Background: Associations between IgA nephropathy (IgAN) and HLA-DRB1 and -DQB1 alleles have been reported in several ethnic groups. We investigated the association of HLA-DRB1 and -DQB1 alleles with the predisposition for IgAN and disease progression to end-stage kidney disease (ESKD) in Korean patients.

Methods: We analyzed HLA-DRB1 and -DQB1 genotypes in 399 IgAN patients between January 2000 and January 2019 using a LIFECODES sequence-specific oligonucleotide (SSO) typing kit (Immucor, Stamford, CT, USA) or a LABType SSO Typing Test (One Lambda, Canoga Park, CA, USA). Alleles with a significant difference in two-digit resolution were further analyzed using in-house sequence-based typing and sequence-specific primer PCR. As controls, 613 healthy hematopoietic stem cell donors were included. Kidney survival was analyzed in 281 IgAN patients with available clinical and laboratory data using Cox regression analysis. Where needed, P-values were adjusted using Bonferroni correction.

Results: The allele frequencies of HLA-DRB1*04:05 (corrected \( \text{Pc} < 0.001 \)), -DQB1*04:01 ( \( \text{Pc} = 0.048 \)), and -DQB1*03:02 ( \( \text{Pc} = 0.021 \)) were significantly higher in IgAN patients than in controls, whereas those of HLA-DRB1*07:01, -DRB1*15:01, -DQB1*02:02, and -DQB1*06:02 ( \( \text{Pc} < 0.001 \) for all) were significantly lower in IgAN patients than in controls. The allele frequency of HLA-DQB1*05:03 ( \( \text{Pc} = 0.016 \)) was significantly lower in the ESKD group than in the non-ESKD group; however, there was no significant difference for ESKD progression between these groups.

Conclusions: We report novel associations of HLA-DRB1*15:01, DQB1*02:02, -DQB1*03:02, and -DQB1*04:01 with IgAN. Further studies of HLA alleles associated with IgAN progression in a larger cohort and in various ethnic groups are needed.

Key Words: IgA nephropathy, Human leukocyte antigen, DRB1, DQB1, Association, End-stage kidney disease, Disease progression

INTRODUCTION

IgA nephropathy (IgAN) is the most frequent form of primary glomerulonephritis exhibiting geographic and ethnic differences, and is prevalent in Asian countries [1, 2]. In many patients, it gradually progresses to end-stage kidney disease (ESKD). IgAN patients in the Asia-Pacific region particularly have a high risk of disease progression [3]. Familial manifestations, along with autoimmune abnormalities, are frequently reported in IgAN patients, which has led to studies on IgAN immunopathogenesis and genetic pathogenesis [4]. Since the 1980s, human leukocyte antigen (HLA) molecules related to T lymphocyte activity have been shown to be associated with genetic susceptibility to IgAN with varying results [5–10]. In several genome-wide asso-
Association studies (GWASs), single-nucleotide variations (SNVs) related to the HLA-DRB1 and -DQB1 loci have been reported to have a strong association with IgAN [11–13]. In Korea, a study on 139 IgAN patients reported associations between IgAN and HLA alleles [14]. The allele frequencies of HLA-DQB1*03:02 and -DQB1*05:03 were higher in pediatric and adult IgAN patients with ESKD than in pediatric IgAN patients with normal kidney function, but the HLA-DR allele frequency showed no difference between these groups. However, a GWAS in 188 Korean IgAN patients did not show significant associations between HLA loci-related SNVs and IgAN [15]. With the aim to expand the knowledge of associations between HLA alleles and IgAN in a larger cohort of Korean patients regardless of age, we analyzed HLA-DRB1 and -DQB1 alleles in 399 Korean IgAN patients and investigated the association between these HLA alleles and IgAN susceptibility and prognosis.

