Genotyping HLA-DRB1 and HLA-DQB1 alleles in Japanese patients with normal tension glaucoma

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**Purpose:** Normal tension glaucoma (NTG) is a subtype of glaucoma in which intraocular pressure is within the statistically normal range. NTG may be associated with an immune disorder. The aim of this study was to determine whether specific alleles in the human leukocyte antigen (HLA)-DRB1 and HLA-DQB1 genes correlated with NTG in Japanese patients.

**Methods:** We genotyped the HLA-DRB1 and HLA-DQB1 alleles in 113 Japanese patients with NTG and in 184 healthy Japanese control subjects using the polymerase chain reaction-sequence-specific oligonucleotide probes (PCR-SSOP) Luminex method. We assessed the allelic diversity in patients and controls.

**Results:** There were no statistically significant differences in the allele frequency of HLA-DRB1 and HLA-DQB1 between NTG patients and control subjects, and no HLA-DRB1-HLA-DQB1 haplotypes demonstrated any significant association with NTG.

**Conclusions:** Our findings suggest that HLA-DRB1 and HLA-DQB1 polymorphisms have no significant effect on the development of NTG in Japanese patients.
autoimmune mechanism may elicit damage to the optic nerve, resulting in glaucomatous injury. He additionally suggested that autoimmunemediated glaucoma injury occurs most often in NTG patients. There have been several reports of autoantibodies against ocular antigens that are upregulated in the serum of patients with glaucoma, such as heat shock proteins (HSPs) [14], gamma-enolase [15], glutathione S-transferase [16], anti-phosphatidylserine [17], and glycosaminoglycans [18]. Therefore, NTG might actually be an organ-specific autoimmune disorder.

Human leukocyte antigen (HLA) genes regulate the immune system and the predisposition to most autoimmune disorders. HLA class II alleles have been shown to be significantly associated with glaucoma. Gil-Carrasco et al. [19] reported a higher frequency of the HLA-DR3 antigen in Mexican POAG patients compared with controls; further, an increased frequency of the HLA-DRB1*0407-DQB1*0302 haplotype was significantly associated with POAG in Mexican patients [20]. Ferreri et al. [21] showed a significant association between DR11 and DQ1 alleles and POAG in the Italian population. Therefore, HLA class II gene polymorphisms may influence the development of autoimmunity in glaucoma. On the other hand, HLA class I alleles have also been shown to be associated with glaucoma [22-24]. However numerous studies have reported no significant correlation between HLA class I alleles and glaucoma [25-28], and thus the possibility of HLA class I alleles being associated with the pathogenesis of NTG is deemed low.

The aim of this study was to clarify the role of HLA class II gene polymorphisms in the development of NTG by assessing the association of polymorphisms in HLA-DRB1 and HLA-DQB1 genes with NTG in Japanese patients.

**METHODS**

Subject: We recruited 113 unrelated Japanese patients with NTG and 184 unrelated healthy Japanese control subjects at the following Japanese universities: Yokohama City University, Yamanashi University, Gifu University, Kobe University, Yamaguchi University, Kumamoto University, Hokkaido University, Tokyo University, Niigata University, Kanazawa University, Hiroshima University, Tajimi municipal hospital, and Tokai University. Patients were diagnosed using the following strict inclusion criteria: the presence of glaucomatous optic neuropathy with corresponding visual field loss; normal open angle with angle width of Shaffer grade 2 or higher; absence of IOP greater than 21 mmHg on repeat pressure measurement using Goldmann applanation tonometry without medication; and lack of a pathological basis for optic nerve changes upon neurologic, rhinologic, and general medical examination, including magnetic resonance imaging. Glaucomatous optic nerve change was diagnosed when the vertical cup/disc ratio of the optic nerve head was 0.7 or higher, the rim width at the superior (11 to 1 o’clock) or inferior (5 to 7 o’clock) position was less than or equal to 10% of the disc diameter, the difference in the vertical cup/disc ratio between eyes was 0.2 or greater, or a nerve fiber layer defect was found. Glaucomatous visual field loss was defined on a hemifield basis using reliable field data examined by the Humphrey® static visual field analyzer (HFA) C-30–2 program (Carl Zeiss Meditec, Oberkochen, Germany) according to Anderson and Patella’s criteria [29]. The hemifield was considered abnormal when the pattern deviation probability plot revealed a cluster of 3 or more non-edge contiguous points having sensitivity with a probability of less than 5% in the upper or lower hemifield, with one of these points having a probability of less than 1%. In addition, the following inclusion and exclusion criteria were used. We excluded individuals who were diagnosed when they were under 20 years old or over 60 years old with a −8.0D or higher myopic refractive error of spherical equivalence. The selection criteria for the HFA mean deviation were stratified depending on the subjects’ ages to minimize the effect of aging on retinal ganglion cell loss and subsequent visual field defects. Specifically, there was no exclusion if the patient was diagnosed when under 50 years old; when the patient was −10.00 D or worse in at least one eye but was diagnosed between the ages of 50 and 55 years; or when the patients had −15.00 D or worse in at least one eye but the patient was over age 55 when diagnosed. Patients with relatively early onset were selected because early onset suggests a stronger involvement of genetic factors. During diagnosis, patients were excluded if their refraction values had changed due to cataract surgery, refractive surgery, etc. In cases in which glaucomatous visual field loss was present in only one eye, the refraction value and glaucomatous visual field loss of the affected eye were used. In cases in which glaucomatous visual field loss was present in both eyes, the refraction value and glaucomatous visual field loss of the more severely affected eye were used.

