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Relationship of Type 1 Diabetes with Human Leukocyte Antigen (HLA) Class II Antigens Except for DR3 and DR4

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1. Introduction

Type 1 diabetes (T1D) is the form of the disease that occurs primarily as a result of β -cell destruction. The American Diabetes Association (ADA) and the World Health Organization (WHO) have classified T1D into 2 categories, namely, immune-mediated (autoimmune) and idiopathic (Alberti & Zimmet, 1998; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). In autoimmune T1D (type 1A diabetes), the rate of β -cell destruction is quite variable, being rapid in some individuals and slow in others (Zimmet et al., 1994). Markers of immune destruction, including islet cell autoantibodies (ICA), autoantibodies to insulin (IAA), autoantibodies to glutamic acid decarboxylase (GAD65), and autoantibodies to tyrosine phosphatases IA-2, are present in 85–90% of individuals with T1D when fasting diabetic hyperglycemia is initially detected (Verge et al., 1996). The rapid-onset (“classic”) form of T1D is commonly observed in children, but also may occur in adults (Humphrey et al., 1998). The slow-onset form of T1D generally occurs in adults and is sometimes referred to as latent autoimmune diabetes in adults (LADA) (Zimmet et al., 1994). This term has been commonly used to refer to autoimmune forms of diabetes that do not initially require insulin. However, it is now clear that diabetes in these patients is not latent and is not limited to adults (Borg et al., 2003; Fourlanos et al., 2005; Landin-Olsson et al., 1992; Turner et al., 1997). On the other hand, idiopathic T1D (type 1B diabetes) lacks immunological evidence for β -cell autoimmunity (Alberti & Zimmet, 1998; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). A new subtype known as “fulminant T1D” has been described in Japan. The clinical characteristics of this form of diabetes are remarkably abrupt onset of disease, very short (< 1 week) duration of diabetic symptoms, and virtually no C-peptide secretion (< 10 $\mu\text{g}/\text{day}$ in urine) (Imagawa et al., 2000a). Although more than 250 patients with fulminant T1D have been reported in Japan, only few patients with fulminant T1D have been reported outside Japan (Imagawa & Hanafusa, 2005). Therefore, in the Japanese population, in contrast to other ethnic groups, there are 3 prevalent subtypes of T1D: rapid-onset (“classic”), slow-onset, and fulminant T1D.

T1D is a multifactorial disease caused by a complex interaction of genetic and environmental factors. It is beyond doubt that the human leukocyte antigen (HLA) complex constitutes the most relevant susceptibility region. The HLA complex contributes 50% of the

inherited risk for T1D (Steenkiste et al., 2007). An additional 17 genes with variable but small effects, named *IDDM2-IDDM18*, located on different chromosomes, have been described. The HLA gene (*IDDM1*) is located on 6p21.3. The remainder are found on chromosomes 2, 3, 5, 10, 11, 14, 15, and 18, and three additional regions on chromosome 6q. Worldwide studies and many other individual reports have clearly shown that HLA class II loci have the most intense susceptibility determinants for T1D. However, population studies have shown that HLA associations may vary depending on the ethnic origin. In the Caucasian population, susceptibility to T1D is strongly associated with DRB1*03:01-DQA1*05:01-DQB1*02:01 (DR3) and/or DRB1*04-DQA1*03:01-DQB1*03:02 (DR4). These haplotypes are very frequent among Caucasian patients with T1D, and only approximately 10% of Caucasian patients with T1D carry neither of these haplotypes (Rønningen et al., 1991; Sanjeevi et al., 1995). Hence, the subgroup of patients who do not carry these haplotypes is generally very small, and therefore the data have been difficult to evaluate. However, the DR3 haplotype is absent and the DR4 haplotype is rare in the Japanese population, which is probably why Japan has one of the lowest incidences of T1D in the world (Matsuura et al., 1998; Tuomilehto et al., 1995). Therefore, the Japanese population is a good model for understanding the clinical stages of T1D and for examining the susceptibility of HLA DR-DQ haplotypes, except DR3 and DR4, to T1D.

In this chapter, we suggest that T1D can be divided into six subtypes based on the mode of disease onset, markers of immune destruction, and insulin deficiency; thus we intend to classify T1D, but not other types of diabetes such as Type 2 diabetes (T2D) or gestational diabetes. An appropriate staging would improve our understanding of the pathogenesis of T1D and allow for easier discrimination between T1D and T2D. Moreover, we discuss the relationship between HLA class II genes and T1D in the Japanese population based on a comparison with other ethnic groups.

2. Criteria of staging

For the better understanding of the clinical stages of T1D, we selected 3 clinical markers: islet autoantibodies, mode of disease onset, and insulin deficiency. On the other hand, the age at disease onset was the main classification criterion in the early 1970s because the peak incidence of autoimmune and rapid-onset T1D occurs in childhood and adolescence. However, onset of T1D may occur at any age, ranging from childhood to the ninth decade of life (Mølbak et al., 1994). Fulminant T1D also occurs at any age, ranging from 1 to 80 years (Imagawa et al., 2003). Since LADA is considered to be confined to adulthood, terms such as “LADY-like” (latent autoimmune diabetes in the young) (Lohmann et al., 2000) and “LADC” (latent autoimmune diabetes in children) (Aycan et al., 2004) were recently introduced for cases of autoimmune and slow-onset T1D occurring in childhood and adolescence. Based on these findings, we did not include the age at disease onset as a staging criterion.