**MATERIALS AND METHODS**

**Study population and clinical data**

Among the Korean patients diagnosed as having IgAN at Seoul National University Hospital (SNUH, Seoul, Korea) between January 1, 2000 and January 1, 2019, 268 IgAN patients with ESKD and 131 patients with IgAN that did not progress to ESKD were enrolled in this study (Fig. 1). Among the 131 patients, 57 patients did not progress to ESKD after more than 10 years of follow up and 74 patients did not progress to ESKD after less than 10 years of follow up. These patients were diagnosed as having IgAN by kidney biopsy at SNUH or by slide review of biopsy performed outside SNUH. Patients with clinical or laboratory evidence of systemic lupus erythematosus, liver cirrhosis, and Henoch-Schönlein nephritis at the time of diagnosis were excluded. ESKD was defined as the initiation of permanent dialysis or kidney transplantation. Patient data were obtained through retrospective medical record reviews. The observation period ended on December 31, 2019, and data from patients who missed follow-up or with preserved kidney function were censored on the day the last kidney function was confirmed. The Institutional Review Board (IRB) of SNUH (IRB No. 1911-009-1074) approved this study and exempted the requirement of an informed consent.

Kidney survival was analyzed in 281 IgAN patients (153 with ESKD and 128 not progressed to ESKD) for whom all clinical and laboratory data were available at the time of initial biopsy (Fig. 1). For IgAN patients, clinical and laboratory data including sex, age at the time of biopsy, blood pressure, plasma Hb, serum creatinine (Cr) level, estimated glomerular filtration rate (eGFR), serum albumin level, serum IgA level, gross hematuria, microscopic hematuria, and 24-hour urinary protein, were obtained. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or undergoing treatment for hypertension. The eGFR was calculated using the modification of diet in renal disease formula. For each patient, the duration from diagnosis to onset of ESKD was noted. The risk of IgAN progression to ESKD was analyzed based on the clinical and laboratory data and HLA allele types. When analyzing risk factors, the 24-hour urinary protein was classified based on a threshold of 1 g/day.

The characteristics of IgAN patients with all available clinical and laboratory data at the time of kidney biopsy are presented in Fig. 1.
Table 1. Clinical characteristics of IgAN patients with all available clinical data at the time of kidney biopsy (N=281)

| Characteristics          | IgAN patients with all clinical data (N=281) | ESKD (N=153) | not progressed to ESKD (N=128) | P*  |
|--------------------------|---------------------------------------------|--------------|--------------------------------|-----|
| Age (yr)                 | 37 (28–47)                                 | 36 (28–47)   | 38 (28–48)                     | 0.340|
| Sex (male, %)            | 136 (48.4)                                 | 82 (53.6)    | 54 (42.2)                      | 0.057|
| Hypertension (%)         | 176 (62.6)                                 | 109 (71.2)   | 67 (52.3)                      | 0.001|
| Plasma Hb (g/L)          | 132 (115–145)                              | 126 (108–141) | 136 (122–149)                  | <0.001|
| Serum Cr (µmol/L)        | 144.92 (88.40–159.12)                      | 150.28 (114.92–240.89) | 88.40 (74.48–106.08)          | <0.001|
| eGFR (mL/min/1.73 m²)    | 58.8 (38.9–81.9)                           | 41.6 (23.7–60.8) | 77.45 (60.85–92.58)          | <0.001|
| Serum albumin (g/L)      | 39 (36–43)                                 | 38 (34–40)   | 42 (39–44)                     | <0.001|
| Serum IgA (g/L)          | 3.16 (2.50–4.10)                           | 3.15 (2.49–4.10) | 3.20 (2.52–4.10)          | 0.688|
| Gross hematuria (%)      | 62 (22.1)                                  | 27 (17.6)    | 35 (27.3)                      | 0.051|
| Microscopic hematuria (%)| 253 (90.0)                                 | 137 (89.5)   | 116 (90.6)                     | 0.763|
| 24-hr urinary protein (g/day) | 1.6 (0.8–2.9)     | 2.3 (1.5–4.0) | 0.9 (0.5–1.5)                  | <0.001|

Values are presented as median (interquartile range) or number (%). *ESKD vs. not progressed to ESKD

Abbreviations: IgAN, IgA nephropathy; ESKD, end-stage kidney disease; Cr, creatinine; eGFR, estimated glomerular filtration rate.

In Table 1. There were significant differences in blood pressure, plasma Hb level, serum Cr level, eGFR, serum albumin level, and 24-hour urinary protein between ESKD patients and those who did not progress to ESKD.

