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# The Relationship Between Human Leukocyte Antigen Class II Genes and Type 1 Diabetes, Autoimmune Thyroid Diseases, and Autoimmune Polyendocrine Syndrome Type 3

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Additional information is available at the end of the chapter

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## 1. Introduction

Common genetic risk factors have been associated with type 1 diabetes (T1D) and autoimmune thyroid diseases (AITD). Graves' disease (GD) and Hashimoto's thyroiditis (HT) are typical AITD. T1D and AITD are major components of autoimmune polyendocrine syndrome (APS)-2 and/or APS-3. The human leukocyte antigen (HLA) has been extensively studied in these diseases [1]. However, population studies have shown that HLA associations may vary depending on the ethnic origin [2]. In Caucasian populations, the highest-risk HLA haplotype for T1D is DRB1\*03:01-DQA1\*05-DQB1\*02 (DR3) and/or DRB1\*04-DQA1\*03:01-DQB1\*03:02 (DR4) [2, 3], and the corresponding haplotype for AITD is DR3 [4, 5]. DRB1\*15-DQB1\*06:02 and DRB1\*07:01-DQA1\*02:01 (DR7) haplotypes confer strong protection against both T1D [2, 3] and AITD [6, 7]. However, in the Japanese population, the DR3 haplotype is absent, and the DR4 and DR7 haplotypes are rare [8–10], which may be more helpful for examining the susceptibility and resistance to T1D and AITD of HLA DR-DQ haplotypes, with the exception of DR3, DR4, and DR7.

DR3 and DR4 haplotypes occur very frequently among Caucasian patients with T1D, and only a small percentage (approximately 10%) of Caucasian patients with T1D carry neither of these haplotypes [11, 12]. At the DQB1 locus, "non-Asp" alleles, which code for an amino acid other than aspartate at codon 57, confer an increased risk for T1D in Caucasian populations [13]. The risk due to DR4 haplotypes is primarily attributable to an association with the DQB1\*03:02 allele, which codes for an Ala at codon 57 [14]. The risk conferred by the DR3 haplotype may be associated with DQA1 alleles that encode the amino acid Arg at codon 52, such as

DQA1\*05:01 [15]. Recently, a similar mechanism was shown to be important in the etiology of AITD. Tomer et al. identified an Arg at position 74 of the HLA-DR $\beta$ 1 chain (DR $\beta$ -Arg-74), encoded by the DRB1\*03:01 allele, as the critical DR amino acid conferring susceptibility to GD [16, 17]. Further analysis has shown that the presence of Gln at position 74 was protective not only for GD [16] but also for APS-3 [18].

In the Japanese population, in contrast to Caucasians and other Asians, the DRB1\*04:05-DQA1\*03:03-DQB1\*04:01 haplotype, which differs from the DR4 haplotype in Caucasians, and the DRB1\*08:02-DQA1\*03:01-DQB1\*03:02, DRB1\*09:01-DQA1\*03:02-DQB1\*03:03 (DR9), and DRB1\*13:02-DQA1\*01:02-DQB1\*06:04 (DR13) haplotypes confer susceptibility to T1D [9, 19]. The DRB1\*15:01-DQB1\*06:02, DRB1\*15:02-DQB1\*06:01, and DRB1\*08:03-DQB1\*06:01 haplotypes confer protection against T1D [9, 10, 19]. On the other hand, the DRB1\*08:03-DQB1\*06:01 and DR9 haplotypes confers susceptibility to AITD [19–23], whereas the DR13 and DRB1\*15:01-DQB1\*06:02 haplotypes confer protection against AITD [7, 23–29]. Taken together, regarding susceptibility and resistance to T1D and AITD, the DR3, DR4, DR7, DR9, and DRB1\*15:01-DQB1\*06:02 haplotypes have the same effect. On the contrary, DRB1\*08:03-DQB1\*06:01 and DR13 haplotypes have an adverse effect on these diseases.

