Genetic Polymorphisms in the Angiotensin II Receptor Gene and Their Association with Open-Angle Glaucoma in a Japanese Population

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for The Glaucoma Gene Research Group

PURPOSE. The local renin–angiotensin system (RAS) is present in the ciliary body and plays a role in regulating aqueous humor dynamics and thus intraocular pressure (IOP). The purpose of this study was to determine whether gene polymorphisms in the RAS increase the risk of development of glaucoma in the Japanese.

METHODS. A case–control study was performed in 698 Japanese subjects: 190 patients with primary open-angle glaucoma (POAG), 268 patients with normal-tension glaucoma (NTG), and 240 normal subjects. Ten polymorphisms in seven genes—AGT7Thr174Met and AGT7Met235Thr; REN/H11001→G; ACE/H11002→G; AGTR1/H11001→G, AGTR1/H11002→G, and AGTR1/H11002→A; and CYP11B2/H11022→C were examined. The age, IOP, and visual field defects, all at diagnosis, were examined to determine whether they were associated with the polymorphisms. The effects of oral angiotensin II receptor blocker (ARB) on IOP were examined in association with the AGTR1 and AGTR2 polymorphisms in 20 normal subjects.

RESULTS. Of the 10 polymorphisms, the AGTR2/H11002→A polymorphisms had a significantly different distribution in female patients with NTG; the frequency of the CA+AA genotypes was significantly higher than in female control subjects (P = 0.0095 for CC versus CA+AA). Although no significant difference was seen in the clinical characteristics of female patients with NTG who carried the AGTR2/H11002→A genotype, patients with CC in the AGTR2 gene had significantly worse visual field scores if they carried ACE/DD+DD (i.e., D carriers; P = 0.012). ARB significantly lowered IOP in normal subjects, but the male subjects with the AGTR2/H11002→A genotype had significantly less lowering of IOP than those with the C genotype (P = 0.014).


Open-angle glaucoma (OAG), the second most common cause of blindness worldwide, affects more than 100 million people, almost 2% of the global population older than 40 years.1 The disease is characterized by an elevation of intraocular pressure (IOP) to >21 mm Hg, resulting in an excavation of the optic disc, which is associated with visual field changes. Patients with these findings have a diagnosis of primary open-angle glaucoma (POAG). Normal-tension glaucoma (NTG) is a form of OAG in which the typical glaucomatous cupping of the optic nerve head and visual field loss are present, but IOP does not exceed 21 mm Hg at any time.2 The risk factors for glaucoma include high IOP, advanced age, ethnicity, positive family history, myopia, presence of diabetes and/or hypertension, and specific genetic factors.3–6 Although the exact pathogenesis of glaucomatous optic neuropathy remains uncertain, IOP is generally considered to be a major risk factor,7 and thus, current treatments for glaucoma consist of interventions to lower IOP.8 However, in some patients with glaucoma—for example, those with NTG or advanced POAG—the reduction of IOP does not prevent progression of the disease.9,10 which indicates that factors other than an elevated IOP are involved in the progression of glaucoma.11

The association of glaucoma with various systemic vascular diseases including low systemic blood pressure, transient nocturnal decreases in blood pressure, hypertension, migraine, vasoospasm, and diabetes have been reported.6,11–15 The presence of optic disc hemorrhages in patients with NTG suggests that vascular insufficiency is probably involved in the development and progression of NTG.13,14 Many patients with OAG have coexisting vascular disorders, and the most common is systemic hypertension, which occurs in 48% of the total OAG population.15

The renin–angiotensin–aldosterone (RAA) system is involved in vasoconstriction, regulation of electrolyte balance, and vascular remodeling. Local renin-angiotensin (RA) regulation is present in the eye.16,17 Angiotensin II (ATII) is a potent vasoconstrictive agent, and recently two RAS components, angiotensin-converting enzyme (ACE) and ATII, have been

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identified in the human ciliary body and aqueous humor.18,19 These findings suggest that the RA system (RAS) is probably involved in the regulation of aqueous humor dynamics and thus IOP. This interpretation is strongly supported by the observation that local or systemic ACE inhibitors20 and ATII receptor blockers (ARBs) lower IOP.21,22

The purpose of this study was to determine whether single-nucleotide polymorphisms (SNPs) or insertion–deletion (I/D) polymorphisms in the seven RAA system genes are associated with OAG in the Japanese population. In addition, SNPs in the ATII receptor gene were studied to determine whether they are associated with the reduction of IOP after the oral administration of ARB.

