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Type 1 diabetes in Japan

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Abstract Type 1 diabetes is a multifactorial disease which results from a T-cell-mediated autoimmune destruction of the pancreatic beta cells in genetically predisposed individuals. The risk for individuals of developing type 1 diabetes varies remarkably according to country of residence and race. Japan has one of the lowest incidence rates of type 1 diabetes in the world, and recognises at least three subtypes of the condition: acute-onset ('classical'), slow-onset, and fulminant type 1 diabetes. The incidence rate of type 1 diabetes in children aged 0–14 years in Japan increased over the period from 1973–1992, but remained constant over the last decade, averaging 2.37 cases per 100,000 persons per year; the incidence does not appear to have increased in older age groups. Although there are few reports regarding the incidence and prevalence of type 1 diabetes in adult-onset patients, it appears that the prevalence of type 1 diabetes in adults is more than twice that in childhood-onset patients and that two-thirds of them have a slow-onset form of type 1 diabetes. Differences and similarities in the association of MHC and non-MHC genes with type 1 diabetes are observed in Japan and in countries with Caucasoid populations. Highly susceptible class II HLA haplotypes identified in patients of Caucasoid origin are rarely seen in Japanese patients, whereas

protective haplotypes are universal. Non-MHC genes associated with susceptibility to type 1 diabetes in both Japanese and Caucasoid patients include polymorphisms in the insulin gene, the cytotoxic T-lymphocyte antigen 4 (*CTLA4*) gene, the interleukin-18 (*IL18*) gene and the major histocompatibility complex class I chain-related gene A (*MICA*) gene. Fulminant type 1 diabetes is a unique subtype of type 1 diabetes that accounts for about 20% of acute-onset type 1 diabetes, and is seen mainly in adults. The challenge for the future is to investigate the underlying pathogenesis of beta cell destruction, including the genetic or environmental factors that may modify the form of onset for each subtype of Japanese type 1 diabetes.

Keywords Adult · Epidemiology · Fulminant · Genetics · HLA · Japanese · Non-HLA · Type 1 diabetes

Abbreviations *CTLA4*: cytotoxic T-lymphocyte antigen-4 · GADAb: anti-glutamic acid decarboxylase antibodies · IA-2: insulinoma associated antigen-2 · ICA: islet cell antibodies · ICA512: islet cell antigen 512 · Lyp: lymphoid phosphatase · *PTPN22*: protein tyrosine phosphatase, non-receptor type 22 · SNP: single nucleotide polymorphism

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Introduction

Type 1 diabetes is an organ-specific autoimmune disease characterised by T-cell-mediated destruction of pancreatic beta cells, resulting in absolute dependence on insulin for survival and maintenance of health [1]. Approximately 90% of cases are sporadic, occurring in individuals with no family history of type 1 diabetes. However, first-degree relatives of patients with type 1 diabetes are at increased risk compared to the general population. In Caucasians, the risk of type 1 diabetes in the general population is 0.4% by age 30 [2] and the risk for siblings of affected individuals is about 6% [3]. Thus λ_s , the ratio of the risk for siblings of type 1 diabetic patients and the risk in the general population, is approximately 15 in Caucasoid populations [4]. In contrast, λ_s for type 1 diabetes in Japan is estimated

to be more than 250 (3.8 vs 0.014%), much higher than that in Caucasoid populations [5]. The reason why the incidence rate of type 1 diabetes is so low in Asian countries, including Japan, is largely unknown.