In this chapter, we will review HLA class II genes that confer susceptibility and resistance to T1D and AITD, and discuss the relationship between HLA class II genes and T1D, AITD, and APS-3. Furthermore, we focus on amino acids at position 74 of the HLA-DR $\beta$ 1 chain, position 52 of the HLA-DQ $\alpha$ 1 chain, and position 57 of the HLA-DQ $\beta$ 1 chain as key factors involved in susceptibility and resistance to T1D and AITD, and we discuss key amino acids and their involvement in susceptibility and resistance to T1D and AITD.

## 2. Nomenclature

In 1980, Neufeld and Blizzard suggested a classification of APS based on clinical criteria alone, and described four main types [30]. Of the four types, APS-2 and APS-3 are mainly associated with AITD and/or T1D. APS-2 is characterized by Addison's disease (AD) associated with AITD and/or T1D. APS-2 is quite rare with an incidence of 1.4–4.5 cases for every 100,000 individuals [31, 32]. While all patients with APS-2 have AD [30, 32–35], AITD and T1D are reported to occur in 69–82% and 30–52% of patients with APS-2, respectively [30, 34, 35]. APS-3 has been defined as an association between a clinical entity of AITD and an additional autoimmune disease such as T1D (Type 3A), chronic atrophic gastritis, pernicious anemia (Type 3B), vitiligo, alopecia, myasthenia gravis (Type 3C). AD and/or chronic hypoparathyroidism were categorically excluded from APS-3 [30]. Although AITD consists of HT, idiopathic myxedema, asymptomatic thyroiditis, GD, endocrine ophthalmopathy, and pretibial myxedema, GD or HT comprise the majority of AITD. Thus, in discussing the relationship between HLA and T1D and/or AITD, it is necessary to focus on APS type 3A (APS-3A) rather than APS-2 or APS type 3B/3C, and GD or HT may be considered as AITD.

In Caucasian populations, including those in Northern Europe, the incidence rates of T1D are high, in excess of 30 cases/100,000 individuals per year. In contrast, the Japanese population

has one of the lowest incidence rate of T1D in the world, at 1.6 cases/100,000 individuals per year, suggesting that the Japanese population may either lack an important susceptibility gene or have a unique T1D protective gene [36, 37]. However, AITD is the most frequent autoimmune disease in the population, present in approximately 7–8% of the general population [38, 39]. When thyroid disease is caused by environmental factors such as levels of iodine, incidence rates have been found to vary between locations and over time [40–43]. Studies regarding the incidence rates of AITD have come from a limited range of geographical areas. Therefore, it is difficult to comment on the absence or presence of variances in incidence rates of AITD between different geographical locations. Coexistence of T1D and AITD is common, with 15 to 30% of T1D subjects having AITD [44–46], whereas the prevalence of glutamic acid decarboxylase antibodies (GADAb) in AITD patients is around 5% [47, 48]. There is a need to distinguish T1D with AITD (T1D+AITD, APS-3A) from T1D without AITD (T1D-AITD). Conversely, we may not need to distinguish AITD with T1D from AITD without T1D (AITD-T1D). Abbreviations are listed in Table 1.

Abbreviations		AITD		T1D
		GD	HT	
AITD-T1D	GD-T1D	+	-	-
	HT-T1D	-	+	-
T1D-AITD		-	-	+
T1D+AITD (APS-3A)	T1D+GD	+	-	+
	T1D+HT	-	+	+

+, present; -, absent

**Table 1.** Relationship among T1D, AITD, and APS-3A

### 3. T1D

HLA class II genes are closely related to the onset of T1D in all ethnic groups. Recently, Thomson et al. investigated whether HLA DR-DQ haplotypes and genotypes show the same relative predispositional effects across populations and ethnic groups using data from 38 studies worldwide [49]. They introduced a new static, the patient/control (P/C) ratio of haplotype or genotype frequencies within a study that allows comparison of absolute penetrance values within and across studies. Mean P/C ratios are listed in Table 2. When the mean P/C ratio is >1.10, we consider that the haplotype confers susceptibility to T1D, whereas when the mean P/C ratio is <0.90, we consider that the haplotype confers protection against T1D. When the mean P/C ratio is 0.90–1.10, we consider the haplotype as neutral to T1D.