To calculate the HLA allele frequency in the controls, we used data from 613 healthy Korean hematopoietic stem cell donors collected between January 2006 and July 2014 and analyzed in previous study [16].

HLA-DRB1 and -DQB1 genotyping

HLA-DRB1 and -DQB1 typing of 399 IgAN patients were performed using PCR-SSP or SBT, according to the reported methods and primer design [19, 20]. The PCR conditions were as follows: initial denaturation at 94°C for 5 minutes; 35 cycles of denaturation at 94°C for 30 seconds, annealing at 62°C for 30 seconds, and elongation at 72°C for 60 seconds; and a final elongation step at 72°C for 7 minutes. For SBT, each ExoSAP-IT (Affymetrix, Santa Clara, CA, USA) PCR product was sequenced using the primers used for PCR, deionized water, and BigDye Terminator Ready Reaction Mix (Life Technologies, Foster City, CA, USA); electropherograms were analyzed using Chromas Lite 2.1.1 (Technelysium, South Brisbane, Australia).

Statistical analysis

All data were analyzed using SPSS software (version 26.0, IBM Corp., Armonk, NY, USA). Continuous variables (age, plasma Hb, serum Cr, eGFR, serum albumin, serum IgA, 24-hours urinary protein) are presented as medians and interquartile ranges, and categorical variables (sex, hypertension, gross hematuria, microscopic hematuria) are shown as frequencies and percentages. Clinical characteristics, laboratory data, and HLA allele frequencies were compared between the groups using the Mann-Whitney test, chi-square test or Fisher’s exact test, as appropri...
### Table 2. HLA-DRB1 and -DQB1 allele frequencies in IgAN patients and controls

