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TABLE 5. Comparison of Clinical Characteristics of Female Patients with NTG, According to ACE (I/D) and *AGTR2* Genotypes (3123C→A)

Clinical Characteristics at Diagnosis	ACE II		ID + DD		
	CC	CA + AA	CC	CA + AA	*P*
Age (y)	63.6 ± 10.9 (n = 15)	57.0 ± 11.2 (n = 47)	56.2 ± 14.1 (n = 23)	58.5 ± 12.0 (n = 51)	0.313
IOP (mm Hg)	16.0 ± 2.2 (n = 16)	16.5 ± 2.6 (n = 43)	16.1 ± 2.7 (n = 20)	16.5 ± 2.2 (n = 49)	0.75
Visual field score	2.47 ± 0.51 (n = 17)	2.64 ± 0.53 (n = 47)	3.13 ± 0.76 (n = 23)	2.65 ± 0.59 (n = 52)	0.012†

† $P < 0.05$ by Kruskal-Wallis test.

anterior chamber routes results in a significant increase in IOP in rats.[40,41] In humans, systemic ATII receptor blockers lower the IOP.[21,22]

The RAA system contains at least seven genes. Initially, we selected candidate polymorphisms in association with glaucoma as follows: (1) polymorphisms associated with cardiovascular diseases in the Japanese population, because the frequency of polymorphisms varies among races; (2) heterozygosity of polymorphisms >0.1 in Japanese; and (3) polymorphisms associated with the function of the gene, if possible, or polymorphisms located in the promotor region. We did not select polymorphisms that are rare in Japanese. Our study, designed to detect the involvement of 10 SNPs of the RAA system in glaucoma, showed that the *AGTR2* polymorphism was associated with NTG. Other gene polymorphisms in the RAA system were not associated with POAG or NTG. It is uncertain whether the −713T→G polymorphism in the *AGTR1* gene is actually associated with POAG, because neither a dominant model nor a recessive model of this polymorphism showed any significant difference in the genotype frequency. However, as the frequency of the GG genotype was higher in patients with POAG (3.2%) than in control subjects (0.4%), further studies are needed to confirm this finding or to identify other functional variants of the *AGTR1* gene.

We found a gender-specific association between the *AGTR2*/3123C→A polymorphism and NTG. Women with NTG who had the CA+AA genotype (i.e., A carriers) were significantly more likely to develop NTG than those with the CC genotype (non-A carriers; $P = 0.0095$). Although there was no difference between three clinical features and genotypes of the *AGTR2*/3123C→A, only the visual field score was significantly worse ($P = 0.012$) in the female patients with NTG with the CC genotype than those with the CA+AA genotype if they were D carriers of the *ACE* gene. These results indicate that the effect of the *AGTR2* polymorphism on the progression of visual field defects in NTG may depend on the *ACE* I/D polymorphism. As for that polymorphism, the D allele was associated with increased plasma ACE concentration, which appears to result in increased ATII formation in the plasma.[42] Genetic interaction may be essential for the development or the susceptibility to diseases.[43–46] As the IOP at diagnosis in female patients with NTG was not associated with this effect, the progression of visual field defects may be independent of IOP in the RAS in these patients.

Although the gender-specific association cannot be readily explained, some previous studies have shown a similar gender-specific tendency or association between this polymorphism and hypertension[47] and hypertrophic cardiomyopathy.[48] However, the pattern of frequencies of the genotypes in hypertensive patients differed from that in patients with NTG. Women with the AA genotype were significantly more likely to have hypertension than those with the CC+CA genotype, in this Japanese group ($P = 0.0058$).[47]

Because the *AGTR2*/3123C→A polymorphism is located in the 3′ noncoding region of the gene, the amino acid sequence of the receptor is not altered. The *AGTR2*/3123C→A polymor-

