The HLA DRB1*1501-DQB1*0602-DPB1*0501 Haplotype Is a Risk Factor for Toluene Diisocyanate-Induced Occupational Asthma

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Key Words
Toluene diisocyanate • Asthma • Human leukocyte antigen class • Immunoglobulin E

Abstract
Background: Although the pathogenesis of toluene diisocyanate (TDI)-induced occupational asthma (TDI-OA) is incompletely understood, several studies have suggested immunologic mechanisms, including specific IgE responses. A few studies have suggested human leukocyte antigen (HLA) associations with TDI-induced asthma in Western countries, but this is the first investigation of associations between HLA class I and II alleles and TDI-induced asthma patients in Asia, using high-resolution analysis. Methods: Patients with TDI-OA (n = 84), asymptomatic exposed controls (AECs, n = 47) and unexposed normal controls (NCs, n = 127) were enrolled. HLA class I and II genotyping was performed by the direct DNA sequencing analysis. Specific serum IgE antibodies to the vapor type TDI-albumin conjugate were measured by ELISA. Results: There was no significant association between the allele frequencies and the phenotype of TDI-OA. However, the frequency of the HLA DRB1*1501-DQB1*0602-DPB1*0501 haplotype was significantly higher in TDI-OA patients (19%) than in AEC (2.1%, p = 0.007, OR 4.429, CI 1.497–13.103) or NC (3.1%, p < 0.001, OR 7.235, CI 2.236–22.510) subjects, with statistical significance persisting after correction for multiple comparisons. DQB1*0402 was significantly associated with the presence of specific IgE to TDI-albumin conjugates in serum (p = 0.006, OR 4.552, CI 1.540–13.449). This p value remained significant after correction for multiple comparison. Conclusion: The HLA DRB1*1501-DQB1*0602-DPB1*0501 haplotype may be a genetic marker for the development of TDI-induced asthma in Koreans. Several HLA alleles that enhance specific IgE sensitization in exposed subjects are indicated. Copyright © 2009 S. Karger AG, Basel

Introduction
Isocyanates, which constitute a group of low-molecular-weight cross-linking agents, are commonly identified as causes of occupational asthma worldwide [1, 2]. Three major isocyanates, diphenylmethane diisocyanate (MDI), hexamethylene diisocyanate (HDI) and toluene diisocyanate (TDI), are used in the manufacture of polyurethane foam, furniture, rubber and spray paint [1, 2]. TDI is the
most common cause of occupational asthma in Korea, with a prevalence of 2.1–13% in exposed workers [3, 4], which is similar to the prevalence range of 5–15% reported for TDI production workers [1, 2, 5]. The clinical manifestations of TDI-induced occupational asthma (TDI-OA) resemble those of allergic asthma in many respects, i.e. a relatively low prevalence of asthma in exposed subjects, a sensitization period, and asthma attacks after low-dosage TDI exposure, which suggests that TDI-OA has an immunologic basis [1].

Although the pathogenesis of TDI-OA remains unclear, several immunologic mechanisms have been suggested [6–9]. Isocyanate-specific IgE and IgG antibodies have been detected in some sensitive individuals [10, 11], and activated CD4+ T cells and increased levels of cytokines produced by Th2 cells have been reported [12, 13]. Furthermore, the involvement of autoimmune reactions to isocyanate-airway epithelial cell protein conjugates has been proposed [14, 15].

Human leukocyte antigens (HLAs) play a central role in the immune recognition of foreign proteins [16]. Differences in HLA genotype may contribute to the variability in immunologic responses to allergens or haptons. There have been a few HLA association studies in patients with isocyanate-induced asthma. An association of TDI-OA with HLA-DQB1*0503 and an inverse relationship with HLA-DQB1*0501 was found in a European population [17–19], whereas no significant HLA association was found in another European study [20]. Recently, we investigated the HLA associations in TDI-OA and found an association between this disease and the DRB1*15-DPB1*05 haplotype in a Korean population, which suggested a susceptible gene marker for TDI-induced asthma [21]. Therefore, our preliminary study performed a low-resolution analysis of HLA class I and class II genes with a limited number of patients. Therefore, the data reported to date are still inconsistent. Moreover, there is no published study on the potential association of specific HLA alleles with immunologic markers, such as specific IgE directed against TDI which is known as one of the intermediate phenotype of TDI-OA [22, 23].

