IOP (30.48 ± 11.66 mm Hg) were found to be very close. According to the definition used in our study, after IOP correction, the number of HTG patients and NTG patients would be reclassified to 919 and 238, respectively, from the initial 860 and 297. However, the association results showed almost no change before and after correction when comparing HTG or NTG versus controls. The P values of SNPs rs53912345 and rs10483727 at SIX1/SIX6 after correction for CCT were one order of magnitude lower than those without correction in the quantitative analysis of IOP (Supplementary Tables S1, S2). A high similarity between P values also was acquired when doing linear regression analysis of maximum IOP after adjusting for CCT (Supplementary Table S3).

**DISCUSSION**

In this study, we replicated the association of POAG with 4 identified loci including TMCO1, CDKN2B-AS1, ATOH7, and SIX1/SIX6 in a Chinese Han population. The SNPs rs4656461 and rs7555523 at TMCO1, rs523096 and rs2157719 at CDKN2B-AS1, as well as rs53912345 and rs10483727 at SIX1/SIX6 were validated, exhibiting association with POAG in our cohorts. The minor alleles for SNPs at CDKN2B-AS1 and SIX1/SIX6 demonstrated protective effects for POAG. After stratification by IOP, the association of rs523096 and rs2157719 at CDKN2B-AS1 remained significant in the HTG and NTG subgroups; however, they showed stronger association in the NTG subgroup. The two SNPs at SIX1/SIX6 showed significant association in the HTG subgroup, but only marginal association in the HTG subgroup. In contrast, the SNPs at TMCO1 showed statistically significant association only in the HTG subgroup and not in the NTG subgroup.

The most significant region to be identified so far by independent research groups as having an association with POAG in different ethnic populations is the CDKN2B-AS1 region on chromosome 9p21. This region was first reported to be associated with POAG. In our study, we also identified a strong association of these two SNPs (rs10483727, rs33912345) at SIX1/SIX6 with POAG in our full dataset and in the NTG subgroup; there is only mild association in our HTG subgroup. Our results demonstrated that SIX1/SIX6 may
influence the phenotypic features in patients with NTG more than HTG.

The IOP is a well-established risk factor for glaucoma and an important inheritable endophenotype in glaucoma.20,30 Multiple SNPs at CDKN2B-AS1 (rs523096, rs2157719) and SIX1/SIX6 (rs35912345, rs10483727) also exhibited association with IOP. Consistent with previous studies,26 the minor alleles, which also were the protective alleles, were associated with higher IOP. Thus, the SNPs at CDKN2B-AS1 and SIX1/SIX6 were associated with IOP as a quantitative trait and as a dichotomous variable. The enrichment of the risk alleles in patients with glaucoma, but with IOP in the normal range suggests that in patients with these particular risk alleles, glaucoma is more likely to develop in the absence of elevated IOP. This is consistent with our findings of a stronger association between these two genes and NTG than with HTG.

Additionally, it has been demonstrated that CDKN2B-AS1 and SIX1/SIX6 SNPs contribute to variation in VCDR in normal individuals11,18,28 and in POAG patients.15,17,26 However, VCDR showed no association with SNPs at any of the four loci in our dataset. It is possible that because VCDR is a diagnostic feature of POAG and was used as an inclusion criterion for the definition of glaucoma, the sample was skewed toward the top end of the normal distribution for this phenotype, and this would decrease the effective power. When the controls with recorded measurements of VCDR were added to the analysis to test this potential bias, the SNPs at both CDKN2B-AS1 (rs523096, rs2157719) and SIX1/SIX6 (rs35912345, rs10483727) did reach statistical significance (Supplementary Table S4).

