Acta Med. Nagasaki 47 : 81－88

Review Article

Immunogenetic Heterogeneity of Type 1 Diabetes in Japan

Eiji KAWASAKI[1)], Akane IDE[2)], Norio ABIRU[1)], Katsumi EGUCHI[2)]

1)Unit of Metabolism / Diabetes and Clinical Nutrition, Nagasaki University School of Medicine
2)First Department of Internal Medicine, Graduate School of Biochemical Sciences, Nagasaki University

Type 1 diabetes is an organ-specific autoimmune disease characterized by T-cell mediated destruction of pancreatic β-cells. In Japanese population, the incidence of type 1 diabetes in children is very low compared to European countries. However, there are more patients with type 1 diabetes in adults, including latent autoimmune diabetes in adults (LADA). A variety of environmental and genetic factors are involved in the development of the disease. The human leukocyte antigen (HLA) class II genes (termed IDDM1) are the major genes associated with susceptibility to type 1 diabetes. HLA-DRB1*0405-DQB1*0401, HLA-DRB1*0901-DQB1*0303 and HLA-DRB1*0802-DQB1*0302 are three major haplotypes in Japanese patients with type 1 diabetes. Other genetic factors reported in Japanese type 1 diabetes include the polymorphisms in insulin gene (IDDM2), CTLA-4 gene (IDDM12), MICA gene, Neuro D/Beta 2 gene, and IL-10 gene.

The circulating autoantibodies to multiple islet autoantigens including GAD, insulin, and IA-2 are the important immunological features of type 1 diabetes. The prevalences of anti-islet autoantibodies in patients with Japanese type 1 diabetes are 60-70% for GAD autoantibodies, 45-50% for insulin autoantibodies (IAA), and 60-65% for IA-2 autoantibodies at disease onset, which are similar to those reported in Caucasian patients. With combinatorial analysis of these autoantibodies ninety percent of patients express at least one of these autoantibodies and are classified as immune-mediated type 1 diabetes. Although the majority of patients with type 1 diabetes are young, lean, and ketosis-prone, there are number of patients with type 1 diabetes initially diagnosed as having type 2 diabetes at disease onset. These slow-onset diabetic patients with anti-islet autoantibodies often progress toward insulin-deficient state within several years after diagnosis. High level of GAD autoantibodies has a high predictive value for future insulin deficiency in slow-onset patients with type 1 diabetes. In conclusion, Japanese patients with type 1 diabetes are clinically heterogenous and the determination of immunological and genetic features are helpful to clarify the characteristics of the Japanese type 1 diabetic syndrome.

ACTA MEDICA NAGASAKIENSIA 47 : 81－88, 2002

Key Words: type 1 diabetes, autoantibodies, genetics, heterogeneity, immunology, autoantigen

Address Correspondence: Eiji Kawasaki, M.D.
Unit of Metabolism/Diabetes and Clinical Nutrition, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
Recipient of **Tsunoo Scientific Award**, Nagasaki University School of Medicine, 2002
TEL: +81-95-849-7550 FAX: +81-95-849-7552
E-mail: eijikawa@net.nagasaki-u.ac.jp

Introduction

Multiple types of diabetes mellitus have been defined by the recent reports of an American Diabetes Association Expert Committee and a WHO Consultation based on our current understanding of pathogenesis rather than the requirement for insulin therapy[1,2)]. Type 1 diabetes is often associated with chronic and progressive autoimmune destruction of islet β-cells with a long prodromal phase. This type of type 1 diabetes is classified as "immune-mediated" (type 1A) diabetes. Another type of type 1 diabetes is a disease with no evidence of an autoimmune disorder at disease onset and classified as "idiopathic" (type 1B) diabetes . On the other hand, type 2 diabetes results from defect in insulin secretion, almost always with a major contribution from insulin resistance.

Type 1A diabetes is characterized by T cell-mediated destruction of β-cells in genetically susceptible individuals[1)] and is associated with the presence of autoantibodies to multiple islet cell antigens[3)]. During the past decade, there has been a remarkable increase in the number of candidate genes for susceptibility of type 1 diabetes and biochemically defined autoantigens found to be targets of the autoimmune process.