In the present study, we extended our preliminary study on HLA associations in the development of TDI-OA in a Korean population, now using high-resolution genotyping of HLA class I (A, B, C) and HLA class II (DRB1, DQB1, DPB1) genes in a larger cohort of TDI-OA patients, and compared these patients with asymptomatic TDI-exposed controls (AECs) and unexposed normal controls (NCs). We also evaluated the association of specific HLA alleles with the prevalence of specific IgE antibodies directed against TDI-albumin conjugates in patient serum.

**Materials and Methods**

**Subjects**

Patients with TDI-OA (n = 84) were enrolled from 4 university hospitals in Korea (Ajou, Soonchunhyang, Yonsei and Inha University Hospitals). As control subjects, 47 AECs and 127 unexposed NCs were also enrolled. TDI-OA was diagnosed based on documented exposure to TDI in the workplace, work-related asthmatic symptoms and a positive response to a bronchial challenge test with methacholine and TDI, performed as described previously [22, 23]. Atopy was defined as 1 or more positive reactions in skin prick tests with the following common allergens (Bencard Co., UK): *Dermatophagoides pteronyssinus*, *D. farina*, cat, dog, cockroach, tree pollen mixture, grass pollen mixture, mugwort, ragweed, Hop Japanese, *Aspergillus*, *Alternaria*, as well as histamine and a saline control. Total IgE concentrations were measured using the ImmunoCAP system (Phadia, Uppsala, Sweden), according to the manufacturer’s protocol.

All subjects provided informed consent. The study protocols were approved by the ethics committee of Ajou University Hospital, Suwon, Korea.

**Preparation of Vapor TDI-Albumin Conjugates**

Vapor TDI-albumin conjugates were prepared using our previously described isocyanate vapor phase exposure system [23, 24]. Briefly, TDI vapor concentrations in the range of 0.14 to 1.4 mg/m³ (approximately 1–10 µmol/m³) were passively generated in a closed circuit system and monitored with an Autoset® monitor (GMD, Pittsburgh, Pa., USA). Low endotoxin human albumin at a concentration of 5 g/l (73 µmol/l) in PBS (pH 7.2) was exposed in open 60-mm Petri dishes (Becton Dickinson, Franklin Lakes, N.J., USA) overnight. The exposure unit was sterilized with 70% ethanol, and protein solutions were passed through a 0.2-µm filter before and after exposure, to ensure sterility. Vapor TDI-albumin conjugates were prepared with an 80:20 mixture of 2,4-TDI:2,6-TDI.

**ELISA for Specific IgE Antibodies to TDI-Albumin Conjugates**

Specific IgE antibodies in serum were determined by ELISA, as described previously [23]. Briefly, the TDI-albumin conjugate or a mock conjugate was dissolved in normal saline and used to coat ELISA plates (Corning, N.Y., USA) at 10 µg/well at 37°C for 2 h, followed by incubation at 4°C overnight. After washing with PBS-Tween-20, the plates were blocked with 350 µl of blocking buffer (PBS that contained 5% BSA and 0.05% Tween-20). For specific IgE measurements in the preliminary experiments, diluted serum aliquots (50 µl) from patients or controls (1:2 dilution) were incubated for 1 h at 25°C in both TDI-albumin-coated and mock albumin-coated wells and washed 4 times. Goat anti-IgE human antibody (1:1,000; Kirkegaard & Perry Laboratories, Gaithersburg, Md., USA) was added to each well, incubated for 1 h at room temperature, and washed. Then, 100 µl of substrate solution (Sigma Chemical Co., St. Louis, Mo., USA) was added. After 15 min of incubation at room temperature, an ELISA read-
er was used to read the absorbance at 405 nm, with the reference reading at 450 nm. To quantify antibody binding specific to TDI, the optical density (OD) values of the mock-conjugated albumin wells were subtracted from those of the TDI-albumin-coated wells. Positive cutoff values (0.13 for IgE) were based on the mean plus 2 SD of the OD values from tests of 80 unexposed healthy controls. Specificity for TDI-albumin in the positive samples was confirmed by a >50% reduction in OD in an inhibition ELISA with an autologous TDI-albumin conjugate and a lack of inhibition (<10%) with control (mock) albumin.

