Human Leukocyte Antigen Class II Haplotypes Affect Clinical Characteristics and Progression of Type 1 Autoimmune Hepatitis in Japan

Takeji Umemura1*, Yoshihiko Katsuyama2, Kaname Yoshizawa1,4, Takefumi Kimura1, Satoru Joshita1, Michiharu Komatsu1, Akihiro Matsumoto1, Eiji Tanaka1, Masao Ota3*

1 Department of Medicine, Division of Hepatology and Gastroenterology, Shinshu University School of Medicine, Matsumoto, Japan, 2 Department of Pharmacy, Shinshu University Hospital, Matsumoto, Japan, 3 Department of Gastroenterology, Shinshu University School of Medicine, Matsumoto, Japan, 4 Department of Legal Medicine, Shinshu University School of Medicine, Matsumoto, Japan

Abstract

Although we earlier demonstrated that the human leukocyte antigen (HLA) DRB1*04:05 allele was associated with susceptibility to autoimmune hepatitis (AIH) in Japan, the precise relationship of HLA haplotype and the role of amino acid alignment with disease susceptibility and progression has not been fully clarified. We reinvestigated HLA class I A, B, and C and HLA class II DRB1, DQB1, and DPB1 alleles and haplotypes in a larger new cohort of 156 Japanese patients with type 1 AIH and compared them with the published data of 210 healthy subjects. The DRB1*04:05-DQB1*04:01 haplotype was significantly associated with AIH susceptibility (30% vs. 11%, P = 1.2×10−10; odds ratio [OR] = 3.51) and correlated with elevated serum IgG (3042 vs. 2606 mg/dL, P = 0.041) and anti-smooth muscle antigen positivity (77% vs. 34%, P = 0.000006). No associations with HLA-DPB1 alleles were found. The HLA A*24:02 and C*01:02 alleles were associated with disease susceptibility (corrected P = 0.0053 and 0.036, respectively), but this likely constitutes of a long ranged haplotype including DRB1*04:05-DQB1*04:01 haplotype. Conversely, the DRB1*15:01-DQB1*06:02 haplotype was associated with protection from both disease onset (5% vs. 13%, P = 0.000057; OR = 0.38) and the development of hepatocellular carcinoma (25% vs. 5%, P = 0.017; OR = 6.81). The frequency of the DRB1*08:03-DQB1*06:01 haplotype was significantly higher in patients who developed hepatic failure (22% vs. 6%, P = 0.034; OR = 4.38). In conclusion, this study established the role of HLA haplotypes in determining AIH susceptibility and progression in the Japanese population. Additional sequencing of the entire HLA region is required to more precisely identify the genetic components of AIH.

Introduction

Autoimmune hepatitis (AIH) is characterized by chronic inflammation of the liver, elevated transaminase levels, hyper-gammaglobulinemia, serum autoantibodies, histologic evidence of interface hepatitis, and a favorable response to immunosuppressive treatment.[1–3] Although this disease is believed to result from a combination of genetic and environmental factors, its exact etiology remains unclear. In previous studies, the HLA DRB1*04:05-DQB1*04:01 haplotype in Japanese[4,5] and the DRB1*03:01 and/or DRB1*04:01 alleles in Caucasians[6–8] were identified as independent determinants of susceptibility to type 1 AIH. Czaja et al.[8] reported that the HLA DRB1*03:01 allele was associated with a poor treatment response and that DRB1*04:01 was related to a lower frequency of hepatic death or transplantation in Caucasians, but associations between HLA alleles and haplotypes and clinical manifestations were not investigated. Recent long-term follow-up studies have also shown that hepatic failure and hepatocellular carcinoma (HCC) complicating AIH are not as rare as earlier believed;[9,10] however, the genetic predisposition to advanced liver diseases has not been addressed. Strettell et al.[11] found that the HLA-Cw*07:01 allele contributed to disease susceptibility in England, although no supporting data has been reported to date. It was recently proposed that associations with specific HLA-C and HLA-B alleles in autoimmune diseases might result from combinations of these ligands and their corresponding killer cell immunoglobulin-like receptors (KIR) that were expressed by natural killer (NK) cells and a subset of T-lymphocytes.[12,13] Moreover, the importance of HLA-DP alleles was highlighted in genome-wide association studies (GWAS) and comprehensive HLA analyses of patients with autoimmune diseases, which demonstrated HLA-DP gene variations having a strong association with systemic lupus erythematosus, antineutrophil cytoplasmic antibody-associated vasculitis, and granulomatosis with polyangiitis.[14–16] Based on the above reports, we searched for associations of particular HLA
alleles, including HLA class I (A, B, and C) and HLA class II (DRB1, DQB1, and DPB1), and haplotypes with susceptibility, clinical manifestations, and outcome of patients with AIH.

