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Characteristics of Human Leukocyte Antigen Class II Genes in Japanese Patients with Type 1 Diabetes and Autoimmune Thyroid Disease

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Genetic factors, particularly human leukocyte antigen (HLA) class II genes, are known to significantly influence the onset of type 1 diabetes (T1D). Additionally, patients with T1D often develop autoimmune thyroid diseases (AITD). Despite this association, comprehensive research on individuals with both AITD and T1D in Japan, especially regarding the influence of specific HLA alleles, remains insufficient. In this retrospective study, we analyzed 44 inpatients diagnosed with T1D. These patients were predominantly female, with an average onset age of 35 years, poor blood sugar control, and approximately 43.2% had concurrent AITD. We observed significant associations of HLA-DRB1*04:05, HLA-DRB1*09:01 and HLA-DRB1*15:02 alleles with T1D regardless of AITD presence, which had been previously established for T1D in Japanese. In this context, comparing Japanese patients with AITD alone, we noted AITD comorbidity with T1D results in alterations in the frequencies of HLA-DRB1*09:01, HLA-DRB1*04:03, and HLA-DRB1*15:02. Furthermore, HLA-DRB1*04:05, HLA-DRB1*09:01, HLA-DRB1*13:02, and HLA-DRB1*15:01 alleles may be alleles whose susceptibility varies for both conditions. These findings underscore the importance of understanding the relationship between T1D, AITD, and HLA genetics, which may inform personalized treatment strategies and facilitate the development of targeted therapies. Future research endeavors should aim to elucidate underlying mechanisms and validate these findings in larger cohorts.

Keywords: autoimmune thyroid disease, Graves' disease, human leukocyte antigen class II genes, Japanese patients, Type 1 diabetes
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Introduction

Type 1 diabetes (T1D) is characterized by impaired insulin secretion due to the destruction of pancreatic beta cells (Kolb et al. 1995). The Japan Diabetes Society categorizes T1D into three subtypes: "fulminant-onset," "acute-onset," and "slowly progressive" (also known as latent autoimmune diabetes in adults), taking into account the variations in the time it takes for insulin secretion to decline (Kawasaki and Eguchi 2007). The prevalence of T1D in the general Japanese population is low, ranging from 0.01% to 0.02% (Ikegami and Ogihara 1996). However, the occurrence of T1D is notably more common among the siblings of patients, with rates ranging from 1% to 4%, highlighting the significant tendency of T1D to cluster within families (Ikegami and Ogihara 1996). More importantly, the concordance rate of T1D onset among monozygotic twins was higher than that among dizygotic twins (47.3% vs. 7.6%, respectively) who share a lower rate of both genetic and environmental factors, suggesting that genetic factors are involved in the development of T1D (Matsuda and Kuzuya 1994).

Human leukocyte antigens (HLA) play a role in distinguishing between foreign and self-substances in the body, triggering immune responses to external foreign substances (Hudson and Allen 2016). Among the HLAs, class II is present in specific cells, such as dendritic cells, which present

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internalized foreign substances to immune cells to initiate immune responses (ten Broeke et al. 2013). The class II genetic region demonstrates the strongest association with T1D, with the DR and DQ alleles forming haplotypes involved in susceptibility and resistance to T1D onset (Todd et al. 1987). Haplotypes are important for a more comprehensive evaluation of the genetic risk of a disease as they consider the interactions among multiple HLA gene loci. Evaluating alleles individually is also crucial for a detailed investigation of the impact of specific HLA alleles on disease.