| Allele   | Subgroup | IgAN (N = 399 × 2) | Control (N = 613 × 2) | P     | Pc     | OR    | 95% CI       |
|----------|----------|--------------------|------------------------|-------|--------|-------|--------------|
|          |          | N  | %    | N  | %    |       |             |
| DRB1*01  |          | 42 | 5.26 | 79 | 6.44 | 0.274 |             |
| DRB1*03  |          | 15 | 1.88 | 26 | 2.12 | 0.707 |             |
| DRB1*04  |          | 242| 30.33| 259| 21.13| <0.001| 1.63| 1.33–1.99  |
| DRB1*04:01 |       | 4  | 0.50 | 12 | 0.98 |       |             |
| DRB1*04:03 |       | 30 | 3.76 | 38 | 3.10 |       |             |
| DRB1*04:04 |       | 13 | 1.63 | 24 | 1.96 |       |             |
| DRB1*04:05 |       | 119| 14.91| 111| 9.05 | <0.001| 1.76| 1.34–2.32  |
| DRB1*04:06 |       | 56 | 7.02 | 51 | 4.16 | 0.005 | 1.150| 1.74| 1.18–2.57 |
| DRB1*04:07 |       | 1  | 0.13 | 6  | 0.49 |       |             |
| DRB1*04:08 |       | 1  | 0.13 | 0  | 0.00 |       |             |
| DRB1*04:10 |      | 18 | 2.26 | 17 | 1.39 |       |             |
| DRB1*07  |          | 26 | 3.26 | 85 | 6.93 | <0.001| <0.001| 0.45| 0.29–0.71 |
| DRB1*08  |          | 83 | 10.40| 105| 8.56 | 0.164 |             |
| DRB1*09  |          | 57 | 7.14 | 116| 9.46 | 0.068 |             |
| DRB1*10  |          | 23 | 2.88 | 24 | 1.96 | 0.177 |             |
| DRB1*11  |          | 36 | 4.51 | 48 | 3.92 | 0.511 |             |
| DRB1*12  |          | 54 | 6.77 | 93 | 7.59 | 0.488 |             |
| DRB1*13  |          | 84 | 10.53| 135| 11.01| 0.731 |             |
| DRB1*14  |          | 83 | 10.40| 99 | 8.08 | 0.074 |             |
| DRB1*15  |          | 46 | 5.76 | 147| 11.99| <0.001| <0.001| 0.45| 0.32–0.63 |
| DRB1*15:01 |       | 34 | 4.26 | 101| 8.24 | <0.001| <0.001| 0.50| 0.33–0.74 |
| DRB1*15:02 |       | 12 | 1.50 | 46 | 3.75 | 0.003 | 0.390 | 0.21–0.74 |
| DRB1*16  |          | 7 | 0.88 | 10 | 0.82 | 1.000 |             |
| DQB1*02  |          | 40 | 5.01 | 108| 8.81 | 0.001 | 0.007 | 0.55| 0.38–0.79 |
| DQB1*02:01 |       | 14 | 1.88 | 26 | 2.12 |       |             |
| DQB1*02:02 |       | 25 | 3.13 | 82 | 6.69 | <0.001| <0.001| 0.45| 0.29–0.71 |
| DQB1*04  |          | 143| 17.92| 156| 12.72| 0.001 | 0.007 | 1.50| 1.17–1.92 |
| DQB1*04:01 |      | 103| 12.91| 108| 8.81 | 0.003 | 0.048 | 1.53| 1.15–2.04 |
| DQB1*04:02 |       | 40 | 5.01 | 48 | 3.92 |       |             |
| DQB1*05  |          | 139| 17.42| 191| 15.58| 0.274 |             |
| DQB1*06  |          | 189| 23.68| 344| 28.06| 0.029 | 0.203 | 0.80| 0.65–0.98 |
| DQB1*06:01 |       | 74 | 9.27 | 115| 9.38 |       |             |
| DQB1*06:02 |       | 30 | 3.76 | 95 | 7.75 | <0.001| <0.001| 0.47| 0.31–0.71 |
| DQB1*06:03 |       | 6  | 0.75 | 20 | 1.63 |       |             |
| DQB1*06:04 |       | 58 | 7.27 | 62 | 5.06 | 0.040 | 0.640 | 1.47| 1.02–2.13 |
| DQB1*06:09 |       | 21 | 2.63 | 52 | 4.24 |       |             |
| DQ7 (DQB1*03:01) | | 108 | 13.53 | 172 | 14.03 | 0.752 |             |
| DQ8 (DQB1*03:02) | | 111 | 13.91 | 118 | 9.62 | 0.003 | 0.021 | 1.52 | 1.15–2.00 |
| DQ9 (DQB1*03:03) | | 68 | 8.52 | 137| 11.17| 0.553 |             |

Abbreviations: IgAN, IgA nephropathy; Pc, corrected P-value; OR, odds ratio; CI, confidence interval.
ate. P-values were adjusted using the Bonferroni correction, i.e., by multiplying the P-value by the number of comparisons, considering the total number of alleles in patients and controls that could be obtained at each resolution (corrected P [Pc] for two-digit resolution: 13 for HLA-DRB1 and 7 for HLA-DQB1; Pc for four-digit resolution: 30 for HLA-DRB1 and 16 for HLA-DQB1). Odds ratio (OR) was calculated along with 95% confidence interval (CI). Univariate and multivariate Cox regression analysis were used to analyze risk factors associated with ESKD. Pc <0.05 in the allele frequency analysis and P<0.05 in the survival analysis were considered statistically significant.

RESULTS

HLA-DRB1 allele frequencies in IgAN patients

Table 3. Comparison of HLA-DRB1 and -DQB1 allele frequencies between the ESKD and non-ESKD groups*