The CCT is well known to confound the measurement of IOP and significantly influence IOP readings obtained by applanation tonometry.25 Although the influence of CCT on an individual's IOP is controversial, designating patients as elevated or normal IOP after CCT correction might provide a more accurate dichotomy between the arbitrary distinction of NTG and HTG. In this study, we used the method of Kohlhass et al.25 to correct IOP due to the relatively conservative adjustment to the IOP and the similarity to several other metrics assessed by Brandt et al.31 Consistent with results from Burdon et al.20 the correction of IOP had little to no effect on the association statistics, before and after adjustment for other covariates (Supplementary Tables S1, S2). Only during the quantitative trait analysis did the Kohlhass-corrected IOP produce P values one order of magnitude more significant than the uncorrected IOP analysis for SNPs at SIX1/SIX6 (Supplementary Table S3). The SNPs at the CDKN2B-AS1 and SIX1/SIX6 loci were associated both with IOP as a quantitative trait and as a dichotomous variable, with and without correction for CCT. Although CCT is among the strongest independent predictors for the development of POAG,31 none of the genotyped SNPs in our study yielded statistically significant association with CCT.

### Table 3. Allele Frequencies for 13 SNPs and Association With POAG Adjusted for Age and Sex

<table>
<thead>
<tr>
<th>Gene</th>
<th>CHR</th>
<th>SNP</th>
<th>BP</th>
<th>MA</th>
<th>MAF_Case</th>
<th>MAF_Control</th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMCO1</td>
<td>1</td>
<td>rs4656461</td>
<td>G</td>
<td>0.005</td>
<td>0.020</td>
<td>3.70 (1.72–7.97)</td>
<td>8.465 × 10&lt;sup&gt;-4&lt;/sup&gt;</td>
<td>0.002</td>
</tr>
<tr>
<td>TMCO1</td>
<td>1</td>
<td>rs7555523</td>
<td>C</td>
<td>0.005</td>
<td>0.018</td>
<td>3.85 (1.72–8.62)</td>
<td>0.001</td>
<td>0.020</td>
</tr>
<tr>
<td>CDKN2B-AS1</td>
<td>9</td>
<td>rs1063192</td>
<td>C</td>
<td>0.204</td>
<td>0.186</td>
<td>0.88 (0.73–1.05)</td>
<td>0.146</td>
<td>0.001</td>
</tr>
<tr>
<td>CDKN2B-AS1</td>
<td>9</td>
<td>rs523096</td>
<td>G</td>
<td>0.315</td>
<td>0.101</td>
<td>0.70 (0.56–0.87)</td>
<td>0.002</td>
<td>0.063</td>
</tr>
<tr>
<td>CDKN2B-AS1</td>
<td>rs7549105</td>
<td>A</td>
<td>0.361</td>
<td>0.320</td>
<td>0.84 (0.72–0.98)</td>
<td>0.029</td>
<td></td>
<td>0.035</td>
</tr>
<tr>
<td>CDKN2B-AS1</td>
<td>rs2157719</td>
<td>G</td>
<td>0.133</td>
<td>0.099</td>
<td>0.70 (0.56–0.87)</td>
<td>0.002</td>
<td></td>
<td>0.071</td>
</tr>
<tr>
<td>CDKN2B-AS1</td>
<td>rs4977756</td>
<td>G</td>
<td>0.227</td>
<td>0.213</td>
<td>0.90 (0.76–1.07)</td>
<td>0.235</td>
<td></td>
<td>0.280</td>
</tr>
<tr>
<td>CDKN2B-AS1</td>
<td>rs1011627</td>
<td>C</td>
<td>0.311</td>
<td>0.306</td>
<td>0.98 (0.84–1.15)</td>
<td>0.818</td>
<td></td>
<td>0.200</td>
</tr>
<tr>
<td>ATOH7</td>
<td>rs7916697</td>
<td>A</td>
<td>0.391</td>
<td>0.398</td>
<td>1.02 (0.88–1.18)</td>
<td>0.797</td>
<td></td>
<td>0.075</td>
</tr>
<tr>
<td>ATOH7</td>
<td>rs1900004</td>
<td>A</td>
<td>0.391</td>
<td>0.399</td>
<td>1.02 (0.88–1.19)</td>
<td>0.784</td>
<td></td>
<td>0.073</td>
</tr>
<tr>
<td>ATOH7</td>
<td>rs3858145</td>
<td>G</td>
<td>0.393</td>
<td>0.397</td>
<td>1.00 (0.86–1.16)</td>
<td>0.998</td>
<td></td>
<td>0.029</td>
</tr>
<tr>
<td>SIX1/SIX6</td>
<td>rs35912345</td>
<td>A</td>
<td>0.251</td>
<td>0.210</td>
<td>0.80 (0.68–0.96)</td>
<td>0.015</td>
<td></td>
<td>0.176</td>
</tr>
<tr>
<td>SIX1/SIX6</td>
<td>rs10483727</td>
<td>C</td>
<td>0.254</td>
<td>0.219</td>
<td>0.84 (0.71–1.00)</td>
<td>0.046</td>
<td></td>
<td>0.181</td>
</tr>
</tbody>
</table>