Patients with T1D have a higher risk of developing autoimmune thyroid diseases (AITD) such as Hashimoto's thyroiditis and Graves' disease (Osaki et al. 2009; Frommer and Kahaly 2021). The co-occurrence of T1D and AITD is reportedly higher in women, patients with elevated anti-glutamic acid decarboxylase (anti-GAD) antibody levels, and those diagnosed with slowly progressive insulin-dependent diabetes mellitus (SPIDDM) (Osaki et al. 2009). However, comprehensive studies that thoroughly investigate the characteristics of patients with AITD and T1D in the Japanese population are insufficient (Chikuba et al. 1992, 1995; Mimura et al. 1994; Mochizuki et al. 2003; Ikegami et al. 2006; Moriguchi et al. 2011). Moreover, most of these reports have primarily focused exclusively on comparing HLA frequencies in patients with either AITD or T1D against healthy controls. To the best of our best knowledge only one study has compared T1D with and without AITD in Japanese individuals (Horie et al. 2012). Furthermore, while some studies have detailed the analysis of HLA haplotypes, few have thoroughly investigated the influence of specific HLA alleles.

The aim of this study was to investigate the clinical features, including the onset manner of T1D and the presence of AITD, in patients with T1D and to analyze the association between HLA alleles in these three distinct groups: T1D alone, T1D with AITD, and AITD alone.

Materials and Methods

Ethics approval

This study was approved by the Gunma University Institutional Review Board (HS2019-161) and conformed to the provisions of the Declaration of Helsinki (revised in Fortaleza, Brazil, October 2013). Each patient provided written informed consent before undergoing any study-related procedures.

Patients

In total, 60 patients with diabetes who were admitted to the Department of Internal Medicine, Division of Endocrinology and Diabetes, Gunma University Hospital from 2016 to 2022 and underwent HLA testing were reviewed. Among them, 48 were confirmed to have T1D according to the diagnostic criteria of the Japan Diabetes Society (Araki et al. 2020). The diagnosis of SPIDDM involved the following criteria: the presence of anti-islet autoantibodies at some point during the disease course; the absence of ketosis or ketoacidosis at initial diabetes diagnosis with no immediate requirement for insulin treatment to correct hyperglycemia; and a gradual decrease in insulin secretion over time, with insulin treatment required at more than 3 months after diagnosis and the presence of severe endogenous insulin deficiency (fasting serum C-peptide immunoreactivity < 0.6 ng/mL) at the last observed point in time. These three criteria resulted in the diagnosis of "Definite SPIDDM." If only the first two criteria were met, the diagnosis was categorized as "Probable SPIDDM" (Shimada et al. 2024). Both types of SPIDDM were included in this study. Furthermore, 44 individuals were analyzed for the diagnosis of AITD based on the presence of antithyroid antibodies and thyroid ultrasonography. In our study, we've expanded Graves' disease (GD) diagnosis to include probable cases, based on symptoms like rapid heartbeat, weight loss, trembling fingers, and an enlarged thyroid. Lab tests showing high thyroid hormones, low TSH levels, positive anti-TSH receptor antibodies, and increased radioactive iodine uptake also supported diagnosis. We diagnosed GD if a patient had at least one clinical finding and met all four lab criteria. Additionally, we classified patients as probably having GD if they met one clinical finding and three out of the four lab criteria. Moreover, "GD" was defined as patients undergoing or following treatment for GD. Hashimoto's thyroiditis (HT) was defined as the presence of either positive antithyroid peroxidase antibodies (TPOAb) or antithyroglobulin antibodies (TgAb), or both, and confirmed findings of Hashimoto's thyroiditis such as thyroid enlargement on thyroid ultrasound. The baseline characteristics of the patients are shown in Table 1.

Measurements

Anti-GAD antibody levels were measured using an enzyme-linked immunosorbent assay (Cosmic Corporation, Tokyo, Japan). Serum TgAb and TPOAb levels were determined by electrochemiluminescence immunoassay (ECLIA) using the ECLusys anti-Tg and anti-TPO kits (Roche Diagnostics, Basel, Switzerland). Serum thyrotropin receptor antibody (TRAb) levels were determined by ECLIA using the ECLusys TRAb electrochemiluminescence immunoassay kit (Roche Diagnostics). HLA-DRB1 and DQB1 were typed using the polymerase chain reaction - sequence-based typing method, under contract with SRL Inc. (Tokyo, Japan). The HLA allele frequencies of 19,183 Japanese individuals (Ikeda et al. 2015; Katahira et al. 2021) served as normal controls.