| Allele  | ESKD (N=268×2) | Non-ESKD (N=57×2) | P  | Pc  | OR   | 95% CI     |
|---------|----------------|-------------------|-----|-----|------|------------|
|         | N  | %  | N  | %  |      |            |
| DRB1    |     |     |     |     |      |            |
| DRB1*01 | 24 | 4.48 | 4  | 3.51 | 0.802 |            |
| DRB1*03 | 9  | 1.68 | 5  | 4.39 | 0.081 |            |
| DRB1*04 | 171 | 31.90 | 24 | 21.05 | 0.022 | 0.286 1.76 |
| DRB1*07 | 19 | 3.54 | 2  | 1.75 | 0.557 |            |
| DRB1*08 | 55 | 10.26 | 12 | 10.53 | 0.933 |            |
| DRB1*09 | 41 | 7.65 | 5  | 4.39 | 0.217 |            |
| DRB1*10 | 18 | 3.36 | 3  | 2.63 | 1.000 |            |
| DRB1*11 | 23 | 4.29 | 7  | 6.14 | 0.393 |            |
| DRB1*12 | 35 | 6.53 | 13 | 11.40 | 0.071 |            |
| DRB1*13 | 58 | 10.82 | 14 | 12.28 | 0.652 |            |
| DRB1*14 | 52 | 9.70 | 18 | 15.79 | 0.057 |            |
| DRB1*15 | 27 | 5.04 | 6  | 5.26 | 0.921 |            |
| DRB1*16 | 4  | 0.75 | 1  | 0.88 | 1.000 |            |
| DQB1    |     |     |     |     |      |            |
| DQB1*02 | 26 | 4.85 | 7  | 6.14 | 0.569 |            |
| DQB1*04 | 103 | 19.22 | 13 | 11.40 | 0.048 | 0.336 1.85 |
| DQB1*05 | 86 | 16.04 | 23 | 20.18 | 0.284 |            |
| DQB1*05:03 | 24 | 4.48 | 14 | 12.28 | 0.001 | 0.016 0.34 |
| DQB1*06 | 128 | 23.88 | 29 | 25.44 | 0.724 |            |
| DQ7 (DQB1*03:01) | 68 | 12.69 | 21 | 18.42 | 0.106 |            |
| DQ8 (DQB1*03:02) | 74 | 13.81 | 14 | 12.28 | 0.666 |            |
| DQ9 (DQB1*03:03) | 51 | 9.51 | 7  | 6.14 | 0.251 |            |

*Not progressed to ESKD even after 10 years from diagnosis
Abbreviations: ESKD, end-stage kidney disease; Pc, corrected P-value; OR, odds ratio; CI, confidence interval.
HLA-DQB1 allele frequencies in IgAN patients
The HLA-DQB1 allele frequencies for the 399 IgAN patients and controls are shown in Table 2. The allele frequencies of HLA-DQB1*04 and -DQB (DQB1*03:02) were significantly higher in the IgAN patients than in the controls. The allele frequency of HLA-DQB1*02 was significantly lower in the patients than in the controls. In the four-digit resolution analysis, the frequency of HLA-DQB1*04:01 was significantly higher in the IgAN patients than in the controls. In the IgAN patients, the allele frequency of HLA-DQB1*02:02 was significantly lower than that in the controls. Among the HLA-DQB1*06 allele subgroups, the HLA-DQB1*06:02 allele showed a significantly lower frequency in the IgAN patients than in the controls. Conversely, the HLA-DQB1*06:04 allele frequency was slightly, albeit not significantly, higher in the IgAN patients than in the controls.

Comparison of HLA-DRB1 and -DQB1 allele frequencies between ESKD and non-ESKD groups
HLA-DRB1 and -DQB1 allele frequencies were compared between 268 IgAN patients that progressed to ESKD (ESKD group) and 57 IgAN patients with preserved kidney function even after 10 years from the time of diagnosis (non-ESKD group) (Table 3). In the ESKD group, the allele frequencies of HLA-DRB1*04 and -DQB1*04 were slightly, albeit not significantly, higher than those in the non-ESKD group. In the four-digit resolution analysis of HLA-DQB1, the allele frequency of HLA-DQB1*05:03 was significantly lower in the ESKD group than in the non-ESKD group.

Kidney survival analysis and prognostic factors for ESKD
Kidney survival analysis results are shown in Table 4. The duration of disease progression to ESKD from the time of diagnosis was 57 (25–101) months. In univariate Cox proportional hazard models, hypertension, plasma Hb, serum Cr, eGFR, serum albumin, and 24-hour urinary protein >1 g/day were associated with an increased risk of ESKD. Multivariate Cox regression analysis with the variables that were found to be significant in the univariate Cox regression analysis showed that serum Cr levels (P<0.001, hazard ratio (HR)=1.25, 95% CI=1.11–1.42), eGFR (P<0.001, HR=0.98, 95% CI=0.97–0.99), and 24-hour urinary protein >1 g/day (P<0.001, HR=2.88, 95% CI=1.83–4.55) were independent risk factors for ESKD progression. However, HLA alleles were not significant risk factors for ESKD progression.