**Materials and Methods**

**Ethics statement**

This study was approved by the ethical committee of Shinshu University School of Medicine, Matsumoto, Japan, and written informed consent was obtained from all subjects. The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Subjects**

Between January 1979 and March 2013, 156 patients of Japanese descent with type 1 AIH were enrolled in this study. Their clinical and laboratory data at the time of diagnosis are shown in Table 1. The median follow-up period was 118 months (range: 6–403 months). The HLA class I and II allelic genotypes of 201 healthy subjects that were obtained in a previous study [17] were adopted as controls. Normal subjects were unrelated healthy blood donors living in the central region of Japan.

All cases of AIH had been diagnosed according to the scoring system from the International Autoimmune Hepatitis Group.

All subjects were negative for the hepatitis B surface antigen, antibody to hepatitis B core antigen, and antibody to hepatitis C in serum samples and exhibited no evidence of other liver diseases. Alanine aminotransferase (ALT), aspartate aminotransfase (AST), and other relevant biochemical tests were performed using standard methods.

Anti-nuclear antibody (ANA) and anti-smooth muscle antibody (SMA) were determined as reported previously.

Liver cirrhosis was diagnosed by histological examination and/or characteristic clinical signs of advanced liver disease.

HCC was diagnosed by histological examination and/or imaging studies, and hepatic failure was diagnosed by the presence of esophageal varices, ascites, and hepatic encephalopathy. During the follow-up, cirrhosis, hepatic failure, and HCC developed in 16% (25/156), 6% (9/156), and 4% (6/156) of patients.

**Table 1.** Demographic and Clinical Characteristics of 156 Patients with Type 1 AIH.

| Clinical feature   | 62 (57–66) | 118 (6–403) | 138 (89) | 16 (10–23) | 3.7 (1.7–4.6) | 421 (30–5586) | 494 (21–7436) | 1.9 (0.4–3.02) | 2770 (826–7248) | 150 (96) | 66/112 (59) |
|--------------------|------------|-------------|----------|-----------|-------------|--------------|-------------|--------------|---------------|---------|------------|
| Age at diagnosis (years) |            |             |          |           |             |              |             |              |               |         |            |
| Observation period (months) |           |             |          |           |             |              |             |              |               |         |            |
| Female, n (%) |             |             |          |           |             |              |             |              |               |         |            |
| AIH score |             |             |          |           |             |              |             |              |               |         |            |
| Albumin (4.2–5.1 g/dL) | 138 (89)   | 3.7 (1.7–4.6) | 421 (30–5586) | 494 (21–7436) | 1.9 (0.4–3.02) | 2770 (826–7248) | 150 (96) | 66/112 (59) |
| ALT (7–45 IU/L) | 421 (30–5586) | 494 (21–7436) | 1.9 (0.4–3.02) | 2770 (826–7248) | 150 (96) | 66/112 (59) |

Values are expressed as median (range) unless otherwise noted. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ANA, anti-nuclear antibody; SMA, anti-smooth muscle antibody.

doi:10.1371/journal.pone.0100565.t001

**Results**

**Table 2.** Associations of HLA Class I and II Typing

| Allele                      | Frequency | P-value | OR (95% CI) |
|----------------------------|-----------|---------|-------------|
| DRB1*04:05                  | 4.0       | 3.7     | 1.84 (1.32–2.55) |
| DRB1*04:05                  | 3.7       | 6.8     | 1.81 (1.24–2.65) |
| DQB1*04:01                  | 10.0      | 2.9     | 0.38 (0.22–0.67) |
| DQB1*04:01                  | 2.9       | 3.8     | 0.22 (0.05–1.0) |

**HLA Class I and II Typing**

Genomic DNA from patients and healthy individuals was isolated by phenolic extraction of sodium dodecyl sulfate-lysed and protease K-treated cells, as described previously.