The risk for individuals of developing type 1 diabetes varies remarkably based on the country of residence and race. In Caucasian populations, including those in Northern Europe, type 1 diabetes incidence rates are high with rates in excess of 30 cases/year/100,000 individuals. In contrast, Japanese population have one of the lowest incidence rate of type 1 diabetes in the world, 1.6 cases/year/100,000 individuals, suggesting that Japanese population may lack an important susceptibility gene or may have a unique protective gene of type 1 diabetes[4,5]. Rigorous efforts are being made to characterize the immunogenetic heterogeneity of type 1 diabetes in Japan. In this paper we review the genetic and immunological research findings on Japanese type 1 diabetes and attempt to clarify the characteristics of the Japanese type 1 diabetic syndrome.

GENETICS OF TYPE 1 DIABETES IN JAPAN

As type 1 diabetes is an etiologically and genetically heterogeneous disease, the expression of disease phenotype is influenced by a number of susceptibility genes as well as environmental factors. Recent advances in research on type 1 diabetes include the genome-wide search for susceptibility genes[6]. More than 20 putative diabetes-predisposing genes identified by linkage and association studies (Table 1). Among these, most of the genetic susceptibility for type 1 diabetes is determined by HLA genes. These HLA region susceptibility genes are collectively referred to as IDDM1. Although genes responsible for most IDDM loci are still unknown, the gene for IDDM2, IDDM12, and IDDM18 have been identified. In this section, we will review the HLA and non-HLA genes that contribute to diabetes susceptibility and heterogeneity in Japanese type 1 diabetes.

A. HLA Genes (IDDM 1)

Many studies have shown that the human leukocyte antigen (HLA) class II loci on chromosome 6q21.3 including HLA-DRB1, DQB1 and DQA1, are most strongly associated with diabetes risk. HLA class II haplotypes associated with Japanese type 1 diabetes are shown in Table 2[7]. DRB1*0405-DQA1*0301-DQB1*0401, DRB1*0901-DQA1*0301-DQB1*0303 and DRB1*0802-DQA1*0301-DQB1*0302 are three major diabetes-susceptible haplotypes in Japanese. In contrast, DQA1*0301-DQB1*0302 with HLA-DRB1*0401, *0402 or *0405 alleles and DRB1*0301-DQA1*0501-

Table 1. Putative susceptibility loci for type 1 diabetes

	Locus	Candidate gene
IDDM1	6q21.3	HLA
IDDM2	11p15	Insulin gene
IDDM3	15q26	
IDDM4	11q13	LDL receptor related protein 5
IDDM5	6q25	
IDDM6	18q21	
IDDM7	2q31	
IDDM8	6q27	
IDDM9	3q21-q25	CD80 and CD86
IDDM10	10p11-q11	
IDDM11	14q24.3-q31	
IDDM12	2q33	CTLA-4 gene
IDDM13	2q35	
IDDM14	-	
IDDM15	6q21	
IDDM16	14q32.3	
IDDM17	10q25	
IDDM18	5q31.1-q33.1	IL-12 p40 gene
Unnamed	1q42	
Unnamed	16q22-q24	
Unnamed	19p13	
Unnamed	19q13	
Unnamed	Xp13-p11	
Unnamed	7p13	Glucokinase gene
Unnamed	12q14-q15	Interferon γ gene

Table 2. HLA class II haplotypes associated with Japanese type 1 diabetes

DRB1	DQA1	DQB1	Type 1 diabetes (%)	Control (%)	Relative risk
Susceptibility					
0405	0301	0401	35-57	20-28	3-4
0901	0301	0303	35-52	30-33	1-2
0802	0301	0302	10-14	1-3	4-10
0405	0301	0302	3-9	~0	6-27
0301	0501	0201	0-5	0-1	1-5
Resistance					
1501	0102	0602	~1	13-22	~0.1
1502	0103	0601	2-4	14-23	0.1-0.2
0406	0301	0302	0-1	5-7	0.1-0.2

From Awata and Kanazawa[7].