DISCUSSION
Since 1978, when it was reported that a brother who donated a
kidney to his HLA-identical sibling with IgAN was observed to have occult IgAN in a biopsy, there have been many reports on associations between IgAN and HLA alleles [7-10, 14, 22-32] (Table 5). Studies on Japanese and French patients in the 1980s and 1990s reported that the HLA-DR4 allele frequency was significantly higher in IgAN patients [7-9, 23, 25].

We found associations between IgAN and HLA-DRB1*04:05, -DRB1*07:01, -DRB1*15:01, -DQB1*02:02, and -DQB1*06:02 in Korean patients. In China, the HLA-DRB1*04:05 and -DRB1*04:03 allele frequencies were significantly higher in IgAN patients than in controls. HLA-DRB1*04:05 is associated with various autoimmune diseases, including rheumatoid arthritis and type 1 diabetes mellitus (T1DM) [33]. In particular, an association of HLA-DRB1*04:05 with a poor response to immunosuppressive therapy has been reported in Korean patients with aplastic anemia [34].

HLA-DQB1*04 is associated with IgAN in Japanese and Korean populations [27, 31]. However, the association of HLA-DQB1*04:01 with IgAN was newly identified in this study. HLA-DRB1*04:05 and -DQB1*04:01 exhibited a strong linkage disequilibrium (LD) (relative LD, 0.99) in a Korean population [16]. Therefore, the HLA-DRB1*04:05-DQB1*04:01 haplotype should be a strong susceptibility factor for IgAN in the Korean population, as has been reported for a Japanese population [27]. In addition, the HLA-DRB1*04:05-DQB1*04:01 haplotype is strongly associated with fulminant T1DM in Korean patients [35]. The HLA-DQB1*03:02 allele was newly revealed as a susceptibility factor for IgAN in this study.

Regarding protective alleles, HLA-DRB1*07:01 reportedly has a lower frequency in Chinese IgAN patients [28, 30], which is in line with our results. HLA-DQB1*02:01 is reported to be a protective allele in British and Chinese IgAN patients [10, 30, 32]. However, in this study, HLA-DQB1*02:02 was significantly lower in IgAN patients than in controls. The HLA-DRB1*07:01 and -DQB1*02:02 alleles also exhibit strong LD (relative LD, 0.98) in the Korean population [16]. Therefore, HLA-DRB1*07:01 is suspected to play a major role as a protective factor, whereas HLA-DQB1*02:01 or -DQB1*02:02 might be observed due to LD to HLA-DQB1*07:01, depending on ethnicity. HLA-DRB1*15:01 and -DQB1*06:02, which also show strong LD in the Korean population, showed lower frequencies in IgAN patients than in controls in this study. HLA-DQB1*06:02 has been reported to be protective in Finnish IgAN patients [10]. The HLA-DRB1*15:01-DQB1*06:02 haplotype reportedly protects against T1DM [36].

