LETTER

Lack of association of common variants on chromosome 2p with primary open-angle glaucoma in the Japanese population

Primary open-angle glaucoma (POAG) is the most common form of glaucoma, and it is clinically classified into high-tension glaucoma (HTG), in which an elevated intraocular pressure (IOP) is a major feature, and normal-tension glaucoma (NTG), in which the IOPs are consistently within the statistically normal population range. Jiao et al. (1) performed linkage analyses in 146 multiplex families and identified a locus with a major impact on the susceptibility to POAG in the Afro-Caribbean population in Barbados, West Indies. They demonstrated a strong association of rs12994401 and rs1533428 on chromosomes 2p with POAG, according to the findings of subsequent case–control analyses. Genetic associations are biologically more meaningful if they are replicated across different ethnic populations. We tried to replicate these findings in 425 Japanese patients with POAG, including HTG (n = 212) and NTG (n = 213), and 191 control subjects without glaucoma, and these two SNPs were genotyped using an allele-specific primer real-time PCR method. There was no significant association of either of these two SNPs with HTG and NTG in the present cohort (Tables 1 and 2), and this locus was not associated with POAG in the Japanese population. These two SNPs are common variants in the Japanese population as well as in the Afro-Caribbean population, and the present results indicate that these two SNPs are markers of a neighboring susceptible gene polymorphism responsible for POAG in the Afro-Caribbean population, although Jiao et al. (1) reported that they may perform a regulatory role influencing the neighboring gene expression and that, alternatively, one cannot exclude the possibility that they are located within a yet-to-be-annotated gene. A variety of genetic factors would contribute to optic neuropathy in POAG. It is presumed that non–IOP-related genetic factors would predominate in patients with NTG and that, conversely, high IOP–related genetic factors would predominate in patients with HTG. Although it is not yet clear how this locus might act in the Afro-Caribbean population, it is thought that it contributes to optic neuropathy as a high IOP–related genetic factor, because the mean IOP (26.7 mm Hg) of affected individuals is higher than that (17.0 mm Hg) of unaffected individuals ascertained from the family study (1). A direct comparison of the epidemiologic data between different ethnic populations may be difficult, because the diagnostic criteria are not always the same among the epidemiologic studies of glaucoma. In the Afro-Caribbean population, the prevalence of HTG in patients with POAG is higher than that of NTG (2–4). On the other hand, the prevalence of NTG in patients with POAG is extremely high in the Japanese population (92% of patients with POAG have NTG, and only 8% of patients with POAG have HTG) (5). This locus is therefore considered to contribute to the low prevalence of HTG in patients with POAG in the Japanese population. Further studies should be performed to elucidate whether this locus contributes to optic neuropathy in POAG in other ethnic populations.

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Table 1. Genotype, allele, and haplotype frequencies of rs1533428 and rs12994401 in patients with POAG and control subjects

SNP	Genotype/allele/ haplotype	Control (n = 191)	POAG			
			NTG (n = 213)	P value	HTG (n = 212)	P value
rs1533428	Genotype					
	TT	30 (15.7)	34 (16.0)		33 (15.6)	
	CT	84 (44.0)	100 (46.9)	0.79*	92 (43.4)	0.99*
	CC	77 (40.3)	79 (37.1)		87 (41.0)	
	Allele					
	T	144 (37.7)	168 (39.4)	0.66†	158 (37.3)	0.94†
	C	238 (62.3)	258 (60.6)		266 (62.7)	
rs12994401	Genotype					
	TT	16 (8.4)	26 (12.2)		25 (11.8)	
	CT	101 (52.9)	95 (44.6)	0.19*	103 (48.6)	0.46*
	CC	74 (38.7)	92 (43.2)		84 (39.6)	
	Allele					
	T	133 (34.8)	147 (34.5)	0.94†	153 (36.1)	0.71†
	C	249 (65.2)	279 (65.5)		271 (63.9)	
rs1533428–rs12994401	Haplotype‡					
	C-C	0.41	0.41		0.39	
	C-T	0.21	0.20	0.96*	0.23	0.84*
	T-C	0.24	0.24		0.25	
	T-T	0.14	0.15		0.13	

Data are given as number (percentage) for genotype and allele and as frequency for haplotype.
*χ^2 test.
†Fisher exact test.
‡Haplotype frequency was analyzed using expectation maximization algorithm.

Table 2. Results of logistic regression analysis between the POAG patients and control subjects

Variable	rs1533428		rs12994401	
	P value	OR (95% CI)	P value	OR (95% CI)
Age	0.20	1.01 (0.99–1.04)	0.18	1.02 (0.99–1.04)
Male gender	0.55	1.17 (0.69–2.00)	0.56	1.17 (0.69–1.99)
Intraocular pressure	<0.0001	1.93 (1.72–2.17)	< 0.0001	1.93 (1.72–2.17)
Refractive error	0.0001	0.81 (0.73–0.90)	0.0001	0.81 (0.73–0.90)
rs1533428 T allele	0.78	1.05 (0.73–1.51)	—	—
rs12994401 T allele	—	—	0.71	0.93 (0.63–1.38)

rs1533428 and rs12994401 were separately analyzed in this model because these polymorphisms were not independent variables.
OR, odds ratio; CI, confidence Interval.