Statistical analysis

Data are presented as medians (interquartile ranges) or numbers (%) for frequency variables. Comparisons between two groups were conducted using the Wilcoxon rank-sum test for non-normally distributed continuous variables, whereas comparisons among three groups were performed using the Kruskal–Wallis test. Pearson's chi-

Table 1. Characteristics of all subjects screened

	total	acute	fluminant	SPIDDM	*p*
n	44	21	6	17	
Sex (male/female)	17/27	9/12	3/3	5/12	0.578
Age (years)	46 (31.3-60.8)	45 (31-56)	31.5 (21.3-50)	58 (37.5-68.5)	0.059
Age of onset (years)	35 (25-51)	33 (20.5-48)	24.5 (16.8-50)	37 (31.5-58.8)	0.11
PH (years)	1.5 (0-11.8)	9 (0-15)	0 (0-5)	2 (0-7.5)	0.166
FH (%)	15.8	19.0	0.0	11.8	0.507
BMI	21.7 (19.3-24.7)	21.4 (19.5-22.8)	20.4 (17.6-23.3)	24.6 (19.6-26.7)	0.106
HbA1c (%)	8.4 (6.7-10.0)	9.0 (7.6-11.4)	6.6 (6.2-7.7)	7.9 (6.5-10.1)	*0.016**
C-peptide in urine	9.2 (0.2-38.6)	6.1 (0-30.5)	0.48 (0-1.75)	35.3 (11.1-61.9)	*0.006*§
Retinopathy (%)	11.6	10.7	0	18.8	0.438
Neuropathy (%)	16.3	14.3	0	25.0	0.802
Nephropathy (%)	16.3	14.3	16.7	18.8	0.346
TDD	23.5 (13.0-39.0)	23 (14.3-36.3)	42.5 (20.8-60.5)	21.3 (7.3-36.0)	0.151
%bolus (%)	65.9 (54.5-74.4)	64.3 (55.9-72.8)	70.9 (63.2-77.7)	66.7 (52.8-74.8)	0.584
GAD antibody positive (%)	79.0	76.5	40.0	100.0	*0.008*,*§
GAD antibody	835 (21.0-2,000)	2,000 (476.3-2,000)	0 (0-11.8)	549.5 (97.8-1,483)	*0.008*,*§
AITD (%)	43.2	38.1	33.3	52.9	0.572
GD (%)	20.5	14.3	0	35.3	0.115
HT (%)	38.6	33.3	33.3	47.0	0.661

*acute vs. fluminant §fluminant vs. SPIDDM
SPIDDM, slowly progressive insulin-dependent diabetes mellitus; PH, Past history; FH, Family history; BMI, body mass index; HbA1c, glycated hemoglobin; TDD, Total Daily Dose of insulin; GAD, glutamic acid decarboxylase; AITD, autoimmune thyroid diseases; GD, Graves' disease; HT, Hashimoto's thyroiditis.

squared test was used for categorical variables. All tests of significance and resulting *p*-values were two-sided, with the level of significance set at 5%. Statistical analyses were performed using JMP Pro version 15.2.0 (SAS Institute, Cary, NC, USA). The sample size was sufficient to evaluate HLA haplotype frequency in patients with T1D with or without AITD when calculating the setting for α as 0.05 and β as 0.2 (power of 0.80).

Results

Overall, 44 inpatients with T1D who underwent AITD diagnosis with HLA alleles at our hospital from 2016 to 2022 were investigated. These inpatients were predominantly female, with an average age at onset of 35 years (range: 25-51 years). The mean duration of diabetes before hospitalization was 1.5 years. Notably, 15.8% of patients had a family history of T1D (Table 1). The average body mass index (BMI) was 21.7 (range: 19.3-24.7). Although patients with SPIDDM tended to have a higher BMI, no significant difference was observed. Glycated hemoglobin (HbA1c) levels were lower in the fulminant and urinary C-peptide types, indicating endogenous insulin secretion was lower at admission than in the other types. Additionally, while the total daily insulin dose was higher in the SPIDDM group, the difference was not significant. The positivity rate or titer of GAD antibodies was significantly lower in the fulminant group (Table 1). Interestingly, the comorbidity rate of AITD confirmed by autoantibodies and thyroid ultrasound was 43.2%, with 20.5% for "GD" and 38.6% for HT. There were no distinctive features in the three subtypes of T1D when complicated by AITD.