HLA typing was carried out using a Luminex multi-analyzer profiling system with a LAB type SSO One Lambda typing kit (One Lambda, Inc. Canoga Park, CA). HLA genotypes were determined by sequence-based typing, as earlier described.

**Statistical Analysis**

Phenotype frequencies were estimated by direct counting for each HLA allele. The significance of an association was evaluated using chi-square analysis or Fisher’s exact test. P-value was subjected to Bonferroni correction by multiplication by the number of different alleles observed in each locus (Pc).

The Mann-Whitney U test was used to analyze continuous variables where appropriate. A P-value of less than 0.05 was considered to be statistically significant. Association strength was estimated by calculating the odds ratio (OR) and 95% confidence interval (CI).

**Associations of HLA Alleles**

HLA class I (A, B, and C) and class II (DRB1, DQB1, DPB1) were genotyped in 156 patients with AIH. Among the HLA class I alleles, the frequency of A*24:02 and C*01:02 were significantly increased in patients with AIH compared with healthy subjects (35% vs. 22%, P = 0.0053; OR = 1.84, 95% CI = 1.32–2.55, and 23% vs. 14%, P = 0.036; OR = 1.81, 95% CI = 1.24–2.65, respectively) (Table 2).

On the other hand, the frequency of the HLA-C2 allele was significantly reduced in AIH as compared with healthy controls (6% vs. 13%, P = 0.0054; OR = 0.22, 95% CI = 0.14–0.38).

Patients who were homozygous for the HLA-A*02:01 allele were significantly associated with AIH compared with healthy subjects (30% vs. 11%, P = 4.0 × 10–5; OR = 3.47, 95% CI = 2.34–5.14, and 30% vs. 11%, P = 3.7 × 10–5; OR = 3.42, 95% CI = 2.31–5.07, respectively) (Table 2).

Conversely, DRB1*15:01 (6% vs. 13%; P = 0.068) and DQB1*06:02 (5% vs. 13%; P = 0.009; OR = 0.38, 95% CI = 0.22–0.67) conferred a reduced risk of AIH occurrence. However, reevaluation of these alleles after excluding DRB1*04:05 and DQB1*04:01 carriers from the analysis resulted in no significant differences in the frequencies of DRB1*15:01 (9% vs. 15%; P > 0.1) or DQB1*06:02 (9% vs. 15%; P > 0.1). The DQB1*05:01 allele was found at an increased frequency in patients with AIH, which suggested an effect on susceptibility (46% vs. 38%), but this difference was not significant after correction for multiple testing.

**Associations of HLA Haplotypes**

The frequency of the DRB1*04:05-DQB1*04:01 haplotype in patients with AIH was 30% and significantly higher than the 11% observed in healthy subjects (P = 1.2 × 10–10; OR = 3.31, 95% CI = 2.36–5.21) (Table 3).
The DPB1*05:01 haplotype was also significantly correlated with disease (22% vs. 7%, \( P = 4.6 \times 10^{-10} \); OR = 3.79, 95% CI = 2.38–6.06). The A*24:02 and C*01:02 alleles, which were implicated in AIH susceptibility, were included in the fourth most frequent haplotype \( (A*24:02-C*01:02-B*39:01-DRB1*04:05-DQB1*04:01) \) in our cohort. Whereas the DRB1*04:05-DQB1*04:01 haplotype showed the strongest association with disease onset, protective effects were observed for DRB1*15:01-DQB1*06:02 (5% vs. 13%, \( P = 0.00057; \) OR = 0.38, 95% CI = 0.22–0.67).

### Associations between HLA and Clinical Findings

According to clinical and laboratory data, median serum IgG was significantly higher in patients with the DRB1*04:05-DQB1*04:01 haplotype than in those without (3042 vs. 2606 mg/dL, \( P = 0.041 \)). This was also the case for SMA positivity (50 of 65 [77%] vs. 16 of 47 [34%], \( P = 0.000006; \) OR = 6.46). There were no significant differences in the serum levels of albumin, ALT, AST, or bilirubin, nor was there in the frequency of elevated ANA, between patients with or without DRB1*04:05.