Type 1 diabetes has traditionally been considered a disease of childhood, but more recent epidemiological studies have indicated that the incidence is comparable in adults [6]. The age-specific incidence rate of type 1 diabetes shows a bimodal distribution. The first peak of incidence rate in patients of Caucasoid origin is at puberty and the second peak after the age of 40 [7]. Furthermore, it has been reported that incidence rates of type 1 diabetes in children are increasing rapidly in many countries [8]. The incidence of type 1 diabetes in the Japanese population peaks twice: once around the age of four (the first peak) and again at puberty (the second peak), both of which are different from peaks in patients of Caucasoid origin [9]. The development of techniques for high-throughput testing of autoantibodies to a series of islet autoantigens has made it possible to diagnose a subgroup of type 1 diabetes in adulthood, termed slowly progressive type 1 diabetes or latent autoimmune diabetes in adults [10, 11]; this subgroup is often misdiagnosed as type 2 diabetes. There may therefore be more patients with type 1 diabetes in adulthood than previously considered. In addition to acute-onset and slow-onset of type 1 diabetes, a new subtype has recently been described in Japan, known as ‘fulminant type 1 diabetes’ [12]. In this paper we review recent research findings on the epidemiology and immunogenetics of type 1 diabetes in Japan, and consider their similarity and differences as compared to those in Caucasoid populations.

Epidemiology of type 1 diabetes in Japan

Several reports have indicated a rapid increase in the incidence of childhood type 1 diabetes worldwide with a rapid rate of increase in children <5 years of age [8, 13]. The most striking increase has been observed in Finland, which has the highest incidence of type 1 diabetes in the world with a rate in excess of 40 cases per year per 100,000 individuals [13]. In the United States and Western Europe, the current incidence rate for type 1 diabetes is second only to that of bronchial asthma in terms of the severe chronic diseases of childhood. Several European countries such as the United Kingdom and Finland have experienced more

than a doubling in incidence of ‘classical’ type 1 diabetes over the past three decades [14, 15]. In contrast, Asian countries including Japan, Korea and China have a low incidence. Because the Japanese are a genetically homogeneous population [16, 17], geo-ethnic variation in type 1 diabetes risk probably reflects differences in the frequencies of modifier genes (susceptibility or protective) or environmental factors (causative or protective) or some combination thereof [18, 19]. It was reported that monozygotic twins and first degree relatives of patients with type 1 diabetes in Japan had a similar risk of diabetes to twins and relatives of patients in the United States [5], suggesting that most of the between-country variation in diabetes risk might relate to genetic differences rather than environmental factors.

Childhood type 1 diabetes

The population-based, long-term epidemiological study of childhood type 1 diabetes in Japan, conducted by the Childhood IDDM Hokkaido Registry Study Group [20], reported that the incidence rates of ‘classic’ type 1 diabetes under 15 years ranged from 0.98 to 2.53 cases per 100,000 persons per year, and that the annual trend obviously increased over the 20-year period between 1973 and 1992, with an overall annual increase of 5.9% [8] (Table 1). The incidence was greatest among children of 10–14 years of age at onset (Table 1), as in most populations studied worldwide [21]. The increase in Japan was mainly due to a rapid increase in the number of children aged 10–14 years, in contrast to countries with populations of Caucasoid origin (Fig. 1a). Accordingly, age at onset increased overall from a mean of 8.72 to 9.92 (Fig. 1b). A significant sex difference (female preponderance; F/M=1.4–1.5) and lack of geographical variation were also noted in Japan [22, 23]. The increase in the incidence of type 1 diabetes from 1973 to 1992 is almost certainly due to environmental factors. Matsuura and co-workers suggested that the year 1985, which had a high incidence of diabetes in their study, coincided with the 10-year time lag from the lowest breast-feeding rate in Japan, as reported in epidemiological studies from Norway and Sweden [20]. In addition, there was an epidemic of Echo 7 in 1986 and of Coxsackie B3 in 1987, both of which could be linked to the higher incidence in that period [24]. Recent data from the Ministry of

Table 1 Incidence rates per 100,000 person-years of type 1 diabetes for ages 0–14 in Japanese population

	Total				Boys	Girls
	0–4 years	5–9 years	10–14 years	0–14 years	0–14 years	0–14 years
1973–1977	0.65	0.84	1.46	0.98	0.72	1.25
1978–1982	0.93	1.46	2.96	1.79	1.62	1.95
1983–1987	1.14	1.58	3.65	2.23	1.57	2.93
1988–1992	1.03	2.20	3.93	2.53	2.53	2.53
1993–1996	0.86	1.56	3.24	2.00	1.78	2.22
1998–2001	1.71	2.24	3.09	2.37	2.06	2.61

Data for 1973–1996 are from Hokkaido

Health, Labor, and Welfare, Government of Japan [25, 26] indicate that the incidence rate of 'classic' type 1 diabetes in patients aged 0–14 years appears to have remained constant over the past decade (1993–2001), averaging 2.37 cases per 100,000 persons per year (Table 1). The current estimate suggests that about 450 children under the age of 15 develop type 1 diabetes in Japan each year.