Genomic DNA Preparation and High-Resolution HLA Genotyping
Genomic DNA samples from the peripheral blood mononuclear cells of the patients with TDI-OA, the AEC group and the NCs were extracted using the G-DEX Genomic DNA Extraction Kit (Intron Biotechnology, Korea), according to the manufacturer’s protocol. HLA class I (A, B, C) and II (DQB1, DPB1) high-resolution genotyping was conducted with amplified gene products using locus-specific primers, followed by direct DNA sequencing using sequencing primers and the BigDye Termination Cycle Reaction Kit (Applied Biosystems) on an ABI 3100 automated DNA sequencer. In the case of high-resolution genotyping of HLA-DRB1, group-specific PCR for each sample was performed prior to direct DNA sequencing analysis [25].

Statistical Analysis
The Student’s t test and the χ² test were used to compare demographic data between the study groups, using the SPSS version 12.0 software (SPSS, Chicago, Ill., USA). Allele frequencies on each locus were obtained by direct counting. Hardy-Weinberg equilibrium was estimated by exact test using Markov chain (Arlequin version 3.11, 2006), and all of them were in Hardy-Weinberg equilibrium (p > 0.05) [26]. Frequencies of multi-locus (2-, 3-, 4-, 5- and 6-locus) haplotypes were estimated from the data obtained in this study using an EM algorithm with a frequency of >5% (Arlequin version 3.11, 2006) [26]. Logistic regression models were used for the data analysis between 2 groups controlling for age, sex and smoking as covariates. p values were corrected for multiple comparisons by multiplying by 5, since 5 alleles at each locus of the HLA-A, HLA-B, HLA-Cw, HLA-DR, HLA-DQ and HLA-DP were sufficiently common to test for associations with the disease. p values ≤0.05 were deemed to be statistically significant.

Results

Clinical Characteristics of the Study Subjects
There was no significant difference in age or gender between the groups. Smokers were significantly more prevalent in the AEC group than in the TDI-OA group (p < 0.001), and the AEC group was exposed to TDI in the workplace for longer periods than the TDI-OA group (p < 0.001). For the measurement of IgE antibodies specific to TDI-albumin conjugates in the sera of the TDI-exposed groups, i.e. the TDI-OA group and the AEC group, the prevalence of serum IgE specific to TDI-albumin conjugates was significantly higher (p = 0.008) in the TDI-OA group (26.9%) than in the AEC group (6.4%) (table 1).

Allele Frequencies
Tables 2 and 3 show the 9 most common alleles for each HLA class I and II genotype. There were no significant differences among the 3 groups. Although the frequencies of Cw*0303, DRB1*1501 and DQB1*0602 in the TDI-OA group were significantly higher than those in the NCs (p < 0.01), there was no statistically significant difference between the TDI-OA and AEC group in this respect. The allele frequency of DQB1*0602 in the TDI-OA was significantly higher than in the AEC group (p = 0.016); however, the p value did not remain significant after correction for multiple comparison.
Two- and Three-Locus Haplotype Frequencies

Two- and 3-locus HLA haplotypes associated with TDI-OA are listed in Table 4. The frequency of DRB1*1501-DQB1*0602-DPB1*0501 in the TDI-OA group (19.0%) was significantly higher than those in the AEC (21.1%, p = 0.007, \( \phi_c = 0.035 \)) and NC groups (3.1%, \( \phi_c < 0.001 \)). When we analyzed each 2-locus haplotype in the DRB1*1501-DQB1*0602-DPB1*0501 haplotype, significant increases were noted for DRB1*1501-DQB1*0602 and DRB1*1501-DPB1*0501 in the TDI-OA group (27.4 vs. 20.2%), as compared with the AEC group (12.8%, \( \phi_c = 0.08 \) vs. 4.3%, \( \phi_c = 0.006 \)) and the NC group (11.8%, \( \phi = 0.006 \), \( \phi_c = 0.03 \) vs. 3.1%, \( \phi < 0.001 \), \( \phi_c < 0.005 \)).