## Subjects and Methods

### Patients and Control Subjects

Blood samples were collected from 698 subjects at seven Japanese ophthalmologic institutions. The subjects included 190 patients with POAG, 268 patients with NTG, and 240 normal control subjects. None of the subjects was related to any other. The research procedures followed the tenets of the Declaration of Helsinki, and written informed consent was obtained after the nature and possible consequences of the study were explained. Where applicable, the research was approved by the local institutional human experimentation committee.

The clinical features recorded in the patients with glaucoma were age at diagnosis, untreated maximum IOP (defined as IOP at diagnosis), and visual field defects at the initial examination (defined as visual field defects at diagnosis; Table I). The severity of the visual field defects was scored from 1 to 5.23,24 Data obtained with different perimeters were combined using a five-point scale defined as follows: 1, no alteration; 2, early defect; 3, moderate defect; 4, severe defect; and 5, reproducible visual field defects compatible with the glaucomatous cupping; and open angles on gonioscopy. Among the patients with OAG, POAG was diagnosed if the patient had an IOP ≥21 mm Hg at any time during the follow-up period. Patients with exfoliative, pigmented, or corticosteroid-induced glaucoma were excluded.

The patients with NTG had an untreated peak IOP ≥21 mm Hg at all times including the three baseline measurements and that obtained during the diurnal testing (every 3 hours from 6 hours to 24 hours), peak IOP, with or without medication, consistently at <22 mm Hg throughout the follow-up period; and the absence of a secondary cause of glaucomatous optic neuropathy, such as a previously elevated IOP after trauma, steroid use, or uveitis.

Control subjects were recruited from Japanese individuals who had no known eye abnormalities except cataracts. These 240 subjects were older than 40 years, with an IOP below 20 mm Hg, no glaucomatous disc changes, and no family history of glaucoma.

The medical characteristics of the patients with glaucoma and control subjects are shown in Table 1. The prevalence of patients with systemic hypertension in the POAG, NTG, and control groups varied from 20% to 25%, and the differences between the three groups were not significant (P < 0.05; by χ² test).

### Genotyping

Ten polymorphisms in the RAA system were examined in each subject with or without glaucoma. Renin (REN) I848G→A,26 angiotensin II receptor, type 1 (AGTR1) –731T→G, –521C→T, 1166A→C,20,30 angiotensin II receptor, type 2 (AGTR2) 3123C→A,31; cytochrome P45011B2 (CYP11B2) –344T→C,28 and chymase (CMA) –1903A→G,29 were identified by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

The biosynthesis of aldosterone is controlled by aldosterone synthase encoded by the CYP11B2 gene and is regulated by the concentrations of angiotensin II and potassium. Chymase is a major angiotensin-II-forming enzyme in human hearts, and a chymase gene is associated with atherosclerosis.35

Polymorphisms in the ACE I/D were detected by PCR and agarose gel electrophoresis. To avoid false identification of the ACE I/D polymorphism, allele I was amplified specifically, according to the protocol of Lindpaintner et al.26 Genomic DNA was isolated from peripheral blood lymphocytes by phenol-chloroform extraction. The primer sets and restriction enzymes used are listed in Table 2. Angiotensinogen (AGT) Thr174Met (T174M) and Met235Thr (M235T) were genotyped (Invader assay; Third Wave Diagnostics Molecular Diagnostics, Madison, WI).35

### Table 1. Demographic and Medical Characteristics among Patients with Glaucoma and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>POAG (n = 190)</th>
<th>NTG (n = 268)</th>
<th>Control (n = 240)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (y)</td>
<td>58.4 ± 12.0</td>
<td>56.1 ± 13.1</td>
<td></td>
</tr>
<tr>
<td>Age at blood sampling (y)</td>
<td>65.3 ± 11.9</td>
<td>58.8 ± 13.4</td>
<td>69.7 ± 11.2</td>
</tr>
<tr>
<td><strong>Medical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>108/82</td>
<td>129/139</td>
<td>113/127</td>
</tr>
<tr>
<td>Lipid metabolism disorders</td>
<td>26.6 ± 6.1</td>
<td>16.5 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>Migraine (%)</td>
<td>3.09 ± 0.90</td>
<td>2.79 ± 0.69</td>
<td></td>
</tr>
</tbody>
</table>