DRB1	DQB1	Mean P/C ratio	Effect on T1D <sup>a</sup>
*01	*05:01	0.85	P
*03:01	*02	3.72	S
*04	*03:01	0.73	P
*04:01	*03:02	6.23	S
*04:02	*03:02	5.10	S
*04:03	*03:02	0.64	P
*04:05	*03:02	7.15	S
*04:05	*04:01	2.35	S
*04:06	*03:02	0.31	P
*07:01	*02	0.66	P
*08	*03:02	3.25	S
*08	*04:02	1.92	S
*08:03	*06:01	0.38	P
*09:01	*03:03	1.12	S
*12	*03:01	0.47	P
*13	*06:04	0.93	N
*14	*03:01	0.25	P
*15	*06:01	0.46	P
*15	*06:02	0.22	P
*16	*05:02	0.95	N

<sup>a</sup> Effect on T1D is classified as: S, susceptible; N, neutral; P, protective.

**Table 2.** DRB1-DQB1 haplotype P/C ratios with regard to susceptibility to T1D

## 4. AITD

The results of HLA association studies in AITD have been less consistent than in T1D. Moreover, data on HLA haplotypes in HT have been less definitive than on those in GD. A general methodological problem has been disease definition [50]; though the diagnosis of GD may be relatively straightforward, the definition of HT has been more controversial. Three varieties of thyroid autoantibodies are commonly used and widely available in clinical diagnostic laboratories: anti-thyroglobulin antibodies (TgAb), anti-thyroid peroxidase autoantibodies (TPOAb), and antibodies to thyrotropin receptor (TRAb). TgAb and TPOAb are found in almost 100% of patients with HT, whereas these antibodies are also detectable in 50% to 90% of patients with GD and are common in the general population. The low levels of TPOAb and TgAb found in many individuals are of uncertain significance in the presence of normal thyroid function [51].

Table 3 shows previous reports on the relationship between HLA class II and AITD. The most probable HLA-DR and -DQ haplotypes were deduced from linkage disequilibria [8–10]. Alleles in parentheses following the reference number indicate that the reference reported

susceptibility or resistance of the allele, but not the haplotype, to the disease. There is no parenthesis following the reference number if the references reported susceptibility or resistance with 4-digit DRB1-DQB1, DQA1-DQB1, or DRB1-DQA1-DQB1 haplotypes. In cases with more than 2 haplotypes sharing the same allele, the allele is listed redundantly in each haplotype. However, considering the ethnicities that the references examined, the allele is removed from the corresponding haplotypes; for example, the DRB1\*08:02-DQA1\*03:01-DQB1\*03:02 haplotype is rare in Caucasian populations [49] and thus in the reference examining Caucasian populations, the DQA1\*03:01 allele is listed only in the DRB1\*04:01-DQA1\*03:01-DQB1\*03:02 haplotype, and not in the DRB1\*08:02-DQA1\*03:01-DQB1\*03:02 haplotype.