The BP position of each SNP was in reference to NCBI build 37.5. Chr, Chromosome; BP, base pair position; MA, minor allele; MAF, minor allele frequency; MAF_Case, minor allele frequencies in cases; MAF_Control, minor allele frequencies in controls.

### Table 4. Association Results in Comparison of HTG and NTG Patients Versus Controls Adjusted for Age and Sex

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>MA</th>
<th>MAF Control</th>
<th>MAF_Case (OR [95%CI])</th>
<th>P</th>
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<tbody>
<tr>
<td>TMCO1</td>
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<tr>
<td>TMCO1</td>
<td>rs7555523</td>
<td>C</td>
<td>0.005</td>
<td>0.018 (3.85 (1.72–8.62)</td>
<td>0.001</td>
</tr>
<tr>
<td>CDKN2B-AS1</td>
<td>rs1063192</td>
<td>C</td>
<td>0.204</td>
<td>0.186 (0.88 (0.73–1.05)</td>
<td>0.146</td>
</tr>
<tr>
<td>CDKN2B-AS1</td>
<td>rs523096</td>
<td>G</td>
<td>0.315</td>
<td>0.101 (0.70 (0.56–0.87)</td>
<td>0.002</td>
</tr>
<tr>
<td>CDKN2B-AS1</td>
<td>rs7549105</td>
<td>A</td>
<td>0.361</td>
<td>0.320 (0.84 (0.72–0.98)</td>
<td>0.029</td>
</tr>
<tr>
<td>CDKN2B-AS1</td>
<td>rs2157719</td>
<td>G</td>
<td>0.133</td>
<td>0.099 (0.70 (0.56–0.87)</td>
<td>0.002</td>
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<tr>
<td>CDKN2B-AS1</td>
<td>rs4977756</td>
<td>G</td>
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<tr>
<td>CDKN2B-AS1</td>
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<td>C</td>
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<td>0.818</td>
</tr>
<tr>
<td>ATOH7</td>
<td>rs7916697</td>
<td>A</td>
<td>0.391</td>
<td>0.398 (1.02 (0.88–1.18)</td>
<td>0.797</td>
</tr>
<tr>
<td>ATOH7</td>
<td>rs1900004</td>
<td>A</td>
<td>0.391</td>
<td>0.399 (1.02 (0.88–1.19)</td>
<td>0.784</td>
</tr>
<tr>
<td>ATOH7</td>
<td>rs3858145</td>
<td>G</td>
<td>0.393</td>
<td>0.397 (1.00 (0.86–1.16)</td>
<td>0.998</td>
</tr>
<tr>
<td>SIX1/SIX6</td>
<td>rs35912345</td>
<td>A</td>
<td>0.251</td>
<td>0.210 (0.80 (0.68–0.96)</td>
<td>0.015</td>
</tr>
<tr>
<td>SIX1/SIX6</td>
<td>rs10483727</td>
<td>C</td>
<td>0.254</td>
<td>0.219 (0.84 (0.71–1.00)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