The patients were compared based on the presence or absence of AITD (Table 2). While no significant differences in sex were observed, the AITD comorbidity group tended to be older at admission than those without AITD (51 vs. 37 years, respectively; $p = 0.118$) (Table 2). Additionally, the age at onset of T1D was significantly higher in the AITD comorbidity group compared with those without AITD (40 vs. 30.5, $p = 0.013$). The clinical laboratory findings, complications, insulin therapy, GAD antibodies, and onset patterns were not significantly different between patients with T1D with or without AITD (Table 2).

We compared the DRB1 alleles of HLA in patients with T1D who participated in this study with those reported

Table 2. Comparison of patients on the presence or absence of AITD.

	AITD (+)	AITD (−)	*p*
n	19	25	
Sex (male/female)	8/11	9/16	0.68
Age (years)	51 (36-66)	37 (28.5-58)	0.118
Age of onset (T1D, years)	40 (34-60)	30.5 (22.3-43)	0.013
PH (years)	3 (0-11)	1 (0-16.5)	0.941
FH (%)	17.6	14.3	0.778
BMI	21.5 (19.7-24.5)	21.8 (19.3-26.3)	0.749
HbA1c (%)	7.9 (6.6-10.8)	8.5 (6.8-9.8)	0.731
C-peptide in urine	7.9 (0.8-50.1)	13.3(0-35.8)	0.638
Complications (%)	42.1	20	0.111
Retinopathy (%)	15.8	8.3	0.449
Nephropathy (%)	21.1	12.5	0.451
Neuropathy (%)	15.8	16.7	0.938
TDD	22 (10-31)	23 (14.3-36.3)	0.304
%bolus (%)	65.6 (48.5-74.2)	64.3 (55.9-72.8)	0.217
GAD antibody positive (%)	77.8	80.0	0.791
GAD antibody	241 (8.9-2,000)	999 (113-2,000)	0.87
acute	42.1	52	0.572
fluminant	10.5	16	
SPIDDM	47.4	32	
AITD (%)	100	-	
GD (%)	47.4		
HT (%)	89.5		

Table 3. HLA DRB1 haplotype frequency of all subjects screened and control subjects.

	Total (T1D)	Control[†/††]	*p*
Allele number	88	19,183	
T1D Susceptible			
04:05 (%)	27.3	13.5	*0.0002*
09:01 (%)	30.0	14.3	*< 0.001*
08:02 (%)	6.8	4.2	0.2217
T1D Protective			
15:01 (%)	3.4	7.8	0.1215
15:02 (%)	1.1	10.7	*0.0037*
others			
04:03 (%)	3.5	3.1	0.8524
04:10 (%)	2.3	2.2	0.9629
13:02 (%)	8	5.9	0.5291
14:06 (%)	2.3	1.3	0.421
01:01 (%)	2.3	5.8	0.1571

[†]Tissue Antigens 85 252-258 (2015)/[††]Human immunology 82 (2021).

previously. Except for HLA-DRB1*08:02 and HLA-DRB1*15:01, the frequencies of the alleles differed significantly between the patient group and the control group (Table 3). Therefore, the HLA-DRB1 alleles of T1D in this study were consistent with those previously established for T1D in Japanese by Kawabata et al. (2002).