DRB1	DQA1	DQB1		Effect on GD <sup>a</sup>		Effect on HT <sup>a</sup>		Effect on AITD-T1D <sup>a</sup>
Ref. no.				Ref. no.				
*01:01	*01:01	*05:01	P	24 (DR1), 52 (DR1), 21 (DRB1), 26 (DQB1), 27 (DQB1)	–			–
*03:01	*05:01	*02:01	S	21 (DRB1), 29 (DRB1), 27 (DQA1)	S	53 (DR3), 7 (DQB1)	S	57 (DQB1)
*04:01	*03:01	*03:02	P	54 (DQB1)	S	6 (DQA1), 7		–
*04:01	*03:03	*03:01	–		S	6 (DQB1), 55 (DRB1*04-DQB1)		–
*04:05	*03:01	*03:02	–		S	7 (DRB1), 6 (DQA1)		–
*04:05	*03:03	*04:01	S	56	–		N	58 (DRB1)
*07:01	*02:01	*02:02	P	21 (DRB1), 29 (DRB1)	P	7 (DRB1*07), 6 (DRB1*07-DQA1-DQB1*02)		–
*08:02	*03:01	*03:02	S	29 (DRB1)	–			–
*08:02	*04:01	*04:02	S	29 (DRB1)	S	6 (DRB1*08-DQA1-DQB1*04)		–
*08:03	*01:03	*06:01	S	20-22	S	23 <sup>b</sup>		–
*09:01	*03:02	*03:03	–		S	22, 23 <sup>b</sup>	N	58 (DRB1)
*12:02	*06:01	*03:01	P	21 (DRB1), 54 (DRB1)	–			–
*13:02	*01:02	*06:04	P	21 (DRB1), 29 (DRB1)	P	7 (DQB1), (DRB1*13-DQA1-DQB1*06), 23 <sup>b</sup>		–
*14:03	*05:01	*03:01	S	29 (DRB1), 20	–			–
*15:01	*01:02	*06:02	S/P	54 (DRB1) / 27 (DQB1)	P	24 (DR2), 25 (DR2), 6 (DRB1*15-DQA1-DQB1*06), 23 <sup>b</sup> , 26		–
*15:02	*01:03	*06:01	–		P	24 (DR2), 25 (DR2), 6 (DRB1*15-DQA1-DQB1*06)		–
*16:02	*01:02	*05:02	S	54 (DRB1), 21	–			–

<sup>a</sup> Effect on GD, HT, or AITD-T1D is classified as: S, susceptible; N, neutral; P, protective.

<sup>b</sup> HT-T1D

**Table 3.** Effects of HLA DR-DQ genes on GD, HT, or AITD



With the exception of the DRB1\*15:01-DQA1\*01:02-DQB1\*06:02 haplotype, there are no controversial results concerning susceptibility and resistance to AITD. Additionally, except for the DRB1\*04:01-DQA1\*03:01-DQB1\*03:02 haplotype, no haplotype has been found to have an adverse effect on GD and HT. Chen et al. demonstrated, for the first time, that the DRB1\*15:01 allele confers susceptibility to GD and that the DQB1\*03:02 allele confers protection against GD in the Taiwan Chinese population [54]. Further investigations in other ethnic groups may be necessary to confirm whether their conclusions are widely applicable.

5. T1D-AITD and T1D+AITD

Few previous reports have been published on the relationship between HLA class II and T1D-AITD. In contrast, there are a number of reports concerning the relationship between HLA class II and T1D+AITD, which includes T1D+GD and T1D+HT. The results are shown in Table 4. As in Table 3, alleles in parentheses following the reference number indicate that the reference reported susceptibility or resistance of the allele, but not the haplotype, to the disease. There is no parenthesis following the reference number if the references reported the susceptibility or resistance of 4-digit DRB1-DQB1, DQA1-DQB1, or DRB1-DQA1-DQB1 haplotypes to the disease. In cases with more than 2 haplotypes sharing the same allele, the allele is listed redundantly in each haplotype. However, with consideration of the ethnicities that the references examined, the allele may be removed from the corresponding haplotypes.