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Effect of Oral Angiotensin II Receptor Blocker on IOP in Normal Subjects and Its Association with SNPs in the AGTR1 and AGTR2 Genes

This part of the study was performed on 20 healthy volunteers (13 men and 7 woman; age range, 23–28 years) without systemic and eye diseases. In the morning (10:00 A.M.), each subject was given either 12 mg oral candesartan cilexetil (Blopress; Takeda Chemical Industries, Osaka, Japan) or a placebo, in a randomized, crossover, double-blind fashion.

The baseline heart rate, systolic-diastolic arterial pressure (SBP/DBP), and IOP were recorded. The subjects then received oral candesartan cilexetil or placebo, and measurements were repeated hourly for 6 hours and then after 24 hours. One month later, each subject received the alternative treatment. Only the right eye was measured and analyzed.

The ocular perfusion pressure (OPP) is defined as the difference between the pressure in the arteries entering the tissue and the veins leaving it. The OPP can be approximated by the following formula, using the mean blood pressure (BPm) and IOP.

\[
\text{OPP} = 2/3 \times \text{BPm} - \text{IOP}, \text{ where BPm} = \text{DBP} + 1/3 \times (\text{SBP} - \text{DBP}).
\]

A search for polymorphisms in AGTR1 and AGTR2 was performed in the 20 subjects and the correlation determined between the changes in IOP. The research adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained after the nature and purpose of the study were explained. Where applicable, the results were approved by the institutional human experimentation committee for analysis of DNA.

Statistical Analysis

The presence of the Hardy-Weinberg equilibrium was tested by the chi-squared test. Statistical analysis was performed on computer (SPSS Inc., Chicago, IL). \( P < 0.05 \) was considered to be statistically significant.

Results

Genotype Distribution of Polymorphisms in the RAA System in Japanese Subjects

The distributions of the genotypes of candidate gene polymorphisms in patients with glaucoma and control subjects are shown in Table 3. All the genotype frequencies were consistent with the populations being in Hardy-Weinberg equilibrium. Of the 10 polymorphisms in the RAA system, two had a significantly different distribution of genotype frequencies: AGTR1/−713T→G for POAG \((P = 0.021)\) and AGTR2/3123C→A for NTG \((P = 0.045)\). The significant difference in the 3123C→A polymorphism was found only in female patients with NTG.

The genotype ORs for POAG or NTG and 95% CI, assuming a dominant genetic model adjusted for age, are shown in Figure 1. For a dominant genotype model, the frequency of the CA+/AA genotypes in the AGTR2/3123C→A polymorphism was significantly higher in female patients with NTG (71.2%) than in female control subjects (56.7%; \( P = 0.0095 \) for CC versus CA+/AA; OR = 2.18; 95% CI = 1.21–3.93). This polymorphism was not associated with glaucoma in male subjects. In the recessive model, there was no significant difference in the genotype frequency in the 10 polymorphisms (data not shown). Although the AGTR1/−713T→G polymorphism had a significantly different distribution of genotype frequencies among the TT, TG, and GG in patients with POAG (Table 3), it was not significantly different in a dominant model or a recessive model. The frequency of GG genotype was higher in patients with POAG (3.2%) than in control subjects (0.4%, \( P = 0.071 \) for TT+TG versus GG).

Three clinical characteristics of the patients with glaucoma—age, IOP, and visual field score at diagnosis—were examined to determine whether they were associated with the 10 polymorphisms in the RAA system. The patients with glaucoma...
did not show a significant association between clinical characteristics and 10 SNPs (data not shown, except in Table 4).

**Clinical Characteristics of NTG Patients with the**

**AGTR2/3123C→A and ACE I/D Polymorphisms**

No significant association of clinical characteristics (age, IOP, and visual field score) was detected between female glaucoma patients with CC and those with CA+AA genotypes (Table 4). The visual field score had a tendency to be worse in patients with NTG and CC genotype than in those with CA+AA genotypes (P = 0.107).

However, when combined with ACE (I/D) polymorphisms, female patients with NTG who carried CC in the AGTR2 gene as well as ID+DD in the ACE gene had significantly worse visual field scores than did the patients with the other three combined genotypes (P = 0.012; Table 5, Fig. 2). This effect was not observed in patients with POAG (data not shown).