DQB1*0201 are the haplotypes associated with the highest risk for type 1 diabetes in Caucasians. The latter haplotype is rare in Japanese population but DQB1*0201 is almost universally found in excess among patients with type 1 diabetes compared to control even in Japanese[8]. Kawabata and coworkers currently reported an interesting association of genotypic combinations of Asian DRB1-DQB1 haplotypes with susceptibility to type 1 diabetes in Japanese[9]. The frequencies of heterozygotes and homozygotes with DRB1*0405-DQB1*0401 are similarly higher in patients than in control subjects. In contrast, homozygotes, but not heterozygotes, with DRB1*0901-DQB1*0303 are more frequent in patients with type 1 diabetes than in control subjects. They suggest that the contribution of HLA haplotypes to the genetic susceptibility to type 1 diabetes differs depending on the genotypic combination of HLA haplotypes: the DRB1*0405-DQB1*0401 haplotype shows best fit in a dominant model, whereas the DRB1*0901-DQB1*0303 haplotype fits in a recessive model. The DR2 haplotypes, DRB1*1501-DQA1*0102-DQB1*0602 and DRB1*1502-DQA1*0103-DQB1*0601, were negatively associated with type 1 diabetes in Japanese. The latter haplotype is rare in Caucasians and Blacks. However, DRB1*1501-DQA1*0102-DQB1*0602 is also associated with resistance in Caucasians, and the similar DRB1*1503-DQA1*0102-DQB1*0602 is associated with resistance in Blacks, suggesting that DQA1*0102-DQB1*0602 is a primary protective molecules.

B. Non-HLA Region Genes

Table 3 summarizes the non-MHC genes which has been studied in the association with susceptibility to or heterogeneity of type 1 diabetes in Japanese.

IDDM2: Insulin Gene

The insulin gene (INS) on chromosome 11p15 (IDDM 2) has a variable number of tandem repeats (VNTR) in the 5' region of the gene. Polymorphisms in this non-coding region of the insulin gene are associated with the risk of type 1 diabetes and influence thymic insulin mRNA expression. The VNTR is comprised of 14- to 15-bp oligonucleotides and is classified into three classes according to their size: class I (26-63 repeats), class II (approximately 80 repeats) and class III (140-200 repeats). In Caucasians, the shortest class I allele is susceptible to type 1 diabetes, while the longest class III allele is protective[10,11]. In Japanese population, the INS-VNTR region is less polymorphic and approximately 95 % of Japanese are homozygous for class I alleles. Then no significant differences of class I or class III alleles are found between Japanese patients with type 1 diabetes and control subjects[12,13]. However, when class I allele was further divided based on the number of repeats and sequence, the shortest component (1S; 25-38 repeats) was associated with susceptibility to type 1 diabetes in Japan[14].

Table 3. Non-MHC genes associated with susceptibility to or heterogeneity of type 1 diabetes

Gene	Chr.	Region	Allele	Comment.
INS (*IDDM2*)	11p15	5' VNTR	class I,II,III	No association with susceptibility [12,13]
			RUs in class I	Association with susceptibility [14]
IA-2	2q35-36.1	D2S1753E	161,165mu	No association with susceptibility or heterogeneity [50]
CTLA-4 (*IDDM12*)	2q33	3' untranslated	(AT)n	No association with susceptibility in child onset diabetes [17] Association with susceptibility in adult onset diabetes [18]
		at position 49 in exon 4	A/G	Association with heterogeneity (acute-onset diabetes) [20,21]
MICA	6q21	(GCT/AGC)n in TM region	A4, 5, 5.1, 6, 9	A4: association with susceptible haplotype A6: association with protective haplotype A5.1: association with age-at-onset [26]
NeuroD/ BETA2	2q32	Codon 45 in coding region	G/A (Ala45Thr)	Association with susceptibility [51] No association with heterogeneity (acute onset but not slow onset) [27]
VDR	12q12-q14	VDR-FokI	F/f	Association with susceptibility [36]
SDF-1	10q11	3' untranslated	A/G	Association with age-at-onset [37]
IL-18	11q22.2-q22.3	5' promoter region	-607 C/A -137 G/C	Association with susceptibility [33]
TNF-α	6q21.3	5' promoter region	-1,031 C/T -857 C/T -863 C/A	Association with susceptibility haplotype [31]
IFN-γ	12q4	First intron	(CA)n	Association with susceptibility [32]
IL-10	1q31-q32	5' promoter region	-1082 A/G -819 T/C -592 C/A	Association with age-at-onset [30]

IDDM12: CTLA-4 Gene

The cytotoxic T lymphocyte antigen-4 (CTLA-4) gene, on chromosome 2q33, encodes a receptor expressed on activated T cells. The CTLA-4 binds to the CD28/B7 molecule on the antigen-presenting cell, delivers a negative signal to the T cell and mediates apoptosis. Association has been found between CTLA-4 gene polymorphisms, including the (AT)n microsatellite marker in the 3' untranslated region and the A/G polymorphism in the first exon of the CTLA-4 gene, and type 1 diabetes in separate family-based studies in Spanish, French, Mexican-American, Chinese, and Korean populations[15]. The (AT)n polymorphism in the 3' untranslated region of exon 4 of the CTLA-4 gene

was reported to represent a recessive risk factor for type 1 diabetes in Swedish patients[16]. In Japanese population, it has been reported that the frequency of the 86-bp allele is significantly lower in child-onset, especially in early-onset (onset age ≤ 5 years), patients with type 1 diabetes than that in normal control subjects[17]. However, in adult-onset patients with type 1 diabetes, lack of associations with the (AT)n microsatellite was reported[18].