In Japan, there are two population-based systems to detect childhood diabetes which developed during the mid-1970s; a central registry for free medical care for diabetic subjects under 18 years of age, and urine glucose screening for schoolchildren [27]. In 1994, a revision of the school health law made urine glucose screening mandatory for all elementary, middle and high school students in Japan. Although more than two-thirds of cases with positive urine glucose testing prove to have type 2 diabetes, patients with type 1 diabetes whose clinical manifestations are mild and progress slowly to insulin dependence (slow-onset form of type 1 diabetes) can be identified at the stage of mild hyperglycaemia by this screening. An estimated 10% of children with type 1 diabetes fall into this subgroup. In 1996, the overall number of diabetic children registered in this system was 6,509, of whom about 85% were considered to have type 1 diabetes, indicating that the total number and prevalence of type 1 diabetic children can be estimated to be about 5,500 and 22.5 cases per 100,000 individuals, respectively.

Adult onset type 1 diabetes

Although most diabetes registries have studied disease incidence under age 15 years, around half of new-onset patients with 'classical' type 1 diabetes are diagnosed in adult life [28, 29]. The heterogeneity of diabetes increases with age, and it becomes more difficult to diagnose type 1 diabetes. A significant number of patients, particularly adults, presenting to their physician with what appears to be non-insulin-requiring diabetes are at an early stage of type 1 diabetes [30]. Currently, there are no reports regarding the incidence of adult type 1 diabetes in Japan,

and few prevalence studies have been published, mainly because of the difficulty of distinguishing the slow-onset form of type 1 diabetes from insulin-requiring type 2 diabetes in older individuals. However, better diagnosis is now possible because of the availability of autoantibody assays with high sensitivity and specificity [30, 31]. In our cross-sectional study, autoantibodies to GAD (GADAb) were detected in 3.8% of Japanese diabetic patients who had been treated with diet or oral hypoglycaemic agents for more than half a year after the onset of diabetes. Furthermore, 1.5% were both GADAb-positive and insulin-deficient [32]. Takeda and co-workers found a similar prevalence of GADAb in a larger population-based study, which analysed 4,980 patients with adult-onset diabetes aged >20 years [33]. The prevalence of GADAb in such patients is lower than that in patients of Caucasoid origin and with an initial diagnosis of type 2 diabetes [34], suggesting that Asian adults have a lower incidence of type 1 diabetes than Caucasoid populations [35]. Results of a survey in 2002 [36] estimated the number of adults with diabetes in Japan at 7.4 million. If our results are applied to this figure, the number of insulin-deficient patients with GADAb who were initially diagnosed as having type 2 diabetes would be about 110,000. However, this could be an overestimate, given that the mean age of insulin-deficient patients with GADAb was about 45 years, and that only 0.9 million patients with type 2 diabetes are under 50 years. Therefore, the number of adults with slow-onset type 1 diabetes can be estimated at about 15,000–20,000, or around two-thirds of adult type 1 diabetic patients. A nationwide registry is needed to evaluate the true incidence and prevalence of adult-onset type 1 diabetes in Japan.

Another subtype of adult type 1 diabetes in Japan is fulminant type 1 diabetes [12]. It is not clear whether this type of diabetes is unique to the Japanese population. A nationwide multicentre study under the auspices of the Japan Diabetes Society has indicated that this subtype accounts for approximately 20% of abrupt-onset type 1 diabetes [37]. The clinical and immunogenetic features of fulminant type 1 diabetes are described later.