**Effect of an Oral Angiotensin II Receptor Blocker on IOP and Its Association with the AGTR2 Genotype**

The changes in IOP after oral candesartan cilexetil or placebo are shown in Figure 3A. IOP in the subjects who received the placebo was not altered significantly. However, as early as 1 hour after oral candesartan cilexetil, IOP had fallen significantly and remained low for 5 hours (P < 0.0001) compared with placebo. Candesartan cilexetil did not significantly affect perfusion pressure (Fig. 3B). No significant changes in SBP, DBP, and heart rate were detected after a single oral dose of candesartan cilexetil or placebo (data not shown).
The changes in IOP after oral candesartan cilexetil in each of the 20 subjects are shown in Figure 3C. There was no significant association between the effects of candesartan cilexetil and the three SNPs in the \textit{AGTR1} gene in the 20 control subjects (Table 6). For the \textit{AGTR2} genotype, however, four men with the A genotype showed a reduction of IOP by 2.3/0.5 mm Hg, which was the same amount as that of subjects who received placebo and a significantly lesser decrease in IOP than in the nine men with the C genotype (5.0/1.1 mm Hg, \(P = 0.014\)). No woman had the AA genotype in this study.

**DISCUSSION**

Although most cases of glaucoma are classified as POAG or NTG of unknown cause, multiple environmental and genetic factors are likely to be involved in the pathogenesis of glaucoma. SNPs can be used to detect linkage disequilibrium reliably between a marker genotype and a disease of multifactorial origin.\(^{37}\) Using these markers, candidate genes of the RAS system, including \textit{REN}, \textit{AGT}, \textit{ACE}, \textit{AGTR1}, \textit{AGTR2}, \textit{CYP11B2}, and \textit{CMA}, have been investigated in association studies concerning essential hypertension and other cardiovascular diseases.\(^{28–32}\)

The RAS has been strongly implicated in the pathogenesis of essential hypertension, cardiovascular disease, progressive renal disease, and diabetic retinopathy.\(^{38}\) The major biologically active product of the RAS is ATII, which is produced from AGT by the sequential action of renin and ACE or chymase. ATII, the final effector in RAS activity, is both a powerful vasoconstrictor and a potent mediator of cellular proliferation and extracellular matrix protein synthesis and accumulation.\(^{39}\) These effects contribute to progressive fibrotic disease in various organ systems. The effects of ATII are mainly receptor mediated at \textit{AGTR1} and \textit{AGTR2}.\(^{39}\) Administration of ATII by intravenous or

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Genotypic ORs for glaucoma and 95% CI in 10 polymorphisms in the RAA system, assuming a dominant genetic model (major homozygote versus others). \(^* P = 0.0095.\)

<table>
<thead>
<tr>
<th>Phenotype Variable</th>
<th>CC</th>
<th>CA + AA</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POAG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (y)</td>
<td>59.2 ± 11.6 (n = 38)</td>
<td>61.3 ± 11.1 (n = 42)</td>
<td>0.424</td>
</tr>
<tr>
<td>IOP at diagnosis (mm Hg)</td>
<td>25.3 ± 4.3 (n = 35)</td>
<td>26.6 ± 5.9 (n = 39)</td>
<td>0.243</td>
</tr>
<tr>
<td>Visual field score at diagnosis</td>
<td>3.15 ± 0.96 (n = 39)</td>
<td>2.98 ± 0.89 (n = 43)</td>
<td>0.729</td>
</tr>
<tr>
<td><strong>NTG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (y)</td>
<td>59.1 ± 13.3 (n = 38)</td>
<td>57.8 ± 11.6 (n = 98)</td>
<td>0.149</td>
</tr>
<tr>
<td>IOP at diagnosis (mm Hg)</td>
<td>16.0 ± 2.5 (n = 36)</td>
<td>16.5 ± 2.4 (n = 92)</td>
<td>0.32</td>
</tr>
<tr>
<td>Visual field score at diagnosis</td>
<td>2.85 ± 0.74 (n = 40)</td>
<td>2.64 ± 0.56 (n = 98)</td>
<td>0.107</td>
</tr>
</tbody>
</table>

\(^* P\) Probability for logistic regression analysis.
in rats.\textsuperscript{40,41} In humans, systemic ATII receptor blockers lower anterior chamber routes results in a significant increase in IOP.\textsuperscript{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 RAS in these patients.