We next stratified AIH patients according to the development of HCC and hepatic failure. The HLA-DRB1*15:01 and DQB1*06:02 alleles (25% vs. 6%, \( P = 0.038; \) OR = 5.55, 95% CI = 1.37–22.40, and 25% vs. 5%, \( P = 0.017; \) OR = 6.81, 95% CI = 1.66–27.96, respectively) and the DRB1*15:01-DQB1*06:02 haplotype (25% vs. 5%, \( P = 0.017; \) OR = 6.81, 95% CI = 1.66–27.96) were all found to be significantly associated with the development of HCC. When AIH patients with hepatic failure were compared with those without, significant genetic associations of the DRB1*08:03 allele and DRB1*08:03-DQB1*06:01 haplotype (22% vs. 6%, \( P = 0.034; \) OR = 4.38, 95% CI = 1.31–14.68) were seen. No other haplotypes were associated with cirrhosis.

### Amino Acid Residues in HLA-DRB1, DQB1, and DPB1

The amino acid sequences encoded by the second exon of HLA-DRB1, DQB1, and DPB1 were determined for each subject. As shown in Table 4, the prevalence of valine at position 11 (\( P = 1.4 \times 10^{-5}; \) OR = 2.19), histidine at position 13 (\( P = 1.5 \times 10^{-7}; \) OR = 2.38), and serine at position 57 (\( P = 2.5 \times 10^{-6}; \) OR = 2.53) in DRB1 was significantly higher in patients with AIH compared with healthy subjects. The amino acid residue at position 13 affects the binding of antigen side chains associated with the fourth and sixth pockets of the expressed DR molecule, while the amino acid residues at positions 11 and 57 influence the binding of antigen side chains associated with the sixth and ninth binding pockets, respectively (Figure 1). The amino acids at positions 11, 13, and 57 in HLA DRB1 consisted of 12 haplotypes (Table 4). Valine-histidine-serine residues conferred a significantly elevated risk of AIH (\( P = 1.7 \times 10^{-11}; \) OR = 3.52), whereas serine-serine-aspartic acid, leucine-phenylalanine-aspartic acid, and serine-serine-alanine apparently imparted protection against the disease (\( P = 0.035; \) OR = 0.36, 95% CI = 0.17–0.76).
and DQB1*04:01
general, HLA-DP elucidate exactly which allele is associated disease susceptibility. In value for both alleles is 100% in Japan, we cannot presently
bility to AIH. However, because the relative linkage disequilibrium
disposition, either allele may presumably be associated with suscepti-
to the fact that HLA-DP cell surface expression levels tend to be
accumulating data
to the central location of these residues in the peptide-binding groove of
HLA-DRB1 in AIH etiology. Positions 11 and 13 are located in
the DRβ-polypeptide to be a critical determinant of disease
susceptibility in Japan,[28] in contrast to a lysine residue at
b-polypeptide in patients of European
descent.[6,7] In the present study, the incidence of valine-11
b-amino acids. Therefore, the frequency of glutamic acid at position 69 in our patients with AIH
and controls was 35% and 39%, respectively. Hence, amino acid
frequency of glutamic acid at position 69 has been shown to contribute to graft-versus-host disease in otherwise
identical HLA sibling bone marrow transplantation[29] and factor
in the susceptibility to Beryllium disease.[24,26] However, the
frequency of glutamic acid at position 69 in patients with AIH
and controls was 35% and 39%, respectively. Hence, amino acid
residues in DPB1 were not implicated in disease susceptibility.

Discussion

The present study of a larger new cohort of Japanese patients
with AIH confirmed that the HLA-DRB1*04:05 (Pc = 3.9 × 10^{-6})
and DQB1*04:01 (Pc = 3.7 × 10^{-5}) alleles and the DRB1*04:05-
DQB1*04:01 haplotype (Pc = 2.3 × 10^{-10}) are the principal suscepti-
bility alleles for type 1 AIH. As DRB1*04:05 is known to be in
linkage disequilibrium with DQB1*04:01 in the Japanese population,
either allele may presumably be associated with susceptibility
to AIH. However, because the relative linkage disequilibrium
value for both alleles is 100% in Japan, we cannot presently
ecluciate exactly which allele is associated disease susceptibility. In
general, HLA-DP genes have been somewhat neglected in terms of
their impact on human disease relative to HLA-DR and -DQ, partly
because HLA-DPA1 and -DPB1 are less polymorphic and also due
to the fact that HLA-DP cell surface expression levels tend to be
lower than those of HLA-DR and -DQ. Since accumulating data
had indicated that HLA-DP alleles were associated with various
autoimmune diseases,[16,24–27] we investigated whether they
influenced susceptibility to AIH but found no significant associ-
ations.