Fig. 1 Incidence rates of type 1 diabetes per 100,000 persons according to age-group at diagnosis (a) and mean age at onset of type 1 diabetes according to sex (b) in the 0–14-year age range and the period 1973–1992. a 0–4 (●), 5–9 (■), 10–14 (▲) years; b boys (●), girls (■), combined (▲)

Immunogenetic differences between 'classical' type 1 diabetes in Japan and in the West

It has been reported that the genetic background of Japanese type 1 diabetes differs from that of Caucasians (Fig. 2). The high-risk class II HLA haplotype, HLA-*DRB1*0301-DQA1*0501-DQB1*0201*, found in patients of Caucasoid origin with type 1 diabetes, is extremely rare in the Japanese general population. However, *DQB1*0201* is almost universally found in excess among patients with type 1 diabetes when compared to control subjects, even in Japan [38]. The major susceptible haplotypes in Japanese 'classical' type 1 diabetes are *DRB1*0405-DQA1*0301-DQB1*0401* and *DRB1*0901-DQA1*0301-DQB1*0303*. It has been reported that *DQB1*0402*, which differs by only one amino acid from the *DQB1*0401* molecule and is relatively rare in the general population of Caucasoid origin, is a highly susceptible DQ allele in that ethnic group according to the transmission disequilibrium test [39]. Furthermore, the HLA-*DR2* haplotypes, *DRB1*1501-DQA1*0102-DQB1*0602* and *DRB1*1502-DQA1*0103-DQB1*0601*, are negatively associated with type 1 diabetes in Japanese people. Although the latter haplotype is rare in people of Caucasoid origin and in Blacks, *DRB1*1501-DQA1*0102-DQB1*0602* is also associated with disease protection in the former, and the similar *DRB1*1503-DQA1*0102-DQB1*0602* is associated with resistance in Blacks [40], suggesting that *DQA1*0102-DQB1*0602* is a primary protective molecule. This HLA-linked protection from type 1 diabetes is dominant over susceptibility, consistent with observations in the NOD mouse, in which one dose of non-NOD MHC provides strong protection against diabetes [41]. Among Japanese patients with type 1 diabetes both *DRB1*0405-DQB1*0401* and *DRB1*0901-DQB1*0303* confer susceptibility to childhood-onset type 1 diabetes, whereas *DRB1*0405-DQB1*0401* is the only susceptibility class II HLA haplotype in adult-onset type 1 diabetes [42], suggesting that *DRB1*0901-DQB1*0303* may uniquely predispose to early clinical presentation. In contrast to the highest risk seen with the *DRB1*0301/*0401* or **0402* (with *DQB1*0302*) heterozygote in Caucasoid populations, the *DRB1*0405/*0901* heterozygote has no synergistic effect in the Japanese population, which can be explained by the *trans* complementation of the DQ α β heterodimer [43, 44].

Kawabata and co-workers recently reported an interesting association of genotypic combinations of Asian *DRB1-DQB1* haplotypes with susceptibility to type 1 diabetes in Japanese and Koreans [45]. Among the susceptible class II HLA in Japanese 'classical' type 1 diabetes, the odds ratios of homozygotes and heterozygotes with the *DRB1*0405-DQB1*0401* haplotype were similar. In contrast, homozygotes, but not heterozygotes, with the *DRB1*0901-DQB1*0303* haplotype were more frequent in people with type 1 diabetes. The genetic contribution of the *DR4* and *DR9* haplotypes thus differs depending on the genotypic combination of the haplotypes: the *DRB1*0405-DQB1*0401* haplotype predisposes to type 1 diabetes in

Fig. 2 Type 1 diabetes susceptibility HLA-*DRB1* allele in the Japanese, Korean and Caucasoid-origin populations

a dominant fashion, whereas *DRB1*0901-DQB1*0303* predisposes in a recessive fashion. Interestingly, susceptibility to type 1 diabetes in *DRB1*0901-DQB1*0303* homozygotes was also observed in the Korean population, where the HLA-*DRB1*0301-DQB1*0201* haplotype is present in addition to Asian-specific *DRB1*0405-DQB1*0401* and *DRB1*0901-DQB1*0303* haplotypes (Fig. 2), indicating that the *DRB1*0901-DQB1*0303* haplotype in itself confers susceptibility to type 1 diabetes in the absence of other susceptibility haplotypes (Table 2). These findings indicate that the Japanese population lacks the highly susceptible class II HLA haplotype of type 1 diabetes, and that the moderately susceptible *DR-DQ* haplotype may then surface as a major haplotype of the disease, consistent with the low incidence of type 1 diabetes in Japan.