### Table 5. Associations of HLA with IgAN in various ethnic groups

| Ethnicity   | Susceptible HLA allele | Protective HLA allele | Patients (N) | Reference       |
|-------------|------------------------|-----------------------|--------------|-----------------|
| Caucasian   |                        |                       |              |                 |
| French      | DR4                    |                       | 45           | Fauchet, et al. 1980 [7] |
| British     | DRB*04                 |                       | 36           | Li, et al. 1991 [24] |
| French      | DQB1*02:01             |                       | 58           | Raguénès, et al. 1995 [23] |
| British     | DQB1*06:02             |                       | 105          | Fennessy, et al. 1996 [10] |
| Finnish     |                       |                       | 48           |                 |
| Asian       |                        |                       |              |                 |
| Japanese    | DR4                    |                       | 24/42        | Kashiwabara, et al. 1980 [8], 1982 [25] |
|             | B35, DR4, DQ4          |                       | 80/130/50    | Hiki, et al. 1982 [9], 1990 [26], 1991 [27] |
| Chinese     | DRB1*14:05             | DRB1*07:01            | 139          | Cao, et al. 2008 [28] |
|             | DRB1*04:05, *04:03     | DQB1*03:01            | 935          | Jiyun, et al. 2012 [29] |
|             | DQB1*06:01             |                       | 217          | Wang, et al. 2016 [30] |
|             | DRB1*0901-DQB1*06:01   | DRB1*07:01-DQB1*02:01 |              |                 |
| Korean      | B55, DQB1*04           |                       | 69           | Shin, et al. 1998 [31] |
|             | DQB1*03                |                       | 139          | Kim, et al. 2000 [14] |
|             | DRB1*04:05, DQB1*03:02, *04:01 | DRB1*07:01, *15:01, DQB1*02:02, *06:02 | 399          | This study |
| Caucasian+Asian | DQA1*01:01, DQB1*03:01 | DQA*01:02, DQB1*02:01 | 2,747        | Kiryluk, et al. 2014* [32] |

*HLA alleles investigated by imputation from GWAS data.
Abbreviations: HLA, human leukocyte antigen; IgAN, IgA nephropathy; GWAS, genome-wide association study.
In Korean patients with aplastic anemia, HLA-DRB1*15:01 and -DQB1*06:02 have been associated with a good response to immunosuppressive therapy, which suggests a possible role of HLA-DRB1*15:01-DQB1*06:02 in immune-related diseases [34].

The kidney survival rate of IgAN patients varies across studies, ranging from 57% to 91%. Hypertension, decreased eGFR, and increased urinary protein at the time of diagnosis are well-known risk factors for IgAN progression to ESKD [37]. In addition, lower plasma Hb concentrations and pathological results with higher Oxford M or T scores have been reported as risk factors for progression to ESKD [38]. Sex and age at diagnosis show different results in terms of posing risk of IgAN progression to ESKD among studies [37-39]. In our study, kidney survival was analyzed based on the presence of HLA-DRB1*04, -DQB1*04, and -DQB1*05:03 alleles along with patient clinical and laboratory data; however, in the univariate analysis, none of these HLA alleles appeared as a risk factor for IgAN progression to ESKD. In the multivariate analysis, the levels of serum Cr, eGFR, and 24-hour urinary protein >1 g/day were independent risk factors for IgAN progression to ESKD. Neither age nor sex was found to be a risk factor for IgAN progression to ESKD.

Regarding the association of HLA alleles with IgAN progression to ESKD, the allele frequencies of HLA-DRB1*04 and -DQB1*04 were slightly, albeit not significantly, higher in the ESKD group than in the non-ESKD group. In the four-digit resolution analysis, the frequency of HLA-DQB1*05:03 was significantly lower in the ESKD group than in the non-ESKD group. However, the association of HLA-DQB1*05:03 with IgAN progression to ESKD was not significant in Cox regression analysis, possibly due to the small number of patients and limited data available at diagnosis. Cao, et al. [28] reported that HLA-DRB1*03:01 is associated with decreased eGFR. In GWASs, SNVs related to the HLA region have been associated with IgAN progression to ESKD [32, 40]. The association of HLA alleles with IgAN progression to ESKD should be further studied in a larger patient cohort.

The limitations of this study are the relatively small number of IgAN patients with available clinical and laboratory data at diagnosis to analyze the risk factors for ESKD and the lack of pathological results (because the grading systems used for pathological diagnosis differed from patient to patient, depending on the time of diagnosis). However, our study showed that the HLA-DRB1 and HLA-DQB1 alleles are strongly associated with susceptibility to IgAN. While associations of HLA-DRB1*04:05, -DRB1*07:01, and -DQB1*06:02 alleles with IgAN have been previously reported in Chinese and Finnish patients, the associations of the HLA-DRB1*15:01, -DQB1*02:02, -DQB1*03:02, and -DQB1*04:01 alleles with IgAN in Korean patients were newly revealed in this study. Further studies on the association of HLA alleles with disease progression in a larger patient cohort and various ethnic groups are needed.
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