In this context, we analyzed HLA-DRB1 alleles based on the presence or absence of AITD with T1D. The control group comprised AITD cases, excluding T1D (Table 4). The three groups were: T1D + AITD (a), T1D alone (b), and AITD alone (c). We initially compared individuals with T1D with (a) and without AITD (b), as documented by Horie et al. (2012). Our analysis revealed that HLA-DRB1*15:01 and HLA-DRB1*04:03 alleles showed reduced occurrence in T1D alone (b) in contrast to T1D with AITD (a), a pattern not previously observed (Table 4). Moreover, the frequencies of HLA-DRB1*09:01, associated with T1D susceptibility, and HLA-DRB1*04:03 in T1D with AITD (a) were higher compared with AITD alone (c). Conversely, the occurrence of HLA-DRB1*15:02, known for its protective role in T1D, was lower in T1D

Table 4. HLA DRB1 haplotype frequency in T1D + A1TD, T1D alone, and AITD alone.

	T1D + AITD[a]	T1D alone[b]	AITD alone[††,c]	*a vs. b*	*a* v.s. *c*	*b* vs. *c*
Allele number	38	50	650			
T1D Susceptible						
04:05 (%)	18.4	34.0	15.7*			*0.0009*
09:01 (%)	31.6	28.0	15.6**		*0.0095*	*0.0219*
08:02 (%)	7.9	6.0	5.5			
T1D Protective						
15:01 (%)	7.9	0	7.7	*0.0432*		*0.0418*
15:02 (%)	0	2.0	8.62[§]		*0.0059*	*0.0993*
others						
04:03 (%)	8.1	0	2.3	*0.0405*	*0.0317*	
04:10 (%)	5.3	0	3.1			
13:02 (%)	5.4	10	4.5[§§]			*0.0079*
14:06 (%)	0	4	1.2			
01:01 (%)	0	4	2.3[§]			

*GD Susceptible/**HT Susceptible/[§]GD Protective/[§§]HT Protective from Human immunology 82 (2021).
[††]Human immunology 82 (2021).

with AITD (a) compared with AITD alone (c) (Table 4). These data indicated that AITD comorbidity with T1D results in alterations in the frequencies of HLA-DRB1*09:01, HLA-DRB1*04:03, and HLA-DRB1*15:02. Furthermore, the frequencies of HLA-DRB1*04:05 and HLA-DRB1*09:01, linked to T1D susceptibility, and HLA-DRB1*13:02 in T1D alone (b) were elevated compared with AITD alone (c). Conversely, the occurrence of HLA-DRB1*15:01 was lower in T1D alone (b) compared with AITD alone (c) (Table 4). Although AITD and T1D are frequently reported to coexist, these data suggest that HLA-DRB1*04:05, HLA-DRB1*09:01, HLADRB1*13:02, and HLA-DRB1*15:01 alleles may be alleles whose susceptibility varies for both conditions.

Discussion

In our analysis, comparing Japanese patients with AITD alone, we noted AITD comorbidity with T1D resulted in alterations in the frequencies of HLA-DRB1*09:01, HLA-DRB1*04:03, and HLA-DRB1*15:02. Moreover, HLA-DRB1*04:05, HLA-DRB1*09:01, HLA-DRB1*13:02, and HLA-DRB1*15:01 alleles may be those whose susceptibility varies for both conditions. To the best of our best knowledge, this is the first report comparing frequencies of HLA alleles, but not haplotypes, in Japanese patients with T1D with or without AITD compared with AITD only.

Previous studies have demonstrated a significant association between the HLA-DRB1*04:05 and HLA-DRB1*09:01 alleles and T1D (Kawabata et al. 2002; Murao et al. 2004). Moreover, previous reports have linked the DRB1*08:02-DQB1*03:02 alleles to childhood-onset T1DM (Murao et al. 2004) among the HLA haplotypes associated with T1D. In our study, almost all patients had adult-onset T1DM, and the HLA-DRB1*04:05 and HLA-DRB1*09:01 alleles were associated with T1D; however, the HLA-DRB1*08:02 allele was nearly absent. Our analyses were allele-based and our findings align with those of previous reports (Kawabata et al. 2002; Murao et al. 2004).