HTG, high IOP; NTG, normal IOP; MAF, minor allele frequency; P, statistical significance.
The SNP rs4656461 was the initial SNP at TMCO1 reported to be associated with POAG.14 Later, another SNP at TMCO1, rs7555523, also was found to be related to increased IOP in a Caucasian population.12 In our study, although TMCO1 loci showed no association with IOP or the subgroup of NTG patients, statistically significant association was observed clearly in the HTG subgroup and also in the full dataset of POAG. This leads us to believe that TMCO1 may contribute to POAG through the pathway of IOP elevation. However, similar to CAV1/CAV2, due to the very low minor allele frequencies of SNPs in TMCO1, this gene may have limited effect on POAG risk in a population of Chinese Han when compared to Caucasians.

The ATOH7 (rs1900004) gene has been reported to be strongly associated with optic disc area and VCDR in a GWAS involving Australian and U.K. cohorts.36 It then was replicated in a GWAS in The Netherlands and a GWAS in Asia.37,38 Additionally, it was reported to be suggestively associated with POAG in Caucasians39; however, in this study, it was neither recognized to be associated with VCDR nor detected in be associated with POAG, only observed as marginally associated with NTG. Similar results also have been seen in previous reports,18,34 and may result from the different methods applied for the VCDR measurement. In our study, the VCDR was estimated by using a 90-diopter lens, instead of being measured on the stereoscopic fundus photo. The inconsistent results also may be due to the genetic heterogeneity between ethnic groups. Interestingly, in the analysis of NTG cases versus controls, the 3 SNPs at the ATOH7 region yielded marginal P values, ranging from 0.02 to 0.07, compared to no difference seen in the analysis of HTG cases versus controls. This result suggests that ATOH7 still could be mildly related to POAG as a non-IOP related genetic factor.

A variety of genetic factors contribute to optic neuropathy in POAG and can be classified into two main types: high-IOP-related and non-IOP-related (RGC vulnerability-related) genetic factors. It is presumed that non-IOP-related genetic factors would predominate in patients with NTG, whereas high-IOP-related genetic factors would predominate in patients with HTG.18 Our results indicated that CDKN2B-AS1 and SIX1/SIX6 may contribute to glaucomatous optic neuropathy as non-IOP-related genetic factors because these loci showed much stronger association with NTG than HTG. In contrast, TMCO1, together with recently published gene ABCA1,35–37 may contribute to glaucoma as high-IOP-related genetic factors. Furthermore, it is possible that CDKN2B-AS1 SNPs are involved in IOP- and non-IOP-related pathological pathways, because it showed association with NTG and HTG phenotypes. This also may indicate that non-IOP-related factors (RGC vulnerability factors) have a potential role in the pathogenesis of HTG as well.38

Our findings suggested similar genetic associations to those initially found in Caucasian populations; TMCO1, CDKN2B-AS1, and SIX1/SIX6 showed association with POAG in a Han Chinese population, while CDKN2B-AS1 and SIX1/SIX6 loci harbor a tendency toward association with NTG compared to HTG. In contrast, TMCO1 loci harbor a tendency toward association with HTG compared to NTG. Clarification of the different genetic factors and pathophysiological pathways causing each subtype of glaucoma may contribute to understanding the pathogenesis of the disease.

Acknowledgments

The authors thank all the primary open angle glaucoma patients and normal controls for participating in this study. The samples used in this study were all from the EENT Biobank.

Supported by the National Natural Science Foundation of China (81200723), Special Scientific Research Project of Health Professions of China (201302015), the Shanghai Natural Science Foundation (13ZR1406100), and Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry. The authors alone are responsible for the content and writing of the paper.

Disclosure: Y. Chen, None; G. Hughes, None; X. Chen, None; S. Qian, None; W. Cao, None; L. Wang, None; M. Wang, None; X. Sun, None

References