DRB1	DQA1	DQB1		Effect on T1D-AITD <sup>a</sup>		Effect on T1D+AITD <sup>a</sup>	
				Ref no.		Ref no.	
*01:01	*01:01	*05:01	S	59	P	18 (DR1), 63 <sup>b</sup> (DQB1*05)	
*03:01	*05:01	*02:01	S	57 (DQB1), 60	S	18 (DR3), 57 (DQB1), 60	
*04:01	*03:01	*03:02	S	57 (DQB1)	S	18 (DR4), 63 <sup>b</sup> (DQB1), 57 (DQB1)	
*04:05	*03:01	*03:02	S	60	N	60	
*04:05	*03:03	*04:01	S/N	61 (DR4) / 60	S	58 (DRB1), 22, 59, 60	
*07:01	*02:01	*02:02	–		N	18 (DR7)	
*08:02	*03:01	*03:02	S	61 (DQA1)	S	61 <sup>c</sup> (DQA1), 22 <sup>c</sup> , 59	
*08:02	*04:01	*04:02	–		S	22	
*08:03	*01:03	*06:01	P	61 (DQA1)	P	61 (DQA1)	
*09:01	*03:02	*03:03	S	59	S	62 (DR9), 58 (DRB1), 22, 59	
*13:02	*01:02	*06:04	S	59	P	18 (DR6), 60 (DR13)	
*15:01	*01:02	*06:02	P	62 (DR2), 57 (DQB1), 59	P	18 (DR2), 62 (DR2), 57 (DQB1), 59	
*15:02	*01:03	*06:01	P	62 (DR2), 61 (DQA1)	P	62 (DR2), 61 <sup>c</sup> (DQA1)	

<sup>a</sup> Effect on T1D-AITD or T1D+AITD is classified as: S, susceptible; N, neutral; P, protective.

<sup>b</sup> T1D+HT; <sup>c</sup> T1D+GD

Table 4. Effects of HLA DR-DQ genes on T1D-AITD and T1D+AITD

## 6. Relationship between GD and amino acid

Badenhoop et al. demonstrated that Arg at position 52 of the DQ $\alpha$ 1 chain plays an important role in susceptibility to GD [27]. It was recently shown that Arg at position 74 of the DR $\beta$ 1 chain is important for the development of GD in a significant number of patients [16, 17]. Further analysis has shown that the presence of Gln at position 74 of the DR $\beta$ 1 chain was protective for GD [16]. Table 5 shows the susceptibility and resistance of HLA DR-DQ genes to GD, and amino acids at position 74 of the DR $\beta$ 1 chain and position 52 of the DQ $\alpha$ 1 chain. When more than 2 references reported susceptibility, we considered that the haplotype confers susceptibility to GD (abbreviated as "S"). When more than 2 references reported protection against the disease, we considered that the haplotype confers protection against GD (abbreviated as "P"). When only one reference reported susceptibility, we considered that the haplotype either confers susceptibility or is neutral to GD (abbreviated as "S/N"). When only one reference reported a protective effect, we considered that the haplotype either confers protection against or is neutral to GD (abbreviated as "P/N"). Badenhoop et al. showed that susceptibility to GD is conferred by the DQA1\*05:01 allele as well as Arg at position 52 of the DQ $\alpha$ 1 chain [27]. DR $\beta$ -Arg-74 and DR $\beta$ -Gln-74 are always present on DR3 and DR7, respectively [16]. These amino acids are indicated in bold. The amino acids at position 52 of the DQ $\alpha$ 1 chain that are encoded by the haplotypes listed in Table 5 are Arg, Gln, and Ser. The effect on GD of the haplotypes which encode Arg or Ser at position 52 of the DQ $\alpha$ 1 chain varies from susceptible to protective. Amino acids at position 74 of the DR $\beta$ 1 chain that are encoded by the haplotypes listed in Table 5 are Ala, Arg, Gln, and Leu. The effect on GD of these haplotypes also varies from susceptible to protective. However, haplotypes that encode Leu at position 74 of the DR $\beta$ 1 chain, indicated by italics, are virtually all susceptible to GD. Interestingly, DR3 encodes Arg at both position 52 of the DQ $\alpha$ 1 chain and position 74 of the DR $\beta$ 1 chain. Moreover, 3 of 4 haplotypes that encode Leu at position 74 of the DR $\beta$ 1 chain encode Arg at position 52 of the DQ $\alpha$ 1 chain. These findings may indicate that amino acids at position 74 of the DR $\beta$ 1 chain, rather than those at position 52 of the DQ $\alpha$ 1 chain, play an important role in susceptibility or protection for GD.