Prior studies have proposed a histidine residue at position 13 of
the DRβ-polypeptide to be a critical determinant of disease
susceptibility in Japan,[28] in contrast to a lysine residue at
position 71 of the DRβ-polypeptide in patients of European
descent.[6,7] In the present study, the incidence of valine-11
(OR = 2.19), histidine-13 (OR = 2.38), and serine-57 (OR = 2.53)
encoded by DRB1*04:05 was significantly higher in AIH patients.
Moreover, a specific haplotype determined by the amino acids
valine-histidine-serine at positions 11, 13, and 57 in DRB1 was
strongly associated with AIH. This finding is punctuated by the
central location of these residues in the peptide-binding groove of
HLA-DRB1 in AIH etiology. Positions 11 and 13 are located in
the β-sheet floor with their side chains oriented toward the
peptide-binding groove. Meanwhile, the amino acid residue at
position 57 influences the binding of antigen side chains associated
with the ninth pocket of the expressed DR molecule, which might
factor predominantly in susceptibility to AIH in the Japanese.

Especially because the HLA-DRB1*04:05 allele is 95% comprised
of the haplotype valine-histidine-arginine-alanine in Japan, this
allele can be said to play a critical role in AIH pathogenesis. A
single DPB1 amino acid, glutamic acid at position 69, has been
shown to contribute to graft-versus-host disease in otherwise
identical HLA sibling bone marrow transplantation[29] and factor
in the susceptibility to Beryllium disease.[24,26] However, the
frequency of glutamic acid at position 69 in our patients with AIH
and controls was 35% and 39%, respectively. Hence, amino acid
residues in DPB1 were not implicated in disease susceptibility.

Although our prior report showed that no HLA class I alleles
were involved with susceptibility to AIH,[4] this considerably
larger study of new patients uncovered that the A*24:02
(OR = 0.0053) and C*01:02 (OR = 0.036) alleles were associated
with type 1 AIH in the Japanese population. However, neither of these
is believed to be a primary susceptibility allele in AIH. The most
likely explanation for our observations is that these alleles reflect
the known linkage disequilibrium of the HLA-A*24:02-C*01:02-
DRB1*04:05-DQB1*04:01 haplotype in the Japanese. This inter-

![Figure 1. Relative amino acid positions at β11, β13, and β57 on the HLA-DRB1 molecule. Three-dimensional structure of HLA-DRB1 adapted from Stern et al. [40] The molecule is composed of 2 opposing α-helices and a series of supporting β-pleated sheets. The relative positions of the 3 amino acids discussed in this study are indicated by black spots.](Image)

doi:10.1371/journal.pone.0100565.g001

### Table 3. Number of Individuals with Haplotypes Containing HLA-DRB1*04:05-DQB1*04:01.

| Haplotype | Patients (2n = 312) | Controls (2n = 402) | P value |
|-----------|---------------------|---------------------|---------|
| A*02:01-C*02- B*57:01-DRB1*04:05-DQB1*04:01- DPB1*05:01 | 69 (22%) | 28 (7%) | \(4.6 \times 10^{-9}\) |
| A*02:02-C*01:02-B*54:01-DRB1*04:05-DQB1*04:01- DPB1*05:01 | 55 (18%) | 26 (6%) | \(3.1 \times 10^{-6}\) |
| A*02:02-C*01:02-B*54:01-DRB1*04:05-DQB1*04:01- DPB1*05:01 | 44 (14%) | 22 (5%) | \(7.8 \times 10^{-5}\) |
| A*02:02-C*01:02-B*54:01-DRB1*04:05-DQB1*04:01- DPB1*05:01 | 36 (12%) | 13 (3%) | 0.0020 |
| A*02:02-C*01:02-B*54:01-DRB1*04:05-DQB1*04:01- DPB1*05:01 | 28 (9%) | 14 (3%) | 0.0044 |
| A*02:02-C*01:02-B*54:01-DRB1*04:05-DQB1*04:01- DPB1*05:01 | 19 (6%) | 8 (2%) | 0.0044 |

x represents any allele at that locus, including A*24:02, C*01:02, B*54:01, and DPB1*05:01.