Autoimmune type 1 diabetes is a polygenic disorder, and it seems clear that more than one genetic syndrome can cause autoimmune beta cell destruction. Among the genetic factors associated with type 1 diabetes, approximately 50% of the risk is attributable to the HLA region. The much higher rate of concordance in monozygotic twins of patients than HLA-identical siblings indicates that in addition to genes in the HLA region, other genes are involved in genetic susceptibility to type 1 diabetes.

Table 2 Different contribution of HLA-*DRB1*0405* and *DRB1*0901* haplotypes to Japanese or Korean type 1 diabetes

DRB1-DQB1 genotype	Odds ratio	
	Japanese	Korean
<i>DRB1*0405-DQB1*0401/DRB1*0405-DQB1*0401</i>	2.10	2.21
<i>DRB1*0405-DQB1*0401/X</i>	2.81	3.64
<i>DRB1*0901-DQB1*0303/DRB1*0901-DQB1*0303</i>	23.1	13.3
<i>DRB1*0901-DQB1*0303/Y</i>	1.01	3.06

Modified from [45]

X Other than *DRB1*0405-DQB1*0401*, Y other than *DRB1*0901-DQB1*0303*

Although more than 20 putative non-MHC chromosomal regions have been implicated in disease risk, only a few with known function have been identified, including *IDDM2* (insulin gene) [46], *IDDM5* (small ubiquitin-like modifier 4 [*SUMO4*] gene) [47], *IDDM12* (cytotoxic T-lymphocyte antigen-4 [*CTLA4*] gene) [48], and *IDDM18* (*IL12B* gene) [49]. We and others reported the association between non-MHC genes and susceptibility to or heterogeneity of Japanese type 1 diabetes. The insulin gene hypervariable region (chr. 11p15), *CTLA4* gene polymorphism (chr. 2q33), *IL18* gene polymorphism (chr. 11q22), and the major histocompatibility complex class I chain-related gene A (*MICA*) microsatellite polymorphism (chr. 6q21) are associated with type 1 diabetes susceptibility in both Japanese [50–53] and people of Caucasoid origin [54–57]. However, several genes have been reported to be susceptibility genes in Japanese, but not in Caucasoid populations, including the genes encoding IFN- γ [58], NeuroD [59], vitamin D receptor [60], and forkhead box 3 [61]. These discrepancies may be caused by differences in the contribution to disease development of each gene, depending on ethnic group, or by the possible presence of another functional variant in linkage disequilibrium with certain polymorphisms.

Recently, a missense SNP at nucleotide 1858 in codon 620 (R620W) of protein tyrosine phosphatase gene (*PTPN22*), located on chromosome 1p13.3–p13.1, has been reported to be associated with multiple autoimmune diseases including type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, Graves' disease, and Addison's disease [62–66] in Caucasoid populations, implying that the lymphoid phosphatase (Lyp) encoded by *PTPN22* is a critical player in multiple autoimmune disorders. Lyp is expressed in lymphocytes and binds to cytoplasmic tyrosine kinase, Cas-Br-M murine ecotopic enteroviral transforming sequence, and growth factor receptor-bound protein 2, which mediate T cell receptor signalling. Furthermore, Lyp is among the most powerful inhibitors of T cell activation, a task accomplished by dephosphorylation of such molecules. However, we found that this locus was monomorphic in the Japanese population, and that the association was stronger in the promoter SNP than in R620W SNP even in multiplex families of white European origin [67]. These ethnic differences may be associated with susceptibility to or clinical outcomes of type 1 diabetes, and it will be necessary to investigate by biological analysis the mechanisms by which the variants produce disease susceptibility, as well as to investigate the origin of the variants by genetic dissection.