## 7. Relationship between T1D $\pm$ AITD and amino acid

It is well known that DQ $\alpha$ -Arg-52 confer susceptibility to T1D [15]. Todd et al. demonstrated that DQ $\beta$ -Asp-57 is neutral or negatively associated with T1D, and that Ala, Val, or Ser at position 57 of the DQ $\beta$ 1 chain is positively associated with T1D [13]. Table 6 lists the amino acids at position 52 of the DQ $\alpha$ 1 chain and position 57 of the DQ $\beta$ 1 chain in each haplotype. Although the effect on T1D of haplotypes with both DQ $\alpha$ -Arg-52 and DQ $\beta$ -Asp-57 is usually protective or neutral, DRB1\*04:05-DQA1\*03:03-DQB1\*04:01 and DRB1\*09:01-DQA1\*03:02-DQB1\*03:03 haplotypes confer susceptibility to T1D. In addition, the effect of some haplotypes with Ala, Val, or Ser at position 57 of the DQ $\beta$ 1 chain on T1D is protective or neutral (DRB1\*01:01-DQA1\*01:01-DQB1\*05:01, DRB1\*07:01-DQA1\*02:01-DQB1\*02:02, DRB1\*13:02-DQA1\*01:02-DQB1\*06:04, and DRB1\*16:02-DQA1\*01:02-DQB1\*05:02). In Table 6, areas of the



DRB1	DQA1	DQB1	Effect on GD <sup>a</sup>	Amino acid at position 52 of DQα1 chain	Amino acid at position 74 of DRβ1 chain
*01:01	*01:01	*05:01	P	Ser	Ala
*03:01	*05:01	*02:01	S	<b>Arg</b>	<b>Arg</b>
*04:01	*03:01	*03:02	P/N	Arg	Ala
*04:05	*03:03	*04:01	S/N	Arg	Ala
*07:01	*02:01	*02:02	P	Gln	<b>Gln</b>
*08:02	*03:01	*03:02	S/N	Arg	<i>Leu</i>
*08:02	*04:01	*04:02	S/N	Arg	<i>Leu</i>
*08:03	*01:03	*06:01	S	Ser	<i>Leu</i>
*12:02	*06:01	*03:01	P	Arg	Ala
*13:02	*01:02	*06:04	P	Ser	Ala
*14:03	*05:01	*03:01	S	<b>Arg</b>	<i>Leu</i>
*15:01	*01:02	*06:02	S/N, P/N	Ser	Ala
*16:02	*01:02	*05:02	S	Ser	Ala

<sup>a</sup> Effect on GD is classified as: S, susceptible; P, protective; S/N, susceptible or neutral; P/N, protective or neutral.

**Table 5.** Relationship between effect on GD and amino acids

effect on T1D are shaded in the haplotypes that conflict with the theory that DQα-Arg-52 or “non-Asp” at position 57 of the DQβ1 chain confers susceptibility to T1D, and that DQβ-Asp-57 confers protection against T1D.

Table 6 also shows the effects of HLA DR-DQ genes on AITD, T1D-AITD, and T1D+AITD. When more than 2 references reported susceptibility to the disease, we considered that the haplotype confers susceptibility (abbreviated as “S”), regardless of a single report demonstrating that the haplotype confers protection against the disease. When more than 2 references reported protection against the disease, we considered that the haplotype confers protection (abbreviated as “P”), regardless of one report demonstrating to the disease. When only one reference reported susceptibility, we considered that the haplotype confers susceptibility or is neutral (abbreviated as “S/N”). When only one reference reported protection against the disease, we considered that the haplotype confers protection or is neutral (abbreviated as “P/N”). Recently, Menconi et al. demonstrated that amino acids at position 74 of the DRβ1 chain play an important role in susceptibility and resistance to APS-3A, i.e., T1D+AITD as well as GD [18]. DRβ-Tyr-26, DRβ-Leu-67, DRβ-Lys-71, and DRβ-Arg-74 are positively associated with APS-3A, while DRβ-Ala-71 and DRβ-Gln-74 are negatively associated with APS-3A. These amino acids are indicated in bold in Table 6.