2.1 Islet autoantibodies

The presence of islet autoantibodies has provided the main classification criterion for T1D since the ADA and WHO proposed the current classification of diabetes. Markers of immune destruction are also useful in distinguishing T1D from T2D. We divided diabetic patients, which included both T1D and T2D, into two categories; autoimmune and idiopathic. Autoimmune diabetic patients have at least one marker of immunological β -cell destruction

such as ICA, IAA, autoantibodies to GAD65 (GADAb), or autoantibodies to IA-2 (IA-2Ab). In contrast, idiopathic diabetic patients have no markers of immunological β -cell destruction.

2.2 Mode of disease onset

The mode of disease onset allows us to identify three subtypes of the condition: fulminant-onset, rapid-onset, and slow-onset such as LADA. According to the criteria for definitive diagnosis of fulminant T1D (Imagawa & Hanafusa, 2006), the duration of the disease is within 1 week in general and within 2 weeks at most. According to the definition of LADA (Stenström et al., 2005), slow-onset diabetes can be distinguished from rapid-onset diabetes as patients with slow-onset diabetes had no requirement for insulin at diagnosis and for a minimum of 6 months after diagnosis.

2.3 Insulin deficiency

For many years, insulin deficiency was thought to characterize autoimmune and rapid-onset T1D. Insulin deficiency was clinically characterized by decreased urinary and/or serum C-peptide levels. In fulminant-onset diabetes, the urinary C-peptide level is $< 10 \mu\text{g/day}$ (3.3 nmol/day), fasting serum C-peptide is $< 0.3 \text{ ng/ml}$ (0.1 nmol/L), or serum C-peptide is $< 0.5 \text{ ng/ml}$ (0.17 nmol/L) after glucagon injection (or meal) load (Imagawa & Hanafusa, 2006; Imagawa et al., 2003). In rapid-onset diabetes, the urinary C-peptide level is $< 20 \mu\text{g/day}$ (6.6 nmol/day), fasting serum C-peptide is $< 0.4 \text{ ng/ml}$ (0.13 nmol/L), or serum C-peptide is $< 1.0 \text{ ng/ml}$ (0.33 nmol/L) after glucagon injection (or meal) load (Stenström et al., 2005). Fulminant-onset and rapid-onset types of diabetes are insulin deficient when fasting diabetic hyperglycemia is detected, while slow-onset type of diabetes has two stages, i.e., insulin-deficient and non-insulin-deficient.

3. Clinical types of diabetes

Table 1 shows the clinical types of diabetes based on islet autoantibodies, mode of disease onset and insulin deficiency. The first marker is islet autoantibodies—(A) positive (autoimmune) or (B) negative (idiopathic). The second marker is mode of disease onset and insulin deficiency. Therefore, there are 4 clinical stages of T1D (numbered for convenience sake): fulminant-onset (0), rapid-onset (1), slow-onset with insulin deficiency (2), and slow-onset without insulin deficiency (3). Islet autoantibodies are arranged along the vertical axis, and the mode of disease onset and insulin deficiency are arranged along the horizontal axis. The combination of autoimmunity (A or B) and clinical stages (0-3) indicates the clinical types of diabetes.

Insulin deficiency	Insulin-deficient		Non-insulin-deficient	
	Fulminant	Rapid	Slow	
Mode of disease onset				
Clinical stages				
Islet autoantibodies	0	1	2	3
A) positive (autoimmune)	A0	A1	A2	A3
B) negative (idiopathic)	B0	B1	B2	B3

Table 1. Clinical types of diabetes based on islet autoantibodies, mode of disease onset, and insulin deficiency.

In Table 1, the region of T1D is the sum of A0, A1, A2, A3, B0, and B1 areas (shaded region), whereas the areas of B2 and B3 belong to T2D. The region of fulminant T1D is the sum of A0 and B0 areas, that of classic T1D is the sum of A1 and B1 areas, and that of LADA is the sum of A2 and A3 areas, where the onset of disease is in adulthood.

3.1 Fulminant T1D (Clinical stage 0)

3.1.1 Fulminant-onset and autoimmune (A0) area

Although fulminant T1D is a subtype of idiopathic T1D, it has been shown that 4.8% of patients with fulminant T1D were positive for GADAb (Imagawa et al., 2003). The ADA and WHO criteria cannot explain this form of diabetes, which corresponds to fulminant-onset and autoimmune (A0) area in Table 1. Recently, a fulminant T1D patient with positive IA-2Ab has also been reported (K. Katsumata & K. Katsumata, 2005). Although, it has been shown that there are few patients with fulminant T1D among Caucasian populations (Maldonado et al., 2003; Pozzilli et al., 2000), the high incidence of autoimmune T1D might conceal the presence of the A0 type of diabetes amongst Caucasians (Imagawa & Hanafusa, 2005).