Fulminant type 1 diabetes

According to the current classification of diabetes by the American Diabetes Association Expert Committee and the WHO Consultation, type 1 diabetes can be divided into two subtypes, immune-mediated (type 1A) diabetes and idiopathic (type 1B) diabetes [68, 69]. Type 1B diabetes is defined as diabetes not associated with immunological

evidence of beta cell autoimmunity but for which insulin therapy is required for survival. We have screened autoantibodies to multiple islet antigens, including GAD, islet cell antigen 512 (ICA512)/insulinoma-associated antigen-2 (IA-2) and insulin, as well as islet cell antibodies (ICA) in Japanese patients at onset of type 1 diabetes. Our study indicated that about 10% of Japanese patients with type 1 diabetes have type 1B diabetes without expression of any autoantibodies [70]. Furthermore, these patients had different clinical characteristics from African American or North American patients with idiopathic type 1 diabetes, some of whom, in fact, have type 2 diabetes [71, 72].

Type 1B diabetes is probably a heterogeneous insulin-deficient form of diabetes not mediated by autoimmunity. It is well-known that several disorders other than type 1A diabetes lead to extensive pancreatic islet beta cell destruction including MODY1, MODY3, Wolfram's syndrome, and mitochondrial diabetes [1]. Indeed, we found that about 7% of Japanese patients with type 1B diabetes have mutations in the gene encoding hepatocyte nuclear factor 1 α , which are the cause of MODY3 [73]. These disorders often have characteristic inheritance patterns or extra-pancreatic disease manifestations. Imagawa and co-workers proposed that a group of Japanese patients that presented with diabetic ketoacidosis and a low HbA_{1c} level had fulminant type 1 diabetes [12]. Cases resembling fulminant type 1 diabetes were described in Japan as early as 1987 [74]. Fulminant type 1 diabetes exhibits distinct clinical features from type 1A diabetes, and is characterised by: (1) remarkably rapid onset with diabetic ketoacidosis; (2) very short duration of diabetic symptoms; (3) male predominance; (4) onset mainly in adult life; (5) high frequency of 'flu-like' symptoms prior to onset; (6) permanent insulin dependence from diagnosis; (7) negative for islet-related autoantibodies; (8) elevated serum pancreatic enzyme levels; (9) lymphocytic infiltration in the exocrine pancreas; and (10) destruction of pancreatic alpha cells and beta cells. In women, pregnancy may also be a

Diagnostic criteria for fulminant type 1 diabetes

1. Occurrence of diabetic ketosis or ketoacidosis soon after (around 7 days) the onset of hyperglycaemic symptoms (elevation of urinary ketone or serum ketone at onset)

and

2. Plasma glucose > 16.0 mmol/l and HbA_{1c} level < 8.5% at onset

and

3. either
Urinary C-peptide excretion < 10 μ g/day
or
Fasting serum C-peptide < 0.1 nmol/l and serum C-peptide < 0.17 nmol/l after i.v. glucagon or meal load

From the Committee on the Study of Fulminant Type 1 Diabetes, Japan Diabetes Society [85]

risk factor for fulminant type 1 diabetes. The nationwide multicentre study under the auspices of the Japan Diabetes Society suggested that this subtype accounts for approximately 20% of acute-onset type 1 diabetes presenting with ketosis or ketoacidosis [38]. The text box shows the diagnostic criteria for fulminant type 1 diabetes currently established by the Committee for the study of fulminant type 1 diabetes.

The underlying pathogenesis is largely unknown. Class II HLA may contribute to the development of fulminant type 1 diabetes, but if so, susceptible and resistant HLA subtypes differ from those found in type 1A diabetes [75]. Thus, of the type 1A diabetes susceptibility haplotypes, *DRB1*0405-DQB1*0401* and *DRB1*0901-DQB1*0303*, only the former is a susceptibility haplotype in fulminant type 1 diabetes. In addition, *DRB1*1502-DQB1*0601* or *DRB1*1501-DQB1*0602*, two major protective haplotypes in Japanese type 1A diabetes, are not protective in fulminant type 1 diabetes.