Table 2. Distributions of HLA-A, HLA-B and HLA-C genes in the study subjects

<table>
<thead>
<tr>
<th>Allele</th>
<th>TDI-OA (n = 84)</th>
<th>AEC (n = 47)</th>
<th>NC (n = 127)</th>
<th>TDI-OA vs. AEC</th>
<th>TDI-OA vs. NC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A*0201</td>
<td>27 (32.1)</td>
<td>12 (25.5)</td>
<td>35 (27.6)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>A*0206</td>
<td>18 (21.4)</td>
<td>6 (12.8)</td>
<td>22 (17.3)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>A*1101</td>
<td>22 (26.2)</td>
<td>8 (17)</td>
<td>30 (23.6)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>A*2402</td>
<td>29 (34.5)</td>
<td>22 (46.8)</td>
<td>45 (35.4)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>A*2601</td>
<td>6 (7.1)</td>
<td>4 (8.5)</td>
<td>10 (7.9)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>A*2602</td>
<td>8 (9.5)</td>
<td>3 (6.4)</td>
<td>7 (5.5)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>A*3001</td>
<td>6 (7.1)</td>
<td>7 (14.9)</td>
<td>8 (6.3)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>A*3101</td>
<td>7 (8.3)</td>
<td>3 (6.4)</td>
<td>11 (8.7)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>A*3303</td>
<td>18 (21.4)</td>
<td>12 (25.5)</td>
<td>38 (29.9)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Kw*0102</td>
<td>23 (27.4)</td>
<td>12 (25.5)</td>
<td>46 (36.2)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Kw*0302</td>
<td>7 (8.3)</td>
<td>6 (12.8)</td>
<td>17 (13.4)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Kw*0303</td>
<td>26 (31)</td>
<td>13 (27.7)</td>
<td>18 (14.2)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages. Logistic regression analysis was applied to control for sex, age and smoking as covariates. NS = Not significant. Others: A*0101, 0203, 0205, 0207, 0210, 0215, 0301, 0302, 1102, 2407, 2408, 2420, 2603, 2610, 2901, 3004 and 3401; Kw*0103, 0202, 0403, 0501, 0701/06, 0704, 0802, 0803, 1202, 1203, 1403, 1502 and 1505; B*0702, 0705, 0705/06, 0801, 0802, 1301, 1401, 1502, 1507, 1511, 1518, 1521, 1527, 1538, 1801, 2705, 2706, 3511, 3531, 3701, 3802, 3901, 4001, 4002, 4003, 4006, 4402, 4406, 4701, 5001, 5102, 5201, 5501, 5502, 5504, 5513, 5601, 5701, 5901, 6701.

Associations between HLA Alleles and Prevalences of IgE Specific to TDI-Albumin Conjugates in Patient Sera

Some HLA genes were found to have significant associations with the prevalences of specific IgE to TDI in serum samples (Table 5). The frequencies of A*0206-Cw*0102, DRB1*0802, DQB1*0402, were significantly higher in patients who had specific IgE antibodies than in those who did not (p < 0.05). However,
the p values of A*0206, haplotype A*0206-Cw*0102, and DRB1*0802 were not significant after correction for multiple comparisons, whereas the p value of DQB1*0602 remained significant after correction for multiple comparison (p = 0.006, OR 2.588, CI 1.290–5.193).

### Discussion

In the present study, we found a positive association between the 3-locus haplotype DRB1*1501-DQB1*0602-DPB1*0501 and the phenotype of TDI-OA in a Korean population, which suggests that this haplotype is involved in the development of TDI-OA. The present study is the first to be performed in an Asian population and included more subjects than previously reported studies [17–20]. Our preliminary study using low-resolution analysis with 55 TDI-OA patients showed a strong positive association of the DRB1*15-DPB1*05 haplotype with the disease [21], and this is consistent with the results of our current study, since the 2-locus haplotype of DRB1*15-DPB1*05 is a part of DRB1*1501-DQB1*0602-DPB1*0501.