DRB1	DQA1	DQB1	Effect of HLA DR-DQ gene				DQα1	DQβ1	DRβ1			
			AITD <sup>a</sup>	T1D-AITD <sup>a</sup>	T1D <sup>b</sup>	T1D+AITD <sup>a</sup>	52	57	26	67	71	74
*01:01	*01:01	*05:01	P	S/N	P	P	Ser	Val	Leu	<b>Leu</b>	Arg	Ala
*03:01	*05:01	*02:01	S	S	S	S	<b>Arg</b>	Ala	<b>Tyr</b>	<b>Leu</b>	<b>Lys</b>	<b>Arg</b>
*04:01	*03:01	*03:02	S	S/N	S	S	Arg	Ala	Phe	<b>Leu</b>	<b>Lys</b>	Ala
*04:01	*03:03	*03:01	S	–	P	–	Arg	Asp	Phe	<b>Leu</b>	<b>Lys</b>	Ala
*04:05	*03:01	*03:02	S	S/N	S	N	Arg	Ala	Phe	<b>Leu</b>	Arg	Ala
*04:05	*03:03	*04:01	S/N	S/N	S	S	Arg	Asp	Phe	<b>Leu</b>	Arg	Ala
*07:01	*02:01	*02:02	P	–	P	N	Gln	Ala	Phe	Ile	Arg	<b>Gln</b>
*08:02	*03:01	*03:02	S/N	S/N	S	S	Arg	Ala	Phe	Phe	Arg	Leu
*08:02	*04:01	*04:02	S	–	N	S/N	Arg	Asp	Phe	Phe	Arg	Leu
*08:03	*01:03	*06:01	S	P/N	P	P/N	Ser	Asp	Phe	Ile	Arg	Leu
*09:01	*03:02	*03:03	S	S/N	S	S	Arg	Asp	<b>Tyr</b>	Phe	Arg	Glu
*12:02	*06:01	*03:01	P	–	P	–	Arg	Asp	Leu	Phe	Arg	Ala
*13:02	*01:02	*06:04	P	S/N	N	P	Ser	Val	Phe	Ile	Glu	Ala
*14:03	*05:01	*03:01	S	–	P	–	Arg	Asp	Phe	<b>Leu</b>	Arg	Leu
*15:01	*01:02	*06:02	P	P	P	P	Ser	<b>Asp</b>	Phe	Ile	<b>Ala</b>	Ala
*15:02	*01:03	*06:01	P	P	P	P	Ser	Asp	Phe	Ile	<b>Ala</b>	Ala
*16:02	*01:02	*05:02	S	–	N	–	Ser	Ser	Phe	<b>Leu</b>	Arg	Ala

<sup>a</sup> Effect on AITD, T1D-AITD, or T1D+AITD is classified as: S, susceptible; P, protective; S/N, susceptible or neutral; P/N, protective or neutral.

<sup>b</sup> Effect on T1D is classified as: S, susceptible; N, neutral; P, protective.

**Table 6.** Effects of HLA DR-DQ genes on AITD, T1D-AITD, T1D, or T1D+AITD

In this section, we discuss the relationship between the above-mentioned HLA DR-DQ genes, amino acids at positions 26, 67, 71, and 74 of the DRβ1 chain, and T1D with or without AITD.

#### *DRB1\*01:01-DQA1\*01:01-DQB1\*05:01 and DRB1\*13:02-DQA1\*01:02-DQB1\*06:04 haplotypes*

While these haplotypes encode Val at position 57 of the DQβ1 chain, they confer protection or are neutral to T1D. Although they confer protection against AITD and T1D+AITD, they tend to confer susceptibility to T1D-AITD (S/N in Table 6). Since 15 to 30% of subjects with T1D have AITD [44–46], the effect of AITD on T1D may result in resistance of subjects with these haplotypes to T1D.