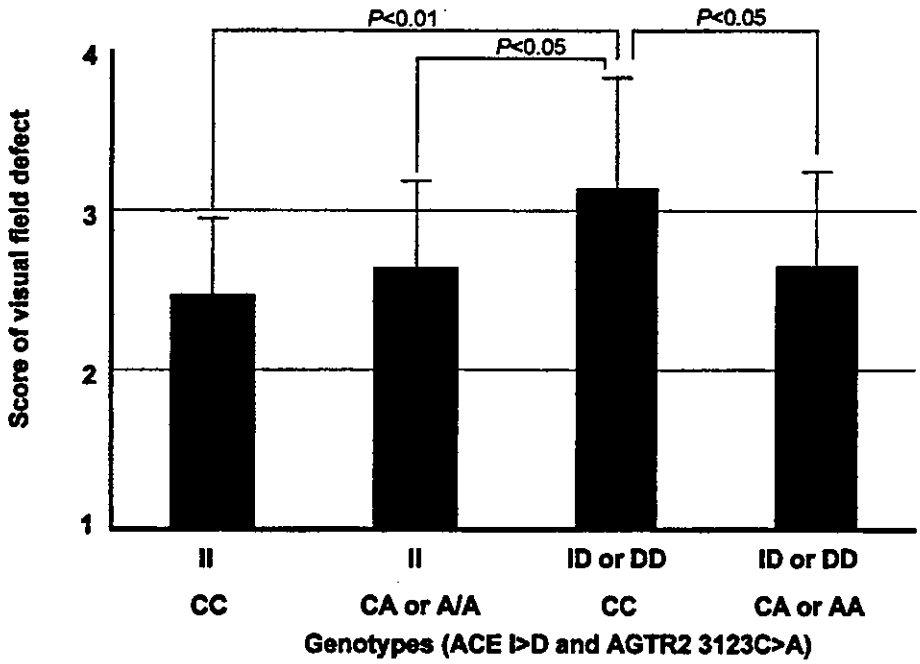

FIGURE 2. Comparison of visual field scores of female patients with NTG, according to *ACE* (I/D) and *AT2* genotypes (3123C→A). Probabilities were obtained by the Scheffé multi-comparison test.

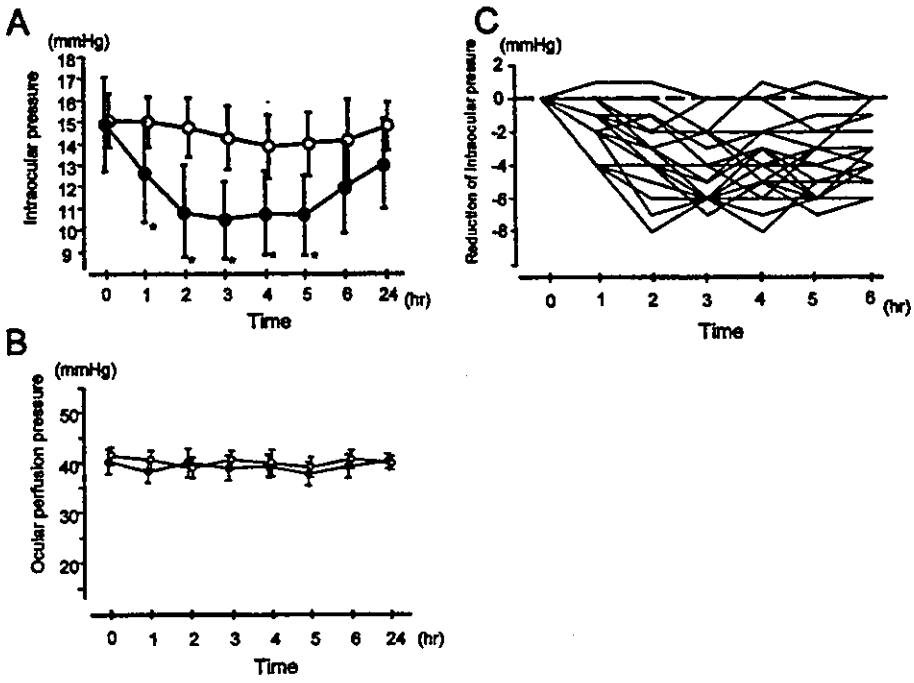

FIGURE 3. Variations in IOP and OPP after oral administration of the angiotensin II receptor blocker candesartan cilexetil (•) or a placebo (○). (A) IOP variations (mean ± SD). ANOVA with the Bonferroni correction, $^*P < 0.0001$. (B) OPP variations (mean ± SD). (C) Reduction of IOP variations in 20 subjects.

phism may be in linkage disequilibrium with an unidentified functional variant of the *AGTR2* gene. Alternatively, the polymorphism may be in linkage disequilibrium with a nearby gene responsible for associations with the clinical end points. Further study is necessary to identify the new functional polymorphisms associated with the *AGTR2*/3123C→A polymorphism.