3.1.2 Fulminant-onset and idiopathic (B0) area

Imagawa et al. reported, for the first time, 11 patients with fulminant T1D who do not have islet autoantibodies and proposed that this form of diabetes is a “nonautoimmune fulminant” T1D (Imagawa et al., 2000a). This form of diabetes corresponds to fulminant-onset and idiopathic (B0) area in Table 1. Although more than 250 patients with B0 area have been reported in Japan, few patients have been reported outside of Japan (Imagawa & Hanafusa, 2005). Despite its classification as an idiopathic form of T1D, the B0 type of diabetes is associated with HLA (Imagawa et al., 2005).

3.2 Rapid-onset T1D (Clinical stage 1)

3.2.1 Rapid-onset and autoimmune (A1) area

Rapid-onset and autoimmune T1D is the most common form of T1D and accounts for the majority of cases of “classic” T1D. This form of diabetes corresponds to rapid-onset and autoimmune (A1) area in Table 1. The A1 type of diabetes has strong HLA associations, with linkage to the DQA and B genes, and is influenced by the DRB genes (Cantor et al., 1995; Huang et al., 1996). These HLA-DR/DQ alleles can be either predisposing or protective.

3.2.2 Rapid-onset and idiopathic (B1) area

This form of diabetes corresponds to idiopathic T1D except for fulminant T1D and has no known etiology. Imagawa et al. called the B1 type of diabetes the nonautoimmune nonfulminant (chronic) T1D in contrast to the B0 and A1 types of diabetes (Imagawa et al., 2000a, 2000b).

3.3 Slow-onset diabetes (Clinical stages 2 and 3)

Although slow-onset T1D is known as LADA throughout the world, it is referred to as slowly progressive T1D in Japan (Kobayashi et al., 1993). However, there are some differences between LADA and slowly progressive T1D (Table 2): LADA patients are typically adults at diagnosis (usually aged >30 years), do not require insulin at least during

the first 6 months after diagnosis, and are not necessarily insulin deficient (Stenström et al., 2005; Tuomi et al., 1999). Patients with slowly progressive T1D, who usually are insulin deficient, have variable age at disease onset, and insulin treatment is typically initiated >12 months after diagnosis (Kobayashi et al., 1993).

	LADA	Slowly progressive T1D	Slow-onset T1D
Islet autoantibodies	Positive	Positive	Positive
Age of diabetes onset	Usually >30 years	Any age	Any age
Duration not requiring insulin after diagnosis	>6 months	>12 months	>6 months
Insulin deficiency	Not necessarily deficient	Usually deficient	Not necessarily deficient

Table 2. Clinical characteristics of LADA, slowly progressive T1D, and slow-onset T1D. LADA, latent autoimmune diabetes in adults; T1D, Type 1 diabetes.

3.3.1 Slow-onset, insulin-deficient and autoimmune (A2) area

This form of diabetes corresponds to insulin-deficient LADA, LADY (Lohmann et al., 2000), and LADC (Aycañ et al., 2004) or slowly progressive T1D in Japan. LADA has strong HLA associations apart from the same contribution of HLA in LADA and classic Type 1 diabetes (Desai et al., 2007; Hosszúfalusi et al., 2003; Stenström et al., 2003; Tuomi et al., 1999). Therefore, it is possible that the A2 type of diabetes is associated with HLA. Previous studies investigating the relationship between HLA class II genes and slow-onset T1D in Japan have focused on the relationship between these genes and the A2 type of diabetes (Kobayashi et al., 1993; Maruyama et al., 1994; Murao et al., 2004; Ohtsu et al., 2005).

3.3.2 Slow-onset, insulin-deficient and idiopathic (B2) area

This form of diabetes corresponds to insulin-deficient T2D. Individuals with extensive insulin secretory defects, and therefore no residual insulin secretion, require insulin for survival. The B2 type of diabetes is thus a form of T2D, not T1D.

3.3.3 Slow-onset, non-insulin-deficient and autoimmune (A3) area

This form of diabetes corresponds to non-insulin-deficient LADA, LADY (Lohmann et al., 2000), and LADC (Aycañ et al., 2004). The A3 type of diabetes is thus a form of T1D, not T2D. The association of the A3 type of diabetes with HLA is unknown. This form of diabetes ultimately progresses to the A2 type of diabetes.

3.3.4 Slow-onset, non-insulin-deficient and idiopathic (B3) area

This form of diabetes corresponds to non-insulin-deficient T2D, where insulin is not required at all or is required for adequate glycemic control, but not for survival. The B3 type of diabetes is “typical” T2D. Progression of this form of diabetes to the B2 type of diabetes is not common.

3.4 Correspondence to previous classification methods

Table 3 shows how various classification methods correspond to each area in Table 1. As stated above, the region of fulminant T1D is the sum of A0 and B0 areas. The region of classic, rapid-onset, or acute-onset T1D is the sum of A1 and B1 areas. The region of insulin-dependent diabetes mellitus (IDDM) is the sum of A0, A1, B0, and B1 areas. The region of autoimmune T1D (type 1A diabetes) is the sum of A0, A1, A2, and A3 areas. The region of idiopathic T1D (type 1B diabetes) is the sum of B0 and B1 areas. The region of slowly progressive IDDM (SPIDDM) is the sum of A2 and B2 areas. The region of LADA is the sum of A2 and A3 areas, where the onset of disease is in adulthood. The region of non-insulin-dependent diabetes mellitus (NIDDM) is the sum of A3 and B3 areas.