Although the pathogenesis of TDI-OA is not fully understood, it involves airway inflammation, including ac-
Activated T lymphocytes, eosinophils and neutrophilic infiltration, suggesting an immunologic basis [6–9]. HLA molecules are highly polymorphic, so variation in their protein structure will determine the specific epitopes presented to T lymphocytes by an individual. Therefore, HLA gene polymorphisms may contribute to the pathogenesis of TDI-OA.

Table 4. Haplotype analysis of the HLA genes in the study subjects

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>TDI-OA (n = 84)</th>
<th>AEC (n = 47)</th>
<th>NC (n = 127)</th>
<th>TDI-OA vs. AEC</th>
<th>TDI-OA vs. NC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A<em>3303-Cw</em>0701/06-B*4403</td>
<td>0 (0)</td>
<td>4 (8.5)</td>
<td>8 (6.3)</td>
<td>NS</td>
<td>0.023 (OR = NA)</td>
</tr>
<tr>
<td>A<em>3303-Cw</em>0701/06</td>
<td>2 (2.4)</td>
<td>4 (8.5)</td>
<td>9 (7.1)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Cw<em>0701/06-B</em>4403</td>
<td>2 (2.4)</td>
<td>4 (8.5)</td>
<td>8 (6.3)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DRB1<em>0901-DQB1</em>0303-DPB1*0501</td>
<td>2 (2.4)</td>
<td>7 (14.9)</td>
<td>8 (6.3)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DRB1<em>0901-DQB1</em>0303</td>
<td>16 (19.0)</td>
<td>9 (19.1)</td>
<td>25 (19.7)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DRB1<em>0901-DPB1</em>0501</td>
<td>1 (1.2)</td>
<td>7 (14.9)</td>
<td>4 (3.1)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DQB1<em>0303-DPB1</em>0501</td>
<td>3 (3.6)</td>
<td>7 (14.9)</td>
<td>9 (7.1)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DRB1<em>1501-DQB1</em>0602-DPB1*0501</td>
<td>16 (19)</td>
<td>1 (2.1)</td>
<td>4 (3.1)</td>
<td>0.007 (OR 4.492, CI 1.497–13.103)</td>
<td>&lt;0.001 (OR 7.235, CI 2.326–22.510)</td>
</tr>
<tr>
<td>DRB1<em>1501-DQB1</em>0602</td>
<td>23 (27.4)</td>
<td>6 (12.8)</td>
<td>15 (11.8)</td>
<td>0.016 (OR 2.024, CI 1.141–3.590)</td>
<td>0.006 (OR 2.815, CI 1.368–5.792)</td>
</tr>
<tr>
<td>DRB1<em>1501-DPB1</em>0501</td>
<td>17 (20.2)</td>
<td>2 (4.3)</td>
<td>4 (3.1)</td>
<td>0.006 (OR 3.127, CI 1.381–7.081)</td>
<td>&lt;0.001 (OR 7.802, CI 2.523–24.132)</td>
</tr>
<tr>
<td>DQB1<em>0602-DPB1</em>0501</td>
<td>16 (19)</td>
<td>0 (0)</td>
<td>4 (3.1)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages. Logistic regression analysis was applied to control for sex, age and smoking as covariates. NS = Not significant; NA = not applicable.

Table 5. Associations between HLA alleles and prevalences of serum-specific IgE to TDI-albumin conjugates in TDI-exposed subjects