doi:10.1371/journal.pone.0100565.t003

OR = 0.62; P = 0.029; OR = 0.41, and P = 0.042; OR = 0.42, respectively. Amino acids in DQβ1 that were associated with
disease susceptibility included glycine at position 26
\((P = 1.8 \times 10^{-5} ); \text{OR} = 1.97) \text{ and leucine at positions 53
\((P = 9.0 \times 10^{-6}; \text{OR} = 1.99) \text{ and 56 (}P = 2.2 \times 10^{-11}; \text{OR} = 3.36).\text{ There were no significant associations among DPB1 amino acids.\text{}}
| HLA-DRB1 allele | Allele frequency | Patients | Controls | P-value | OR  | 95% CI |
|-----------------|-----------------|----------|----------|---------|-----|--------|
| DRB1*04:05, *04:10, *04:17 | Val His Ser | 0.333 | 0.124 | 0.0035 | 1.70 | 0.62–0.97 |
| DRB1*04:05-DQB1*04:01 | Ser Gly Ser | 0.071 | 0.087 | 0.42 | 0.80 | 0.46–1.39 |
| DRB1*08:03-DQB1*06:01 | Ser Gly Asp | 0.035 | 0.037 | 0.88 | 0.94 | 0.43–2.08 |
| DRB1*11, *13, *14:03, *14:05, *14:06, *14;18 | Val His Val | 0.077 | 0.102 | 0.25 | 0.80 | 0.46–1.39 |
| DRB1*15:01-DQB1*06:02 | Ser Ser Asp | 0.0109 | 0.0164 | 0.73 | 0.80 | 0.46–1.39 |
| DRB1*15:01-DQB1*06:02 | Ser Ser Ala | 0.022 | 0.052 | 0.42 | 0.80 | 0.46–1.39 |
| DRB1*11, *13, *14:03, *14:05, *14:06, *14;18 | Val His Asp | 0.077 | 0.102 | 0.25 | 0.80 | 0.46–1.39 |
| DRB1*15:01-DQB1*06:02 | Gln Tyr Val | 0.003 | 0.002 | 0.59 | 1.29 | 0.08–20.7 |
| DRB1*11, *13, *14:03, *14:05, *14:06, *14;18 | Leu Phe Asp | 0.026 | 0.060 | 0.41 | 0.80 | 0.46–1.39 |

Abbreviations: HLA, human leukocyte antigen; AIH, autoimmune hepatitis; OR, odds ratio; CI, confidence interval.

In conclusion, the DRB1*04:05-DQB1*04:01 and DRB1*15:01-DQB1*06:02 haplotypes are associated with AIH susceptibility and protection, respectively, in the Japanese population. DRB1*04:05-DQB1*04:01 is associated with elevated serum IgG and SMA positivity. DRB1*15:01-DQB1*06:02 as well as DRB1*08:03-DQB1*06:01 are novel haplotypes that are related to AIH progression. In addition, specific amino acid residues in the DRβ1 chain appear to contribute to susceptibility or resistance to AIH. We have recently developed super high-resolution single-
molecule sequenced-based typing of HLA loci using next generation sequencing.[39] This method is able to amplify entire HLA gene sequences from the enhancer-promoter region to the 3' untranslated region and detect 8-digit level HLA alleles. With this technique, resequencing of the entire HLA region is expected to provide more precise genetic information on susceptibility and progression in AIH in Japan.

Acknowledgments
The authors thank Yuki Akahane and Asami Yamazaki for their technical assistance, and Trevor Ralph for his editorial assistance.

Author Contributions
Conceived and designed the experiments: TU MO. Performed the experiments: YK. Analyzed the data: TU MO. Contributed reagents/materials/analysis tools: TU KY TK SJ MK AM ET. Contributed to the writing of the manuscript: TU MO.