Classifications of diabetes	Area(s) of diabetes
Fulminant T1D	A0 + B0
Nonautoimmune fulminant T1D	B0
Classic (rapid-onset or acute-onset) T1D	A1 + B1
Insulin-dependent diabetes mellitus (IDDM)	A0 + A1 + B0 + B1
Autoimmune T1D (type 1A diabetes)	A0 + A1 + A2 + A3
Idiopathic T1D (type 1B diabetes)	B0 + B1
Nonautoimmune nonfulminant (chronic) T1D	B1
Slowly progressive IDDM (SPIDDM)	A2 + B2
Latent autoimmune diabetes in adults (LADA)	A2 + A3
T1D	A0 + A1 + A2 + A3 + B0 + B1
Non-insulin-dependent diabetes mellitus (NIDDM)	A3 + B3
T2D	B2 + B3

Table 3. Correspondence of various classifications of diabetes to area(s) of diabetes. T1D, Type 1 diabetes; T2D, Type 2 diabetes.

4. HLA class II genes and T1D in the Japanese population

More than 90% of patients with T1D of Caucasian origin are carriers of DR3 or DR4 (Rønningen et al., 1991; Sanjeevi et al., 1995). In the Japanese population, in contrast to Caucasians and other Asians, DRB1*04:05-DQA1*03:03-DQB1*04:01 – which is different from the DR4 haplotype in Caucasians –, DRB1*08:02-DQA1*03:01-DQB1*03:02 (DR8), 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. In this section, we discuss the relationship between HLA class II genes and T1D in the Japanese population based on a comparison with other ethnic groups.

4.1 DRB1*04:05-DQA1*03:03-DQB1*04:01 haplotype

The DRB1*04:05-DQA1*03:03-DQB1*04:01 haplotype is frequently observed in East Asians, including the Japanese, but is rare in other ethnic groups such as Caucasians and Blacks (Thomson et al. 2007). Among East Asians, this haplotype confers susceptibility to T1D only in the Japanese, Taiwanese (Chuang et al., 1995; Huang et al., 1995), and Filipinos (Bugawan et al., 2002), but not in Koreans (Park et al., 2000), Hong Kong Chinese (Chang et al., 1998), and Singapore Chinese (Chan et al., 1995). DRB1*04:05-DQA1*03:03-DQB1*04:01 and DR9

are the most frequently observed susceptibility haplotypes in the Japanese (Awata et al., 1992; Imagawa et al., 2005; Kawabata et al., 2002; Kobayashi et al., 1993; Maruyama et al., 1994; Murao et al., 2004; Tanaka et al., 2002; Yasunaga et al., 1996). However, studies conducted before the discovery of fulminant T1D may have included patients with fulminant T1D. Fulminant T1D accounts for approximately 20% of rapid-onset T1D in the Japanese population (Imagawa et al., 2003). A nationwide survey in Japan revealed that 41.8% of fulminant T1D patients possessed the DR4-DQ4 (encoded by DRB1*04:05-DQA1*03:03-DQB1*04:01) haplotype (Imagawa et al., 2005). Table 4 shows the phenotype frequencies of DRB1*04:05-DQA1*03:03-DQB1*04:01 and DR9 haplotypes in rapid-onset T1D with fulminant T1D (A0 + A1 + B0 + B1 areas) (Awata et al., 1992; Kawabata et al., 2002; Kobayashi et al., 1993; Maruyama et al., 1994; Yasunaga et al., 1996), rapid-onset T1D (which includes A1 area and excludes B0 area) (Imagawa et al., 2005; Murao et al., 2004; Tanaka et al., 2002), and fulminant T1D (B0 area) (Imagawa et al., 2005; Tanaka et al., 2002).

Mode of onset	Author (publication year)	Area(s) of diabetes	DRB1*04:05- DQA1*03:03- DQB1*04:01		DR9	
			PF	OR	PF	OR
Rapid-onset T1D	Imagawa et al. (2005)	A1	39.5%	2.2	56.8%	3.4
	Tanaka et al. (2002)	A0 + A1	43.6%	3.0	50.0%	4.3
	Murao et al. (2004)	A1 + B1	46.0%	3.1	65.1%	4.9
Rapid-onset T1D with fulminant T1D	Kobayashi et al. (1993)	A0 + A1 + B0 + B1	48.9%	3.1	44.3%	5.2
	Maruyama et al. (1994)		52.4%	4.3	38.1%	NS
	Awata et al. (1992)		52.5%	4.4	51.5%	2.2
	Kawabata et al. (2002)		53.8%	2.7	34.2%	2.1*
	Yasunaga et al. (1996)		56.8%	3.6	36.0%	1.3
Fulminant T1D	Imagawa et al. (2005)	B0	65.9%	6.6	36.3%	NS
	Tanaka et al. (2002)		68.2%	8.4	36.4%	NS

Table 4. Phenotype frequencies of DRB1*04:05-DQA1*03:03-DQB1*04:01 and DR9 haplotypes in Japanese T1D. DR9, DRB1*09:01-DQA1*03:02-DQB1*03:03; T1D, Type 1 diabetes; PF, Phenotype frequency; OR, Odds ratio; NS, not significant. Corrected $P < 0.05$ with haplotype frequency.