In our study, the HLA-DRB1*15:02 allele, which has been reported to suppress both T1D and HT (Katahira et al. 2021), might exhibit even stronger suppression in the presence of T1D than AITD alone. The HLA-DRB1*04:03 allele was reportedly involved in HT (Wan et al. 1995) but was more prevalent in T1D complicated with AITD. Similarly, the HLA-DRB1*13:02 allele has been reported to be suppressed in HT (Katahira et al. 2021); however, its occurrence was higher in cases of T1D complicated without AITD in our study, indicating differences in allele occurrences between T1D with and without AITD.

Previous reports have suggested that AITD occurs in approximately 40% of patients with T1D in the Japanese population (Katahira et al. 2009). Our investigation of all inpatients revealed similar rates of AITD occurrence (43.2%). Most patients had inadequate blood glucose management, including at the initial presentation; despite this, we observed a comparable positivity rate. Similarly, utilizing health examination data from the Japanese population, the rates of positive anti-Tg and anti-TPO antibodies were 24.7% and 21.7%, respectively (Mori 2010), reaffirming a significantly increased frequency of AITD in individuals with T1D compared with healthy individuals. Moreover, cases of AITD complications with T1D are common, and a previous report has highlighted a higher occurrence in females, instances of elevated GAD antibodies, and a higher prevalence of SPIDDM (Osaki et al. 2009). However, when examining the presence or absence of AITD, we did not find significant differences in sex, GAD antibody levels upon admission, or onset patterns. This may be attributed to the fact that all our participants were

inpatients. Nevertheless, a noteworthy finding was the higher age at onset in cases in which AITD coexisted with T1D. This observation is consistent with previous reports and suggests a stronger association between age at onset and AITD co-occurrence, which is potentially more influential than sex or onset patterns. However, given both the limited sample size and the timing of AITD onset, including whether it precedes T1D or not in longitudinal studies, may have an influence, as observed in our study (Horie et al. 2012; Hughes et al. 2019).

A few limitations of this study must be considered when interpreting the findings. First, this study utilized a retrospective cross-sectional design with a small sample size and was performed at only one hospital. Therefore, our patient profiles may differ from those of other hospitals in Japan. Second, typically, patients were admitted owing to poor blood sugar control, including those experiencing their first episode. Consequently, the medical history revealed 0 years for fulminant onset (fulminant), whereas for acute onset (acute), the median duration was 9 years. The mean duration for SPIDDM was 2 years. These discrepancies in median duration observed between SPIDDM and acute onset type diabetes can be explained by the distinct clinical profiles of these conditions. SPIDDM patients often retain some endogenous insulin secretion, leading to better glycemic control and shorter durations of illness before hospitalization. Conversely, acute onset diabetes presents with more severe symptoms and patients often experience repeated admissions, resulting in hospitalization at a later stage in the illness duration investigated. These differences underscore the varied disease trajectories within our hospitalized patient cohort. Third, while this paper exclusively focuses on the Japanese population, it is pertinent to acknowledge and discuss the characteristics of HLA in other racial groups to provide a broader context. Variations in HLA allele frequencies among different ethnicities have been well-documented and can significantly impact disease susceptibility and manifestation. Therefore, a comparative analysis of HLA associations with T1D in diverse populations could elucidate potential ethnic-specific differences in disease pathogenesis and genetic predisposition. Such discussions could enrich the understanding of the interplay between genetic factors and disease susceptibility across different racial backgrounds.

In summary, this study aimed to explore the clinical features and HLA allele associations in Japanese patients with T1D, with a particular focus on the co-occurrence of AITD. Comparative analysis of HLA alleles revealed distinct patterns among T1D alone, T1D with AITD, and AITD alone, underscoring the involvement of specific HLA alleles in disease susceptibility. Overall, these findings provide valuable insights into the intricate interplay between T1D, AITD, and HLA genetics in the Japanese population, potentially guiding future research and treatment strategies for these autoimmune conditions.

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Author Contributions

Conceived and designed the experiments, analyzed the data, and wrote the paper: E.Y. Collected and analyzed the data and wrote the paper: R.K., H.T. Analyzed the data: S.Y., S.M., K.H., S.O., and M.Y.

Conflict of Interest

The authors declare conflict of interest.

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