<table>
<thead>
<tr>
<th>Allele/haplotype</th>
<th>IgE to TDI-albumin conjugates</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>positive (n = 17)</td>
<td>negative (n = 82)</td>
</tr>
<tr>
<td>A*0206</td>
<td>6 (35.3)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>A<em>0206</em>Cw0102</td>
<td>3 (17.6)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>DRB1*0802</td>
<td>3 (17.6)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>DQB1*0402</td>
<td>3 (17.6)</td>
<td>2 (2.4)</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages. Logistic regression analysis was applied to control for sex, age and smoking as covariates.
There have been several investigations into the relationship between HLA genotypes and TDI-OA, typically focusing on the HLA class II genes [17–21]. Bignon et al. [17] investigated HLA specificity in 28 patients with TDI-OA, comparing them with 16 asymptomatic exposed workers, in a European population. In a subsequent study, these results were confirmed in another European cohort of TDI-OA patients, and it was reported that aspartic acid was present in DQB1*0503 and valine in DQB1*0501 at position 57 of HLA-DQB1, which suggests that the amino acid present at residue 57 of HLA-DQB1 is an important determinant of susceptibility to isocyanates in exposed workers [18, 19]. However, Rihs et al. [20] did not find any significant association between a specific HLA class II allele or DQB1-Asp57+ and isocyanate-induced asthma in a German population, although this study had some limitations. First, subjects exposed to different kinds of isocyanates (TDI, MDI, HDI) were enrolled. Second, asymptomatic exposed workers were not enrolled as controls, and third, the diagnosis was based on work-related symptoms rather than on the results of bronchal challenge tests. Another study in a North American population did not find any significant association between HLA-DR or HLA-DQ antigens and isocyanate-induced asthma, including asthma induced by TDI, MDI or HDI, although the study was performed in a very small and heterogeneous population using a low-resolution genotyping technique [27]. We also found no significant association of DQB1-Asp57+ in 84 patients with TDI-OA, as compared with 47 asymptomatic exposed workers, in a Korean population (data not shown). Instead, we found a strong positive association between the DRB1*1501-DQB1*0602-DPB1*0501 haplotype and this disease, which is largely consistent with our preliminary results using low-resolution analysis [21]. The lack of consistency among the studies from Western countries could be partly due to the low numbers of study subjects and ethnic differences [19, 27]. It is noteworthy that our study population is the largest one, based on racially homogeneous patients with asthma induced exclusively by TDI, among the previous HLA association studies, considering that TDI-OA is a relatively uncommon disease [17–20]. Further studies with larger cohorts from homogenous populations are required to confirm these specific associations, which should also be replicated in other ethnic populations.

Regarding the cellular mechanisms underlying TDI-OA, CD8+ T-cell activation has been implicated [28]. CD8+ T cells recognize antigens that are presented on cell surface HLA class I molecules [16], which suggests that HLA class I polymorphisms contribute to the pathogenesis of TDI-OA. For HLA class I genes, there is one reported study showing a lack of any significant association with TDI-OA in an Italian population [29]. In the present study, we conducted allele and haplotype analyses of the HLA class I genes. However, we found no significant association with TDI-OA, which was consistent with our previous data using low-resolution analysis. Thus, these results suggest that HLA class I genes are not involved in the development of TDI-OA.

Although the natural history of isocyanate-induced asthma generally resembles that of the type I hypersensitivity response in allergic asthma, specific IgE antibodies to isocyanates are not detected in the majority of isocyanate-induced asthma patients [1]. When present, isocyanate-specific serum IgE is strongly predictive of isocyanate-induced asthma [9]. This lack of specific IgE antibodies to isocyanates may be attributable to technical problems, including a poor understanding of isocyanate antigens and carrier proteins [9]. Recently, we reported that the prevalence of specific IgE in serum, when using vapor type TDI-albumin conjugates, was increased to 43.9% in TDI-OA patients, as compared with the prevalences in asymptomatic exposed workers and unexposed healthy controls [23], indicating that specific IgE is an intermediate phenotype in TDI-OA. In the current study, when we analyzed the association between HLA genes and the prevalences of specific IgE antibodies to vapor type TDI-albumin conjugates in the exposed subjects, we found a significant association between DQB1*0402 and the presence of specific serum IgE directed against vapor type TDI-albumin conjugates. Thus, we propose that the exposed workers with HLA allele DQB1*0402 may be more susceptible to develop the sensitization to specific IgE against TDI-albumin conjugate, which may ultimately contribute to the development of TDI-OA.

In conclusion, we hypothesize the involvement of the DRB1*1501-DQB1*0602-DPB1*0501 haplotype or unidentified genes closely linked to this haplotype in the development of TDI-OA in a Korean population. Further investigations will be needed to explore the exact mechanism underlying TDI-OA.

Acknowledgment

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HLA Association with Isocyanate-Induced Asthma

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