It has recently been reported that GAD-reactive or insulin-B9-23-reactive Th1 cells were identified in peripheral blood lymphocyte from patients with fulminant type 1 diabetes [76]. Furthermore, insulinitis has also been reported following autopsy of a fatal case of fulminant type 1 diabetes [77]. These findings suggest that the aetiology of fulminant type 1 diabetes might be heterogeneous and in part autoimmune. The mechanism of beta cell destruction in fulminant type 1 diabetes requires further investigation.

Conclusion

Although the incidence and prevalence of type 1 diabetes are much lower in Japan than in countries with Caucasoid populations, the recurrence risk in siblings of patients with type 1 diabetes is much higher, indicating that in Japanese people type 1 diabetes clusters in families. If genetic factors are responsible for the high λ_s value for type 1 diabetes in a low-prevalence population such as the Japanese, susceptibility genes whose frequencies are very low in the general population may be segregating in type 1 diabetes families. It is, however, also possible that some environmental factors common to type 1 diabetic families are responsible for the high λ_s value for type 1 diabetes in Japan.

It has been suggested that, in Asian populations, the protective HLA-*DR4* (*DRB1*0403* or **0406*) is associated with the susceptible *DQ* allele (*DQB1*0302*) encountered in Caucasoid populations, while the neutral/protective *DQ* allele (*DQB1*0401*) is associated with the susceptible *DR4* allele (*DRB1*0401*, **0402*, **0405*) [78]. This counterbalancing between susceptible *DRB1* and protective *DQB1*, and vice versa, might be an important contributory factor to the low incidence of type 1 diabetes in the Japanese population.

Clinical features of Japanese type 1 diabetes are heterogeneous in terms of age at onset, mode of onset, and aetiology. However, the prevalence and expression of a series of anti-islet autoantibodies are comparable to those

in patients of Caucasoid origin [70], indicating that the humoral immune responses to islet antigens in Japanese patients are similar to those in patients of Caucasoid origin. There are at least three subtypes of type 1 diabetes in Japan, acute-onset 'classical', slow-onset, and fulminant type 1 diabetes. In childhood type 1 diabetes, about 90% have the 'classical' form, and the remainder belong to the slow-onset form, with minimal or no clinical symptoms of diabetes at disease onset. The slow-onset form of type 1 diabetes in children is detected by urine glucose screening at school, and affects 1/20,000 school children [79]. It is further estimated that <1% of patients with childhood-onset type 1 diabetes have fulminant type 1 diabetes [38]. In contrast, about two-thirds of adult patients have the slow-onset form, and about 20% of those with acute-onset type 1 diabetes fall into the category of fulminant type 1 diabetes. The different proportions of each subtype in childhood-onset and adult-onset type 1 diabetes may be influenced by MHC and non-MHC genes affecting the age of onset [80].

Fulminant type 1 diabetes is a subtype that is distinct from type 1A diabetes in terms of clinical features, genetic background, and (probably) mechanisms of beta cell destruction. It is currently unknown how far this is unique to the Japanese population, but a few cases have been reported from Western countries [72, 81]. The underlying pathogenesis remains unclear, although the high frequency of 'flu-like' symptoms just before the onset of fulminant type 1 diabetes suggest that it might be associated with viral infection. Two case reports have described fulminant type 1 diabetes developing after the reactivation of human herpes virus-6 or infection with the herpes simplex virus [82, 83]. Elevation of IgA antibodies to enterovirus has also been observed in patients with fulminant type 1 diabetes [84], suggesting that recurrent enterovirus infection may be one of the triggers for the development of fulminant type 1 diabetes.

The challenge for the future is to identify all the MHC and non-MHC genes or environmental factors involved in the pathogenesis of beta cell destruction for each subtype of Japanese type 1 diabetes. Furthermore, the elucidation of their pathogenic roles should facilitate the development of rational therapies for the prevention of type 1 diabetes.

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