Before the existence of fulminant T1D was clarified (Imagawa et al., 2000a), the frequency and odds ratio (OR) of the DRB1*04:05-DQA1*03:03-DQB1*04:01 haplotype were higher than those of the DR9 haplotype in rapid-onset T1D with fulminant T1D (Awata et al., 1992; Kawabata et al., 2002; Kobayashi et al., 1993; Maruyama et al., 1994; Yasunaga et al., 1996). However, the frequency and OR of the DRB1*04:05-DQA1*03:03-DQB1*04:01 haplotype in rapid-onset T1D are lower than those of the DRB1*04:05-DQA1*03:03-DQB1*04:01 haplotype in rapid-onset T1D with fulminant T1D and those of the DR9 haplotype in rapid-onset T1D (Imagawa et al., 2005; Murao et al., 2004; Tanaka et al., 2002). On the other hand, the frequency and OR of the DRB1*04:05-DQA1*03:03-DQB1*04:01 haplotype in fulminant T1D are higher than those of the DRB1*04:05-DQA1*03:03-DQB1*04:01 haplotype in rapid-onset T1D. The DR9 haplotype is less frequent in fulminant T1D than in rapid-onset T1D and does not confer susceptibility to fulminant T1D (Imagawa et al., 2005; Tanaka et al., 2002).

The role of HLA class II has been emphasized in the context of the antigen-presenting process in autoimmune T1D (Eisenbarth et al., 2003), but it remains to be elucidated how a certain HLA class II can contribute toward the molecular mechanisms of β -cell destruction in fulminant T1D. One possibility is that the HLA molecule is associated with immune reaction of fulminant T1D similar to autoimmune T1D; another is that it may interact with some type of virus, as shown in mice (Wykes et al., 1993). The HLA gene, or a gene showing linkage disequilibrium to the HLA gene, contributes to the development of fulminant T1D (Imagawa et al., 2006). It is suggested that idiopathic T1D (B0 + B1 areas) accounts for approximately 40% of rapid-onset T1D with fulminant T1D (A0 + A1 + B0 + B1 areas) in the Japanese (Imagawa et al., 2000b). It is reported that 81.8% of the Japanese with idiopathic T1D (B0 + B1 areas) possess the HLA DRB1*0405 allele compared to the 58.8% with autoimmune T1D (Urakami et al., 2002). Further investigations of idiopathic T1D except fulminant T1D (B1 area) might clarify the relationship between the DRB1*04:05-DQA1*03:03-DQB1*04:01 haplotype and T1D.

4.2 DRB1*08:02-DQA1*03:01-DQB1*03:02 (DR8) haplotype

The DRB1*04:01, *04:02, or *04:05-DQA1*03:01-DQB1*03:02 (DR4) haplotype confers susceptibility to T1D in almost all ethnic groups such as Caucasians, Blacks, and East Asians (Thomson et al., 2007), but is rare in the Japanese. Conversely, the DR8 haplotype confers susceptibility to Japanese T1D (Awata et al., 1992; Kawabata et al., 2002; Kobayashi et al., 1993; Murao et al., 2004; Ohtsu et al., 2005; Yasunaga et al., 1996) and is present only in Japanese and Korean T1D (Thomson et al., 2007). However, some studies have found no evidence that the DR8 haplotype confers susceptibility to Japanese T1D (Maruyama et al., 1994; Murao et al., 2004; Tanaka et al., 2002). Table 5 shows the phenotype frequency of the DR8 haplotype and the mean onset age of T1D in previous studies.

Mode of onset	Author (publication year)	Area(s) of diabetes	DR8		Mean onset age
			PF	OR	
Rapid-onset T1D with or without fulminant T1D	Murao et al. (2004)	A1 + B1	18.8%	3.8	8
	Ohtsu et al. (2005)	A1 + B1	12.9%	4.6	8
	Kawabata et al. (2002)	A0 + A1 + B0 + B1	13.6%	6.0	16
	Kobayashi et al. (1993)	A0 + A1 + B0 + B1	30.7%	5.2	22
	Awata et al. (1992)	A0 + A1 + B0 + B1	14.1%	9.7	26
	Maruyama et al. (1994)	A0 + A1 + B0 + B1	8.3%	NS	30
	Tanaka et al. (2002)	A0 + A1	15.4%	NS	34
	Murao et al. (2004)	A1 + B1	7.9%	NS	39
Slow-onset T1D with or without rapid-onset T1D	Ohtsu et al. (2005)	A2 + B2	6.3%	NS	11
	Maruyama et al. (1994)	A2 + B2	6.3%	NS	35
	Katahira et al. (2008)	A1 + A2 + B1	14.5%	4.2	35
	Kobayashi et al. (1993)	A2 + B2	18.8%	NS	38
	Takeda et al. (2002)	A1 + A2	16.9%	3.3	41
	Murao et al. (2004)	A2	10.7%	NS	47

Table 5. Phenotype frequencies of the DR8 haplotype and the mean onset age in Japanese T1D. DR8, DRB1*08:02-DQA1*03:01-DQB1*03:02; T1D, Type 1 diabetes; PF, Phenotype frequency; OR, Odds ratio; NS, not significant.