Patients ranged in age between 24 and 59 years (mean 47.4±6.9 years), and 47.8% were male. The mean refraction value was −3.82±3.02 D, and the mean deviation observed in the Humphrey® static visual field determination (Carl Zeiss Meditec) was −10.15±8.01 dB. The control subjects were healthy volunteers from a geographic region similar to that of the NTG patients. They had no glaucoma or ophthalmological or systemic diseases that might cause glaucoma or optic nerve changes, and they had either no myopia or mild myopia with refractive errors of −3.00 D or less. Of the control subjects, 44.6% were male.

**HLA-DRB1 and HLA-DQB1 genotyping:** Genotyping of the HLA-DRB1 and HLA-DQB1 alleles was performed using the PCR-SSOP Luminex method using LABType SSO (One Lambda Inc., Canoga Park, CA), a reverse SSO DNA typing system, according to the manufacturer’s instructions. Briefly, target DNAs were PCR-amplified using HLA-DRB1 or HLA-DQB1 group-specific primers. The biotinylated PCR products
were denatured and hybridized to locus-specific probes conjugated to fluorescently coded microspheres. A flow analyzer, LABScanTM 100, identifies the fluorescent intensity of phycoerythrin on each microsphere. The determination of the HLA allele was based on the reaction pattern compared to patterns associated with published HLA allele sequences.

Statistical analysis: Allelic frequencies were determined by direct counting. The significance of the allelic distribution between the patients with NTG and normal controls was first analyzed using Fisher’s exact probability test. The probability of association was corrected by the Bonferroni inequality method, i.e., by multiplying the p values with the number of alleles. A corrected p (pc) value of <0.05 was considered statistically significant.

Haplotype frequencies and linkage disequilibrium (LD) in the multi-locus analyses were calculated using PyPop [30]. Haplotype frequencies were determined using the iterative expectation-maximization algorithm. LD was measured using Hedrick’s multiallelic D’ statistic [31]. D’ weights the contribution of specific allele pairs to the LD using the product of their allelic frequencies. The measure is normalized to fall between zero and one, with higher values indicating a stronger LD contribution.

RESULTS
The gene frequencies of HLA-DRB1 and HLA-DQB1 alleles in 113 Japanese patients with NTG and in 184 healthy control subjects are shown in Table 1 and Table 2, respectively. A total of 27 HLA-DRB1 alleles and 14 HLA-DQB1 alleles were identified in NTG patients and healthy controls. The frequencies of HLA-DRB1*1301 and HLA-DQB1*0603 were higher in patients with NTG compared with healthy controls, although this increase did not reach statistical significance after performing the Bonferroni correction. We found no significant differences in the frequency of other HLA-DRB1 and HLA-DQB1 alleles between the patients and controls.

The magnitude of LD between HLA-DRB1 and HLA-DQB1 was extremely high, with a pair-wise D’>0.85.

### Table 1. Allele Frequencies of HLA-DRB1 in Japanese Patients with Normal Tension Glaucoma.

| HLA-DRB1 | Frequency, n (%) | p | pc |
|-----------|-----------------|---|----|
| 0101      | 17 (7.5%        | 0.38 |    |
| 0301      | 0 (0.0%         | 1   |    |
| 0401      | 0 (0.0%         | 1   |    |
| 0403      | 6 (2.7%         | 0.81 |    |
| 0405      | 27 (11.9%       | 1   |    |
| 0406      | 5 (2.2%         | 0.79 |    |
| 0407      | 1 (0.4%)        | 1   |    |
| 0410      | 8 (3.5%)        | 0.28 |    |
| 0802      | 12 (5.3%)       | 0.72 |    |
| 0803      | 15 (6.6%)       | 0.53 |    |
| 0901      | 30 (13.3%)      | 0.72 |    |
| 1001      | 2 (0.9%)        | 0.14 |    |
| 1101      | 5 (2.2%)        | 1   |    |
| 1201      | 9 (4.0%)        | 0.65 |    |
| 1202      | 7 (3.1%)        | 0.59 |    |
| 1301      | 5 (2.2%)        | 0.032 | NS |
| 1302      | 16 (7.1%)       | 0.87 |    |
| 1303      | 0 (0.0%)        | 1   |    |
| 1307      | 0 (0.0%)        | 1   |    |
| 1401      | 7 (3.1%)        | 1   |    |
| 1403      | 1 (0.4%)        | 0.42 |    |
| 1405      | 2 (0.9%)        | 0.49 |    |
| 1406      | 4 (1.8%)        | 0.44 |    |
| 1412      | 0 (0.0%)        | 1   |    |
| 1501      | 17 (7.5%)       | 0.61 |    |
| 1502      | 28 (12.4%)      | 0.90 |    |
| 1602      | 2 (0.9%)        | 1   |    |
Haplotype analyses indicated complete LD between the HLA-DQB1*0603 alleles, and the HLA-DRB1*1301-HLA-DQB1*0603 haplotype had an increased frequency in patients; this was not significant after correction (Table 3).