The CTLA-4 with G allele at position 49 (codon 17) is less effective in inhibiting the proliferation of activated T-cells than that with A allele, possibly because the Thr/Ala substitution in the leader peptide may alter endocytosis or surface tracking of the CTLA-4 molecule[19]. The frequency of the G allele has been reported to be associated with type 1 diabetes with acute-onset or insulin-depletion[20]. Our data demonstrated that the presence of IA-2 autoantibodies, but not GAD autoantibodies, was associated with allele frequencies of A/G polymorphism. As shown in Table 4 the frequency of G allele was significantly increased in type 1 diabetic patients with IA-2 autoantibodies compared to that in IA-2 autoantibody-negative patients[21]. However, lack of associations between the A/G polymorphism and type 1 diabetes was observed in slow onset diabetic patients with GAD autoantibody-positive in adults[18,22]. These results suggest that the CTLA-4 gene A/G polymorphism at position 49 may contributes the mode of onset and immunological heterogeneity of type 1 diabetes in Japanese population.

Table 4. CTLA-4 gene polymorphism in Japanese patients with type 1 diabetes and GAD autoantibody-positive NIDDM

		Genotype				Allele	
	n	GG	GA	AA	*p* value	G allele frequency	*p* value
Type 1 diabetes	75	44 (59)	26 (35)	5 (6)	0.007*	114 (76)	0.002*
GAD Ab^+ NIDDM	51	15 (29)	24 (47)	12 (24)	0.118*	54 (53)	0.060*
IA-2Ab^+ type 1	21	14 (67)	7 (33)	0 (0)	0.028†	35 (83)	0.004†
IA-2Ab^- type 1	48	18 (37)	21 (44)	9 (19)		57 (59)	
Normal controls	445	177 (40)	207 (46)	61 (14)		561 (63)	

Data are n (%). *Comparison between GAD Ab^+ NIDDM and type 1 diabetes with normal controls by χ^2 test;†Comparison between IA-2Ab^+ and IA-2Ab^- type 1 diabetes by χ^2 test.
Ab, autoantibodies

MICA Gene

The MHC class I genes termed MICA (MHC class I chain-related genes) was identified near the HLA-B gene on the short arm of chromosome 6[23,24]. It has been reported that the triplet repeat microsatellite polymophism of (GCT/AGC)n (designated A4, A5, A5.1, A6, A9) in the TM region (exon 5) of MICA gene and an allele of A6 is strongly associated with Japanese patients with Behçet disease[25]. In Japanese patients with type 1 diabetes, A4 allele was associated with disease susceptibility, while A6 allele showed the protective effect[26]. However, A4 allele is associated with a susceptible haplotype DR4 and A6 allele with protective haplotype, DR2, suggesting the association of MICA with type 1 diabetes susceptibility may be due to linkage disequilibrium with HLA class II haplotype.

Other Non-MHC Genes

The polymorphisms (Ala45Thr) of NeuroD/BETA2 gene, encodes a transcription factor of the insulin gene and is located on chromosome 2q32 where the IDDM7 gene has previously been mapped, has been reported to be associated with predisposition of typel diabetes. Yamada and coworkers found a significant difference in Ala45Thr allele frequency between acute-onset patients with type 1 diabetes and control subjects, regardless of the presence of anti-islet autoantibodies. However, no difference was found between slow-onset patients with type 1 diabetes and control subjects, suggesting that NeuroD/BETA2 may affect the ability of regeneration of β-cells, leading to a difference in the onset pattern and clinical course of type 1 diabetes[27].