This haplotype appears to confer susceptibility to rapid-onset T1D where the mean onset age is young (≤ 26 years) (Awata et al., 1992; Kawabata et al., 2002; Kobayashi et al., 1993; Murao et al., 2004; Ohtsu et al., 2005). Even if the mean onset age is older than 30 years old, this haplotype appears to confer susceptibility to rapid-onset T1D with slow-onset T1D (which includes both A1 and A2 areas) (Katahira et al., 2008; Takeda et al., 2002). However, there are no studies reporting that this haplotype confers susceptibility to slow-onset T1D (which includes A2 area and excludes A1 area) even if the mean onset age is young (Kobayashi et al., 1993; Maruyama et al., 1994; Murao et al., 2004; Ohtsu et al., 2005).

The effects of DRB1*04 subtypes on the DQA1*03:01-DQB1*03:02 haplotype vary from susceptibility to T1D (DRB1*04:01, *04:02, or *04:05) to protection against T1D (DRB1*04:03 or *04:06). The Korean population is unique in that the DR8 haplotype is present in addition to the DRB1*04-DQA1*03:01-DQB1*03:02 haplotype. Table 6 shows the frequencies of DRB1*04 and DRB1*08 subtypes linked to the DQA1*03:01-DQB1*03:02 haplotype in available Japanese (Kawabata et al., 2002; Murao et al., 2004) and Korean (Park et al., 2000) studies.

Ethnic	Japanese						Korean		
	Kawabata et al. (2002)			Murao et al. (2004)			Park et al. (2000)		
Author (publication year)	n	%	OR	n	%	OR	n	%	OR
DRB1 allele									
*04:01	0	0	—	0	0	—	15	27.8	13.9
*04:02	0	0	—	0	0	—	2	4.1	NS
*04:03	4	12.5	NS	1	5.3	0.16	2	3.7	NS
*04:04	0	0	—	0	0	—	5	9.3	NS
*04:05	5	15.6	13.3	0	0	—	11	20.4	10.1
*04:06	1	3.1	0.12	0	0	—	3	5.6	NS
*04:07	4	12.5	NS	2	10.5	NS	7	13.0	13.6
*08:02	18	56.3	5.67	16	84.2	4.88	9	16.7	NS
Total	32	100	—	19	100	—	54	100	—

Table 6. Frequencies of DRB1*04 and DRB1*08 subtypes linked to the DQA1*03:01-DQB1*03:02 haplotype in Japanese and Korean rapid-onset T1D. T1D, Type 1 diabetes; OR, Odds ratio; NS, not significant.

The DRB1*08:02 subtype is the most frequent in DRB1*04 and DRB1*08 subtypes linked to the DQA1*03:01-DQB1*03:02 haplotype (56.3% and 84.2%, respectively) and confers susceptibility to rapid-onset T1D in the Japanese population, whereas the DRB1*08 subtype is the third most frequent (16.7%) after DRB1*04:01 and *04:05 and does not confer susceptibility to rapid-onset T1D in the Korean population. The susceptibility of the DR8 haplotype to Japanese rapid-onset T1D might originate from the distribution of DRB1*04 and DRB1*08 subtypes linked to the DQA1*03:01-DQB1*03:02 haplotype.

4.3 DRB1*09:01-DQA1*03:02-DQB1*03:03 (DR9) haplotype

As with the DRB1*04:05-DQA1*03:03-DQB1*04:01 haplotype, the DR9 haplotype is frequently observed in East Asians, including the Japanese. However, although the DR9 haplotype is present in Caucasians, it is rare in Blacks and Mexican-Americans (Thomson et al., 2007). This haplotype confers susceptibility to T1D in East Asians such as the Japanese,

Koreans (Park et al., 2000), and Filipinos (Bugawan et al., 2002), but generally not in Caucasians (Hermann et al., 2003; Koeleman et al., 2004; Lambert et al., 2004). However, exploratory analyses revealed that the DR9 haplotype confers risk for T1D in Norwegians who do not carry the DR3 or the DR4 haplotype (Undlien et al., 1999). Moreover, Graham et al. demonstrated that the risk of T1D decreased with age for the DR9 haplotype in a Swedish population (Graham et al., 1999). In the Japanese population, it has been reported that the frequency of the DR9 haplotype with an onset age <5 years is greater than that with an onset age >5 years of age at onset (61.5% vs. 43.1%) in childhood-onset T1D (Ohtsu et al., 2005), whereas the ratio of the DR9/DR4 frequency increases with the onset age in childhood- or adult-onset T1D (Murao et al., 2004). Fig. 1 shows the relationship between the frequency of the DR9 phenotype and the mean onset age in previous studies where the DR9 haplotype confers susceptibility to adult-onset T1D in the Japanese (Awata et al., 1992; Imagawa et al., 2005; Kawabata et al., 2002; Kobayashi et al., 1993; Murao et al., 2004; Tanaka et al., 2002). A significant positive correlation is observed between the frequency of the DR9 phenotype and the mean onset age ($r^2 = 0.742$, $P = 0.0274$). The frequency of the DR9 phenotype increases with the mean onset age of T1D in adult-onset Japanese T1D.