References
1. Krawitt EL (2006) Autoimmune hepatitis. N Engl J Med 354: 34-66.
2. Czaja AJ, Manns MP (2010) Advances in the diagnosis, pathogenesis, and management of autoimmune hepatitis. Gastroenterology 139: 58-72 e54.
3. Heneghan MA, Yeoman AD, Verma S, Smith AD, Longhi MS (2013) Autoimmune hepatitis. Lancet.
4. Seki T, Ota M, Furuta S, Fukushima H, Kondo T, et al. (1992) HLA class II molecules and autoimmune hepatitis susceptibility in Japanese patients. Gastroenterology 103: 1041-1047.
5. Yoshizawa K, Ota M, Katsuyama Y, Ichijo T, Matsumoto A, et al. (2005) Genetic analysis of the HLA region of Japanese patients with type 1 autoimmune hepatitis. J Hepatol 42: 578-584.
6. Doheery DG, Donaldson PT, Underhill JA, Farrant JM, Duthie A, et al. (1994) Allelic sequence variation in the HLA class II genes and proteins in patients with autoimmune hepatitis. Hepatology 19: 699-615.
7. Saito S, Ota S, Yamada E, Inoko H, Ota M (2000) Allele frequencies and haplotypic associations defined by allelic DNA typing at HLA class I and class II genes in Japanese patients with chronic hepatitis C. Hepatology 33: 517-323.
8. Horroldt B, McFarlane E, Dube A, Basumani P, Karajeh M, et al. (2011) Long-term outcomes of patients with autoimmune hepatitis managed at a nontransplant center. Gastroenterology 140: 1890-1899.
9. Yoshizawa K, Matsunoto A, Ichijo T, Umemura T, Joshita S, et al. (2012) Long-term outcome of Japanese patients with type 1 autoimmune hepatitis. Hepatology 56: 668-676.
10. Serrtett MD, Thomson LJ, Donaldson PT, Bunce M, O'Neil CM, et al. (1997) HLA-C genes and susceptibility to type 1 autoimmune hepatitis. Hepatology 26: 1023-1028.
11. Mandelboim O, Reynburt HT, Vales-Gomez M, Pazzmony L, Colonna M, et al. (1996) Protection from lysis by natural killer cells of group 1 and 2 specificity is mediated by residue 80 in human histocompatibility leukocyte antigen C alleles and also occurs with empty major histocompatibility complex molecules. J Exp Med 184: 913-922.
12. Barber LD, Percival I, Valainte NM, Chen L, Lee C, et al. (1996) The interlocus recombinant HLA-B*4601 has high selectivity in peptide binding and functions characteristic of HLA-A-C. J Exp Med 184: 735-740.
13. Fernandez MM, Freundgen J, Lee A, Morris DL, Boteva L, et al. (2012) Translational mapping of the HMC region in systemic lupus erythematosus identifies new independent and interacting loci at MSH5, HLA-DPB1 and HLA-G. Ann Rev Hum Genet 46: 777-794.
14. Lyon PS, Rayner TF, Trivedi S, Holle JL, Watts RA, et al. (2012) Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med 367: 214-223.
15. Lin G, Rothbard D, Shervira R, Monach PA, Lu EY, et al. (2013) Association of granulomatosis with polyangiitis (Wegener's) with HLA-DPB1*04 and SEMA6A gene variants: evidence from genome-wide analysis. Arthritis Rheum 65: 2457-2468.
16. Saito S, Ota S, Yamada E, Inoko H, Ota M (2000) Allele frequencies and haplotypic associations defined by allelic DNA typing at HLA class I and class II loci in the Japanese population. Tissue Antigens 56: 522-529.
17. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, et al. (1999) International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 31: 929-938.
18. Umemura T, Wang RY, Schechterly C, Shih JW, Kiyosawa K, et al. (2006) Quantitative analysis of anti-hepatitis C virus antibody-secreting B cells in patients with chronic hepatitis C. Hepatology 43: 91-99.
19. Umemura T, Zen Y, Hamano H, Kawa S, Nakamura Y, et al. (2007) Immunoglobin G4-hepatopathy: association of immunoglobin G4-bearing plasma cells in liver with autoimmune pancreatitis. Hepatology 46: 463-471.
20. Umemura T, Tani E, Ota K, Ogawa K, Kinugasa S, et al. (2003) Investigation of SEN virus infection in patients with cryptogenic acute liver failure, hepatitis-associated aplastic anemia, or acute and chronic non-A-E hepatitis. J Infect Dis 188: 1545-1552.