The association between polymorphisms in the cytokine or cytokine receptor gene and type 1 diabetes have also been reported. IL-10 has generally been associated with immunosuppression to prevent diabetes in NOD mice[28]. However, acceleration of diabetes occurs in transgenic mice with constitutive β-cell expression of IL-10[29]. We have recently studied an association between the polymorphisms in the IL-10 gene, located on chromosome 1q31-q32, and disease susceptibility to or heterogeneity of type 1 diabetes in Japanese. The IL-10 gene promoter region polymorphisms were not associated with susceptibility to type 1 diabetes. However, the haplotype of IL-10 gene that relates to low production of IL-10 was strongly associated with older age at onset[30]. Biallelic polymorphisms in the TNF-α gene located on chromosome 6q21.3 were reported to be associated with susceptibility to type 1 diabetes. However, this association was found to be secondary to their linkage disequilibrium with the HLA-B and HLA-DRB1 alleles[31]. IFN-γ gene located on chromosome 12q4 is another gene associated with predisposition to type 1

diabetes in Japanese population, especially in patients with juvenile (<10 years) or abrupt-onset of diabetes[32]. Recently, we found that the polymorphism of the IL-18 gene located on chromosome 11q22.2-q22.3 is associated with a susceptibility to Japanese type 1 diabetes[33].

Vitamin D has important immunomodulatory effects and influences insulin secretion[34] and an administration of vitamin D prevents the development of diabetes in the NOD mouse[35]. The initiation codon polymorphism (F allele/ the FF genotype) in exon 2 of the Vitamin D receptor gene was also reported to influence the genetic susceptibility to type 1 diabetes in Japan[36]. Stromal-derived factor (SDF)-1 (CXC chemokine ligand 12) is a powerful chemoattractant cytokine, which regulate T-cell activation and migration. The SDF-1 gene is located on chromosome 10q11 near IDDM10 and there is a polymorphism in the 3' untranslated region of the gene. We have found that the variant of the SDF-1 gene is associated with age-at-onset of type 1 diabetes in Japanese population[37].

IMMUOLOGY OF JAPANESE TYPE 1 DIABETES

In accordance with the view that development of type 1 diabetes involves heterogeneous mechanisms, different clinical courses of β-cell destruction have been reported in Japanese population. The most prevalent clinical classification of type 1 diabetes is abrupt-onset with severe clinical symptoms with ketoacidosis. The peak age of onset of type 1 diabetes in Japan is 10-12 years old, in accordance with the age-related distribution in the Caucasian population. Other subtype of type 1 diabetes in the Japanese population is a slow-onset from of diabetes as having NIDDM at onset. Slow-onset patients with type 1 diabetes are also referred as "latent autoimmune diabetes in adults (LADA)" or "slowly progressing IDDM"[38~40]. Imagawa and coworkers reported another form of type 1 diabetes characterized by extremely rapid onset and is associated with pancreatic exocrine inflammation among Japanese patients with type 1 diabetes (called as Fulminant type 1 diabetes)[41]. These patients present with diabetic ketoacidosis and a low HbA1c level at disease onset indicating that the diabetes is of very short duration[41]. Although they have severe hyperglycemia associated with diabetic ketoacidosis, these individuals lack the usual diabetes-related autoantibodies. The pathophysiologic mechanisms involved in this type of diabetes are now exploring by the committee on the study of fulminant type 1 diabetes organized by Japan Diabetes Society.

Autoantibodies to multiple islet autoantigens in Japanese type 1 diabetes

A large number of biochemically defined autoantigens including insulin, GAD65, ICA512/IA-2 have been found to be targets of the autoimmune process which precedes type 1 diabetes onset[42]. Expression of multiple autoantibodies confers a high risk for progression to type 1 diabetes[43]. We determined the distribution of autoantibodies to ICA512/IA-2, GAD, and insulin in Japanese type 1 diabetes patients. Of 73 new-onset patients, the prevalence was 71 % for GAD autoantibodies, 48 % for insulin autoantibodies (IAA), 62 % for ICA512/IA-2 autoantibodies, and 62 % for islet cell antibodies (ICA). Eighty-nine % of patients with recent onset of type 1 diabetes express one or more of three autoantibodies. Of note, eight out of 73 (11%) patients with type 1 diabetes were negative for all of these anti-islet autoantibodies and classified as having type 1B (idiopathic) diabetes (Figure 1)[44]. Table 5 summarizes the comparison of diagnostic sensitivity for type 1 diabetes for the combined analysis of biochemically defined islet autoantibodies versus ICA measured by immunohistochemistry. The sensitivity for the diagnosis of type 1 diabetes was markedly increased when the test for GAD autoantibodies was used in addition to the tests for other islet autoantibodies. Thus, the test GAD autoantibodies in addition to ICA512/ IA-2 autoantibodies or IAA increased positivity to 86 % and 79 %, respectively. As expected, at equal specificity, the combined evaluation of autoantibodies to ICA512/ IA-2, GAD, and insulin was more sensitive (89 %) compared to ICA testing for diagnosis of type 1 diabetes.