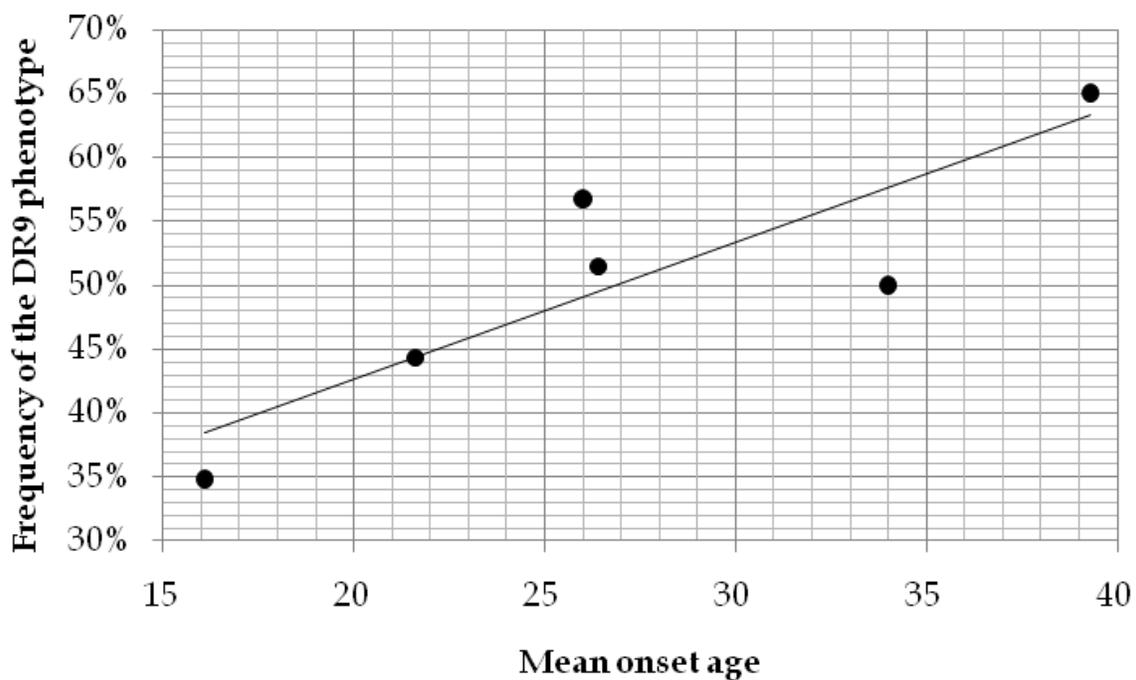


Fig. 1. Relationship between the frequency of the DR9 phenotype and the mean onset age. A significant positive correlation is observed between the frequency of the DR9 haplotype and the mean onset age ($r^2 = 0.742$, $P = 0.0274$). DR9, DRB1*09:01-DQA1*03:02-DQB1*03:03.

4.4 DRB1*13:02-DQA1*01:02-DQB1*06:04 (DR13) haplotype

Although the DR13 haplotype is observed in almost all ethnic groups (Thomson et al., 2007), a few investigators have demonstrated that this haplotype confers susceptibility to T1D in the Japanese (Katahira et al., 2008; Matsuda et al., 1988; Murao et al., 2004), Caucasians (Graham et al., 1999; Undlien et al., 1999), and Latin Americans (Cruz et al., 2004; Balducci-Silano et al., 1994). Table 7 shows the phenotype and haplotype frequencies of the DR13 haplotype in adult-onset Japanese T1D.

Author (publication year)	Mode of onset	Area(s) of diabetes	DR13			Mean onset age
			PF	HF	OR	
Kawabata et al. (2002)	fulminant + rapid	A0 + A1 + B0 + B1	13.6%	6.8%	NS	16
Kobayashi et al. (1993)	fulminant + rapid	A0 + A1 + B0 + B1	13.6%	–	NS	22
Imagawa et al. (2005)	rapid	A1	–	11.7%	NS	26
Awata et al. (1992)	fulminant + rapid	A0 + A1 + B0 + B1	22.2%	–	NS	26
Maruyama et al. (1994)	fulminant + rapid	A0 + A1 + B0 + B1	19.0%	–	NS	30
Tanaka et al. (2002)	rapid	A0 + A1	24.4%	–	NS	34
Katahira et al. (2008)	rapid + slow	A1 + A2 + B1	28.9%	15.1%	3.1	35
Murao et al. (2004)	rapid	A1 + B1	–	7.9%	4.6	39

Table 7. Phenotype and haplotype frequencies of the DR13 haplotype and the mean onset age in Japanese T1D. DR13, DRB1*13:02-DQA1*01:02-DQB1*06:04; T1D, Type 1 diabetes; PF, Phenotype frequency; HF, Haplotype frequency; OR, Odds ratio; NS, not significant.