21. Ota M, Seki T, Nomura N, Sugimura K, Miznik N, et al. (1991) Modified PCR-RFLP method for HLA-DPB1 and -DQA1 genotyping. Tissue Antigens 38: 60-71.
22. Umemura T, Joshita S, Ichijo T, Yoshizawa K, Katsuyama Y, et al. (2012) Human leukocyte antigen class II molecules confer both susceptibility and progression in Japanese patients with primary biliary cirrhosis. Hepatology 55: 506-511.
23. Richeldi L, Sorrentino R, Saltini C (1993) HLA-DPB1 glutamate 69: a genetic marker of beryllium disease. Science 262: 243-244.
24. Varney MD, Valdes AD, Carlson JA, Noble JA, Tait BD, et al. (2010) HLA DPB1, DPB1 alleles and haplotypes contribute to the risk associated with type 1 diabetes: analysis of the type 1 diabetes genetics consortium families. Diabetes 59: 2055-2062.
25. Silveira LJ, McCandless EC, Fingerlin TE, Van Dyke MV, Moz MA, et al. (2012) Chronic beryllium disease, HLA-DPB1, and the DP peptide binding groove. J Immunol 189: 4014-4023.
26. Furukawa H, Oka S, Shinmura K, Sugi S, Hashimoto A, et al. (2013) Association of increased frequencies of HLA-DPB1*0301 with the presence of anti-Ro/SS-A and anti-La/SS-B antibodies in Japanese rheumatoid arthritis and systemic lupus erythematosus patients. PLoS One 8: e53910.
27. Ota M, Seki T, Kiyosawa K, Furuta S, Hino K, et al. (1992) A possible association between basic amino acids of position 13 of DRB1 chains and autoimmune hepatitis. Immunogenetics 36: 49-55.
28. Nomura N, Ota M, Kato S, Inoko H, Tsuchi K (1991) Severe acute graft-versus-host disease by HLA-DPB1 disparity in recombinant family of bone marrow transplantation between serologically HLA-identical siblings: an application of the polymerase chain reaction-restriction fragment length polymorphism method. Hum Immunol 32: 261-268.
29. Donaldson PT (2002) Genetics in autoimmune hepatitis. Semin Liver Dis 22: 353-364.
30. Donaldson PT, Baragiotto A, Henehan MA, Florani A, Venturi C, et al. (2006) HLA class II alleles, genotypes, haplotypes, and amino acids in primary biliary cirrhosis: a large-scale study. Hepatology 44: 667-674.
31. Overvoudt P, Selmi C, Poli F, Frison S, Florani A, et al. (2008) Human leukocyte antigen polymorphisms in Italian primary biliary cirrhosis: a multicenter study of 664 patients and 1992 healthy controls. Hepatology 48: 1906-1912.
32. Montano-Loya AJ, Carpenter HA, Czaja AJ (2008) Predictive factors for hepatocellular carcinoma in type 1 autoimmune hepatitis. Am J Gastroenterol 103: 1944-1951.
33. Hino-Arimaga T, Ide T, Kurotsu M, Miyajima I, Ogata K, et al. (2012) Risk factors for hepatocellular carcinoma in Japanese patients with autoimmune hepatitis type 1. J Gastroenterol 47: 569-576.
34. Migita K, Watanabe Y, Iuchi Y, Nakamura Y, Saito A, et al. (2010) Hepatocellular carcinoma and survival in patients with autoimmune hepatitis. Japanese National Hospital Organization-autoimmune hepatitis prospective study. Liver Int 32: 837-844.
35. Ohara H, Abe K, Takashashi A, Zeniya M, Ichida T (2013) Clinical features of hepatocellular carcinoma in patients with autoimmune hepatitis in Japan. J Gastroenterol 48: 109-114.
36. Ngu JH, Geary RB, Frampton CM, Stedman CA (2012) Mortality and the risk of malignancy in autoimmune liver diseases: a population-based study in Canterbury, New Zealand. Hepatology 53: 522-529.
37. Groubeak L, Vilstrup H, Jeppen T (2013) Autoimmune hepatitis in Denmark: Incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. J Hepatol.
38. Shima T, Suzuki S, Ozaki Y, Taira H, Kikawa E, et al. (2012) Super high resolution for single molecule-sequence-based typing of classical HLA loci at the 1-digit level using next generation sequencing. Tissue Antigens 80: 305-316.
39. Stern LJ, Brown JH, Jardetzky TS, Gorga JC, Urban RG, et al. (1994) Crystal structure of the human class II MHC protein HLA-DR1 complexed with an influenza virus peptide. Nature 368: 215-221.