We found a gender-specific association between the AGTR2/3123C\textrightarrow{}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\textrightarrow{}A, only the visual field score was significantly worse ($P = 0.012$) in the female patients with NTG with the CA 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.\textsuperscript{42} Genetic interaction may be essential for the development or the susceptibility to diseases.\textsuperscript{33–46} 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\textsuperscript{17} and hypertrophic cardiomyopathy.\textsuperscript{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 ($P = 0.0058$).\textsuperscript{47}

Because the AGTR2/3123C\textrightarrow{}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\textrightarrow{}A polymor-

\textbf{Table 5. Comparison of Clinical Characteristics of Female Patients with NTG, According to ACE (I/D) and AGTR2 Genotypes (3123C\textrightarrow{}A)}

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>ACE II</th>
<th>CA + AA</th>
<th>ID + DD</th>
<th>CA + AA</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>63.6 ± 10.9 ($n = 15$)</td>
<td>57.0 ± 11.2 ($n = 47$)</td>
<td>56.2 ± 14.1 ($n = 23$)</td>
<td>58.5 ± 12.0 ($n = 51$)</td>
<td>0.313</td>
</tr>
<tr>
<td>IOP (mm Hg)</td>
<td>16.0 ± 2.2 ($n = 16$)</td>
<td>16.5 ± 2.6 ($n = 45$)</td>
<td>16.1 ± 2.7 ($n = 20$)</td>
<td>16.5 ± 2.2 ($n = 49$)</td>
<td>0.75</td>
</tr>
<tr>
<td>Visual field score</td>
<td>2.47 ± 0.51 ($n = 17$)</td>
<td>2.64 ± 0.53 ($n = 47$)</td>
<td>3.15 ± 0.76 ($n = 23$)</td>
<td>2.65 ± 0.59 ($n = 52$)</td>
<td>0.012†</td>
</tr>
</tbody>
</table>

* $P < 0.05$ by Kruskal-Wallis test.
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 endpoints. 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 pressure but rather by an increase in uveoscleral outflow.

FIGURE 3. Variations in IOP and OPP after oral administration of the angiotensin II receptor blocker candesartan cilexetil (●) or a placebo (E). (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.

<table>
<thead>
<tr>
<th>Polymorphisms</th>
<th>Genotype</th>
<th>Eyes (n)</th>
<th>Maximum Reduction of IOP (mm Hg)</th>
<th>P*</th>
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<tbody>
<tr>
<td>AGTR1 -713T→G</td>
<td>TT</td>
<td>18</td>
<td>4.9 ± 1.8</td>
<td>0.898</td>
</tr>
<tr>
<td></td>
<td>TG</td>
<td>2</td>
<td>5.0 ± 4.2</td>
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</tr>
<tr>
<td></td>
<td>GG</td>
<td>0</td>
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<tr>
<td>AGTR1 -521C→T</td>
<td>CC</td>
<td>18</td>
<td>4.9 ± 1.8</td>
<td>0.117†</td>
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<td></td>
<td>CT</td>
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<tr>
<td></td>
<td>TT</td>
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<td>8</td>
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<tr>
<td>AGTR1 1166A→C</td>
<td>AA</td>
<td>18</td>
<td>5.1 ± 2.0</td>
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<tr>
<td></td>
<td>AC</td>
<td>2</td>
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<td>CC</td>
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<tr>
<td>AGTR2 3123C→A</td>
<td>C (male)</td>
<td>9</td>
<td>5.0 ± 1.1</td>
<td>0.014‡</td>
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<tr>
<td></td>
<td>A (male)</td>
<td>4</td>
<td>2.5 ± 0.5</td>
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<tr>
<td></td>
<td>CC (female)</td>
<td>5</td>
<td>7.0 ± 1.0</td>
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</tr>
<tr>
<td></td>
<td>CA (female)</td>
<td>4</td>
<td>6.0 ± 1.6</td>
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<tr>
<td></td>
<td>AA (female)</td>
<td>0</td>
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* 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 reduc-
tion in IOP for 5 hours after administration.

Miller et al.23 demonstrated a relationship between the
ATIR/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 AGTR2/3125C→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 (2.5 ± 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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