**DISCUSSION**

Several studies have reported associations between HLA and glaucoma, and others have suggested that HLA class II genes may have an effect on the development of POAG [19-21]. The aim of this study was to investigate whether specific alleles in the HLA class II genes affected the development of NTG, which was recently suggested to be an autoimmune disorder. Toward this end, we genotyped the HLA-DRB1 and HLA-DQB1 genes in Japanese NTG patients and in healthy control subjects.

In contrast to previous POAG studies, this study focused on NTG and did not find an allelic distribution of HLA class II genes that was statistically different between NTG patients and controls. Although the frequencies of the HLA-DRB1*1301 and HLA-DQB1*0603 alleles and the HLA-DRB1*1301-HLA-DQB1*0603 haplotype had an increased frequency in patients; this was not significant after correction (Table 3).

*Only haplotypes that reached frequencies >5% in all subjects or that may have an effect on the development of NTG are shown.

**Table 2. Allele Frequencies of HLA-DQB1 in Japanese Patients with Normal Tension Glaucoma.**

| HLA-DQB1         | Cases (n=113) | Controls (n=184) | p  | pc |
|------------------|--------------|-----------------|----|----|
| 0201             | 0 (0.0)      | 1 (0.3)         | 1  |    |
| 0301             | 22 (9.7)     | 37 (10.1)       | 1  |    |
| 0302             | 21 (9.3)     | 40 (10.9)       | 0.58 | |
| 0303             | 35 (15.5)    | 57 (15.5)       | 1  |    |
| 0401             | 26 (11.5)    | 40 (10.9)       | 0.89 | |
| 0402             | 14 (6.2)     | 20 (5.4)        | 0.72 | |
| 0501             | 19 (8.4)     | 21 (5.7)        | 0.24 | |
| 0502             | 5 (2.2)      | 10 (2.7)        | 0.79 | |
| 0503             | 6 (2.7)      | 15 (4.1)        | 0.49 | |
| 0601             | 42 (18.6)    | 77 (20.9)       | 0.53 | |
| 0602             | 14 (6.2)     | 21 (5.7)        | 0.86 | |
| 0603             | 5 (2.2)      | 1 (0.3)         | 0.032 NS|
| 0604             | 16 (7.1)     | 28 (7.6)        | 0.87 | |
| 0611             | 1 (0.4)      | 0 (0.0)         | 0.38 | |

**Table 3. Frequencies of DRB1-DQB1 Haplotypes in Japanese Patients with Normal Tension Glaucoma (NTG).**

| Haplotype*       | Cases (n=113) | Controls (n=184) | p  | pc |
|------------------|--------------|-----------------|----|----|
| DRB1*0901:DQB1*0303 | 29 (12.8)    | 53 (14.4)       | 0.63 | |
| DRB1*1502:DQB1*0601 | 28 (12.4)    | 47 (12.8)       | 1  |    |
| DRB1*0405:DQB1*0401 | 26 (11.5)    | 40 (10.9)       | 0.89 | |
| DRB1*1302:DQB1*0604 | 16 (7.1)     | 28 (7.6)        | 0.87 | |
| DRB1*0803:DQB1*0601 | 14 (6.2)     | 29 (7.9)        | 0.52 | |
| DRB1*0101:DQB1*0501 | 17 (7.5)     | 20 (5.4)        | 0.38 | |
| DRB1*1501:DQB1*0602 | 14 (6.2)     | 19 (5.2)        | 0.59 | |
| DRB1*1301:DQB1*0603 | 5 (2.2)      | 1 (0.3)         | 0.032 NS|

*Only haplotypes that reached frequencies >5% in all subjects or that may have an effect on the development of NTG are shown.
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The study was approved by the ethics committee of Yokohama City University, Yamashita University, Gifu University, Kobe University, Yamaguchi University, Kumamoto University, and Tokai University, and complied with the guidelines of the Declaration of Helsinki. The details of the study were carefully explained to all of the patients and control subjects before we obtained informed written consent for genetic screening. This work was supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (No.16209052) and by a grant from the Ministry of Health, Labor, and Welfare, Japan.

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