The average age at onset of diabetes was relatively low in previous studies (Awata et al., 1992; Imagawa et al., 2005; Kawabata et al., 2002; Kobayashi et al., 1993; Maruyama et al., 1994; Tanaka et al., 2002) which did not find a significant susceptibility to DR13 (16–34 years). In contrast, the average age at onset of diabetes was relatively high in previous studies (Katahira et al., 2008; Murao et al., 2004) which did find susceptibility to DR13 (≥ 35 years). Exploratory analyses revealed that the DR13 haplotype might also confer risk for T1D in subjects in Norway, Sweden (Graham et al., 1999; Undlien et al., 1999), and Venezuela (Balducci-Silano et al., 1994) who do not carry the DR3 or the DR4 haplotype. Moreover, Graham et al. demonstrated that the risk of T1D increased with age for the DR13 haplotype (Graham et al., 1999). It has been demonstrated that the DPB1*0301 allele, which exhibits linkage disequilibrium with the DR13 haplotype in Puerto Ricans, confers susceptibility to T1D in this ethnic group (Cruz et al., 2004).

The DR13 haplotype shares the same DQA1 allele with the DRB1*1501-DQA1*0102-DQB1*0602 haplotype which is strongly associated with T1D protection in almost all ethnic groups (Thomson et al., 2007). Moreover, DQB1*0604 and DQB1*0602 differ at seven amino acids, six of which are within the first external domain at $\beta 9$, $\beta 30$, $\beta 57$, $\beta 70$, $\beta 86$, and $\beta 87$, and one within the second external domain at $\beta 130$. Some investigators have suggested that differences in peptide binding between DQB1*0604 and DQB1*0602 contribute to the mechanism of their association with T1D (Ettinger et al., 2006; Sanjeevi et al., 2002).

4.5 Haplotypes associated with T1D protection

The DRB1*1501-DQA1*0102-DQB1*0602 haplotype confers protection against T1D in almost all ethnic groups such as Caucasians and East Asians (Thomson et al., 2007), and the similar

DRB1*1503-DQA1*0102-DQB1*0602 haplotype confers protection against T1D in Blacks, suggesting that the DQA1*0102-DQB1*0602 haplotype is a primary protective molecule in all ethnic groups. On the other hand, DRB1*1502-DQA1*0103-DQB1*0601 and DRB1*0803-DQA1*0103-DQB1*0601 haplotypes are present in East Asians, but rare in Caucasians and Blacks (Thomson et al., 2007). These haplotypes confer weak protection against T1D in the Japanese (Katahira et al., 2008; Yasunaga et al., 1996) and Koreans (Park et al., 2000). As with the DQA1*0102-DQB1*0602 haplotype, the DQA1*0103-DQB1*0601 haplotype encodes “non-Arg,” an amino acid other than arginine, at position 52 in DQ α and aspartic acid at position 57 in DQ β . These are thought to be strongly negatively associated with the development of T1D (Khalil et al., 1990; Todd et al., 1987). Although the DRB1*11-DQA1*05-DQB1*0301 haplotype is observed in almost all ethnic groups (Thomson et al., 2007) and confers protection against T1D in Caucasians (Hermann et al., 2003; Undlien et al., 1999; Yasunaga et al., 1996) and Latin Americans (Volpini et al., 2001), this haplotype confers very weak (Huang et al., 1995; Awata et al., 1992; Katahira et al., 2008) or no protection (Bugawan et al., 2002; Park et al., 2000) against T1D in East Asians, including the Japanese.

5. Conclusions

T1D can be divided into six subtypes based on the mode of disease onset, markers of immune destruction, and insulin deficiency. The relationship between DRB1*04:05-DQA1*03:03-DQB1*04:01, DR8, DR9 and DR13 haplotypes and T1D depends on the mode of disease onset and the mean onset age of the disease. The DRB1*04:05-DQA1*03:03-DQB1*04:01 haplotype is the most frequent in fulminant T1D and solely confers susceptibility to fulminant T1D. The DR8 haplotype confers susceptibility to rapid-onset T1D with onset at a young age. The DR9 haplotype, the frequency of which increases with the mean onset age of T1D, is the most frequent in rapid-onset T1D. The DR13 haplotype confers susceptibility to rapid-onset T1D, with onset at a relatively old age. On the other hand, the DQA1*0102-DQB1*0602 haplotype is the common protective haplotype against T1D in all ethnic groups.

6. References

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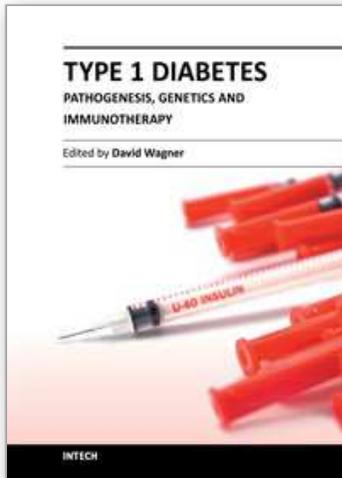
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This book is a compilation of reviews about the pathogenesis of Type 1 Diabetes. T1D is a classic autoimmune disease. Genetic factors are clearly determinant but cannot explain the rapid, even overwhelming expanse of this disease. Understanding etiology and pathogenesis of this disease is essential. A number of experts in the field have covered a range of topics for consideration that are applicable to researcher and clinician alike. This book provides apt descriptions of cutting edge technologies and applications in the ever going search for treatments and cure for diabetes. Areas including T cell development, innate immune responses, imaging of pancreata, potential viral initiators, etc. are considered.

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