#### *DRB1\*04:05-DQA1\*03:03-DQB1\*04:01 and DRB1\*09:01-DQA1\*03:02-DQB1\*03:03 haplotypes*

These haplotypes are the major haplotypes which confer susceptibility to T1D in East Asians, especially in the Japanese population where the DR3 haplotype is absent and the DR4 haplotype is rare [8–10]. While these haplotypes encode Asp at position 57 of the DQ $\beta$ 1 chain, they confer susceptibility to T1D+AITD. DR $\beta$ -Leu-67 in the DRB1\*04:05-DQA1\*03:03-DQB1\*04:01 haplotype and DR $\beta$ -Tyr-26 in the DRB1\*09:01-DQA1\*03:02-DQB1\*03:03 haplotype might play an important role in susceptibility to T1D+AITD. Since 15 to 30% of subjects with T1D have AITD [44–46], the effect of these amino acids on T1D may be susceptibility, and that on T1D-AITD might be susceptibility or neutrality, which is weaker than that on T1D or T1D+AITD.

*DRB1\*07:01-DQA1\*02:01-DQB1\*02:02 and DRB1\*16:02-DQA1\*01:02-DQB1\*05:02 haplotypes*

There are few reports concerning the effect of HLA DR-DQ genes on T1D-AITD in the Caucasian [57], Japanese [59, 61, 62], and Taiwan Chinese [60] populations (Table 4). The DRB1\*07:01-DQA1\*02:01-DQB1\*02:02 and DRB1\*16:02-DQA1\*01:02-DQB1\*05:02 haplotypes are rare in the Japanese population [8–10, 49]. Therefore, it is difficult to explain the protective or neutral effect of these haplotypes with “non-Asp” at position 57 of the DQ $\beta$ 1 chain on T1D by examining the effect of these haplotypes on T1D-AITD. However, Menconi et al. demonstrated that DR $\beta$ -Gln-74 is negatively associated with T1D+AITD, although they failed to demonstrate that the DR7 allele, which encodes Gln at position 74 of the DR $\beta$ 1 chain, confers protection against T1D+AITD [18] (Table 6). The DR3 and DR4 haplotypes encode Ala at position 57 of the DQ $\beta$ 1 chain, which confers strong susceptibility to T1D [2]. Since the DR7 haplotype also encodes Ala at position 57 of the DQ $\beta$ 1 chain, the effect of this haplotype might potentially result in susceptibility to T1D-AITD. Since 15 to 30% of subjects with T1D have AITD [44–46], DR $\beta$ -Gln-74 might play a role in protection against T1D.

There are several reports concerning the effect of HLA DR-DQ genes on T1D+AITD, which also studied Caucasian [18, 57, 63], Japanese [22, 58, 59, 61, 62], and Taiwan Chinese [60] populations (Table 4). The DRB1\*16:02-DQA1\*01:02-DQB1\*05:02 haplotype is rare in the Caucasian population as well as in the Japanese population [49], and Menconi et al. did not examine patients and controls with the DR16 allele [18]. Moreover, the positive effect of DQ $\beta$ -Ser-57 on T1D is weaker than that of DQ $\beta$ -Ala-57 or DQ $\beta$ -Val-57 [2]. To our knowledge, the evidence of the effect of the DRB1\*16:02-DQA1\*01:02-DQB1\*05:02 haplotype on T1D is insufficient.

## 8. Conclusion

T1D and AITD share common genetic risk factors. The prevalence of given HLA haplotypes varies among populations, but given the same DR and DQ haplotypes, the influence of HLA on T1D and/or AITD is similar on populations throughout the world. By clarifying the region of the diseases on which certain reports were focused, we can explain to some extent and speculate on the relationship between HLA haplotypes, specific amino acids, and T1D and/or AITD.

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