Of interest, the *AGTR2* polymorphism was associated with NTG only in women, whereas the *AGTR1* polymorphisms were likely to be associated with POAG. Accordingly, different pathogenetic mechanisms appear to exist in these two diseases, although clinically they are considered to represent parts of a continuum. AGTR1 mediates the vasopressive and aldosterone-secreting effects of ATII. Furthermore, AGTR1 may mediate aqueous humor dynamics and therefore affect IOP,[49] which is strongly supported by the lowering of IOP by systemic use of an ARB.[21,22] However, the function of *AGTR2* is unknown. This receptor is apparently involved in the morphogenesis of the central nervous system and the urinary tract. Allelic variants of *AGTR2* have been associated with mental retardation,[50] and there is also a strong association between allelic variants and increased incidence of congenital anomalies of the kidney and lower urinary tract.[51] Yamada et al.[52] hypothesized that *AGTR2* mediates programmed cell death (apoptosis) which is considered to play an important role in developmental biology.

The effect of the ARB losartan potassium on IOP has demonstrated that drug administration significantly reduces IOP in normal subjects who do or do not have hypertension and in patients with POAG with or without hypertension.[21] The total outflow facility increased significantly in all subjects, and SBP decreased only in hypertensive patients. These results suggest that the mechanism is not mediated by a decrease in blood

TABLE 6. Effects of Angiotensin II Receptor Blocker on IOP in Association with Genotypes of the Angiotensin II Receptor Genes

Polymorphisms	Genotype	Eyes (n)	Maximum Reduction of IOP (mm Hg)	P*
AGTR1 −713T→G	TT	18	4.9 ± 1.8	
	TG	2	5.0 ± 4.2	0.898
	GG	0	0	
AGTR1 −521C→T	CC	18	4.9 ± 1.8	
	CT	1	2	0.117†
	TT	1	8	
AGTR1 1166A→C	AA	18	5.1 ± 2.0	
	AC	2	5.2 ± 1.6	0.405
	CC	0	0	
AGTR2 3123C→A	C (male)	9	5.0 ± 1.1	0.014‡
	A (male)	4	2.3 ± 0.5	
	CC (female)	3	7.0 ± 1.0	
	CA (female)	4	6.0 ± 1.6	0.354
	AA (female)	0	0	

* Probabilities by Mann-Whitney *U* test.
† Probabilities by Kruskal-Wallis test.
‡ $P < 0.05$.

pressure, but rather is more specific, confirming the role of the RAS in the regulation of IOP.[21] We studied the effect of another ARB, candesartan cilexetil, on IOP and demonstrated a reduction in IOP for 5 hours after administration.

Miller et al.[53] demonstrated a relationship between the *AT1R*/1166A→C polymorphism and the renal hemodynamic response to losartan potassium in a Canadian group. In our study, we examined a relationship between the presence of three *AGTR1* polymorphisms or of one *AGTR2* polymorphism and the degree of reduction of IOP by candesartan cilexetil. No relationship was observed for the three *AGTR1* polymorphisms and IOP reduction. For the *AGTR2*/3123C→A polymorphism, however, nine men with the C allele (5.0 ± 1.1 mm Hg, $P = 0.014$) had a significantly greater reduction in IOP than did four men with the A allele (2.3 ± 0.5 mm Hg). Further studies are needed to determine the genetic locus responsible for this effect.

In conclusion, the polymorphisms of the angiotensin II receptor gene in the RAS may be a major genetic risk factor for the development or progression of glaucoma in the Japanese population. The RAS-related genetic background influencing susceptibility may differ between patients with POAG and those with NTG.

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APPENDIX

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