Stronger Association of *CDKN2B-AS1* Variants in Female Normal-Tension Glaucoma Patients in a Japanese Population

We read with great interest the article by Ng et al.[1] entitled "Genetic Association at the 9p21 Glaucoma Locus Contributes to Sex Bias in Normal-Tension Glaucoma," that was recently published in *Investigative Ophthalmology & Visual Science*. As the 9p21 locus was identified by a genome-wide association study (GWAS) to be associated with primary open-angle glaucoma (POAG), and the association was found to be significantly stronger among the normal-tension glaucoma (NTG) subgroup (for review see Ref. 2), Ng et al.[1] extended the analysis to investigate the influence of sex difference on the genetic association at the 9p21 locus. They carefully analyzed the genotype data of 13 variants linked with clinical information and clearly presented the results that: (1) the sex bias was present within advanced NTG cases, (2) the strongest associated variant in all POAG cases showed stronger association in females than in males with a statistically significant difference in female-to-male odds ratio (OR) comparison, and (3) the significant association was observed only in females under the NTG to high-tension glaucoma (HTG) subanalysis along with a significant difference in OR comparison. Although they used a large reliable number of samples and obtained robust results, they honestly pointed out the limitation of the study as the analyses were performed without replication using a cohort derived from a single ethnic background (i.e., Australian of European descent).

Therefore, we reanalyzed our two GWAS datasets[3,4] using our Japanese population in an attempt to assess their findings. We ended up with 975 healthy controls and 1244 POAG cases composed of 545 HTG and 699 NTG patients (HTG and NTG were denoted as HPG and NPG, respectively, in our previous article[4]) for the analysis (Table 1). Among the 13 variants at the 9p21 locus that Ng et al.[1] analyzed, we were able to directly compare the genotype data of three variants on *CDKN2B-AS1* from our previous datasets. With regard to the female-to-male analyses, we indeed observed a stronger association for all of the variants in the female patients (Table 2). Especially rs7049105, a variant in Japanese NTG patients considered to be influenced by sex, because the OR of NTG to control showed a significant heterogeneity ($P = 0.0427$) between the female and male groups (Table 2). Overall, these results suggested that although the allele frequencies of the variants slightly differs between the populations, the stronger association of the female NTG patients seen in the Australian population seemed to be replicated in our Japanese female NTG patients.

In the normal clinical setting, the female NTG patients who we encounter tend to be elderly and thin, and often possess other clinical features such as low blood pressure, myopia, migraine, neck stiffness, and so on. Not only identifying the genetic variants responsible for the disease onset by case-control association studies, but also carefully linking these phenotypes to each identified variant (as Ng et al.[1] performed for the sex difference), should greatly contribute to the elucidation of the complex etiology of glaucoma.

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Table 1. Sample Data

Groups	*n* (mean age ± SD)		
	All	Female	Male
POAG	1244 (62.6 ± 13.6)	649 (62.9 ± 13.5)	595 (62.2 ± 13.8)
HTG	545 (64.1 ± 12.8)	255 (64.3 ± 12.9)	290 (63.9 ± 12.7)
NTG	699 (61.4 ± 14.2)	394 (62.0 ± 13.8)	305 (60.6 ± 14.6)
Control	975 (56.5 ± 14.0)	617 (57.2 ± 13.7)	358 (55.3 ± 14.4)

Table 2. Sex Comparison of CDKN2B-AS1 Variants in a Japanese Population

SNP	Female			Male			Het. *P*‡
	Allele Freq.*	*P* Value†	OR (95% CI)†	Allele Freq.*	*P* Value†	OR (95% CI)†	
POAG versus control							
rs7049105	0.692/0.615	5.38×10^{-5}	1.41 (1.19–1.66)	0.665/0.641	2.99×10^{-1}	1.11 (0.91–1.35)	0.0689
rs4977574	0.501/0.421	7.37×10^{-5}	1.37 (1.17–1.61)	0.485/0.439	4.96×10^{-2}	1.21 (1.00–1.45)	0.2705
rs1333049	0.518/0.444	2.54×10^{-4}	1.34 (1.15–1.57)	0.504/0.462	7.28×10^{-2}	1.19 (0.98–1.43)	0.3053
HTG versus control							
rs7049105	0.648/0.615	2.39×10^{-1}	1.14 (0.92–1.42)	0.649/0.641	7.86×10^{-1}	1.03 (0.82–1.30)	0.5116
rs4977574	0.478/0.421	3.92×10^{-2}	1.25 (1.01–1.53)	0.478/0.439	1.58×10^{-1}	1.17 (0.94–1.46)	0.6188
rs1333049	0.504/0.444	3.03×10^{-2}	1.26 (1.02–1.55)	0.495/0.462	2.50×10^{-1}	1.14 (0.91–1.42)	0.4782
NTG versus control							
rs7049105	0.721/0.615	1.34×10^{-6}	1.62 (1.33–1.97)	0.679/0.641	1.24×10^{-1}	1.20 (0.95–1.51)	0.0427
rs4977574	0.515/0.421	3.72×10^{-5}	1.46 (1.22–1.75)	0.492/0.439	5.10×10^{-2}	1.24 (1.00–1.54)	0.2449
rs1333049	0.527/0.444	3.05×10^{-4}	1.39 (1.16–1.67)	0.513/0.462	5.63×10^{-2}	1.24 (0.99–1.54)	0.3754

* Mean risk allele frequencies of case/control samples in each group.

† Each *P* value and Odds Ratio (OR) adjusted for our two datasets was calculated by using Cochran–Mantel–Haenszel test implemented in PLINK, version 1.07.

‡ The *P* value for OR heterogeneity between female and male in each study was calculated using the Breslow-Day test implemented in PLINK v1.07.

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