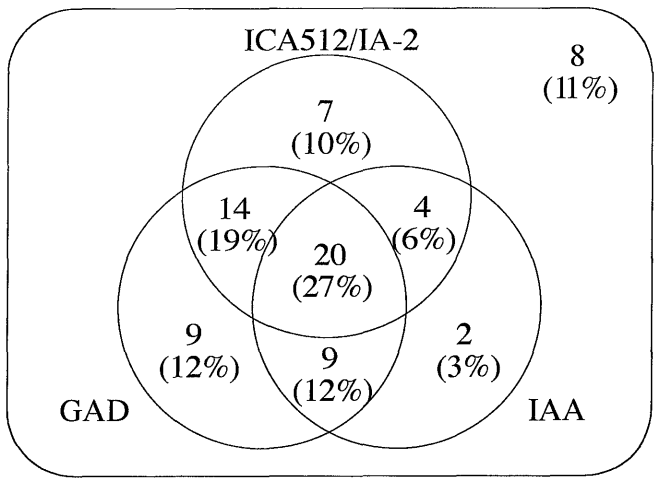

Figure 1. Combinatorial autoantibody analysis in Japanese new-onset patients with type 1 diabetes (n=73) *Modified from Sera et al, J Autoimmun 13,257-265, 1999.*

Table 5. Comparison of diagnostic sensitivity for the combined autoantibody analysis versus ICA

Combination of Autoantibodies	Type 1 diabetes (n=73)	Combined analysis vs. ICA positivity		
		Odds ratio	χ^2	*p* value
ICA512/IA-2 Ab or GAD Ab	63 (86)	3.92	10.28	6×10^{-4}
ICA512/IA-2 Ab or IAA	56 (77)	2.05	3.21	0.036
GAD Ab or IAA	58 (79)	2.41	4.75	0.014
ICA512/IA-2 Ab or GAD Ab or IAA	65 (89)	5.06	13.30	1×10^{-4}
ICA alone	45 (62)	-	-	-

Data are n (%). Ab, autoantibodies

Prediction of insulin-deficiency in LADA

LADA (latent autoimmune diabetes in adults) is a special subgroup of diabetes, which could represent a late manifestation of type 1 diabetes[38]. The autoimmune destructive process is much slower, making it sometimes difficult to distinguish clinically between type 1 and type 2 diabetes. The development of clinical symptoms is often insidious, without features typical or type 1 diabetes such as severe polydipsia, polyuria, weight reduction, or ketoscidosis. Such patients who have a slowly evolving form of type 1 diabetes retain insulin secretion in their initial stage and often diagnosed as type 2 diabetes based on clinical features[45]. Our cross-sectional study revealed that prevalence of GAD autoantibodies is 3-4 % among Japanese patients originally classified as having type 2 diabetes. A high levels of GAD autoantibodies or both positive for GAD autoantibodies and ICA is often associated with low insulin secretion of GAD autoantibody-positive patients[46]. Kobayashi and coworkers suggest that small dose insulin treatment may be helpful to preserve C-peptide secretion in islet-autoantibody positive diabetic patients in adults who still retain their insulin secretion[47]. Based on these results, a longitudinal nation-wide study of LADA commenced in 1996 by 14 centers across west Japan area. A total of 2,658 Japanese type 2 diabetic patients treated by diet and/or OHA were evaluated the GAD autoantibodies and assessed prospectively whether the presence of GAD autoantibodies could predict the requirement of future insulin treatment. The overall prevalence of GAD autoantibodies among patients with non-insulin requiring diabetes was 2.0 %, and 2.8 % of the patients with disease duration of < 5 years and 0.9 % with a longer duration of diabetes. As shown in Figure 2, the patients with higher levels of GAD autoantibodies (≥ 20 units/ml) more often progressed to insulin dependency than the lower titer group (<20 units/ml) during the follow up period[48]. However, there is a certain number of patients with high titer of GAD autoantibodies who do not progressed to insulin dependency for many years and the predictive value of GAD autoantibody positivity for future insulin requirement is estimated about 67 % by Baye's theory. Thus accurate predictive strategies of future insulin deficiency in patients with LADA using autoantibody epitope analysis, genetic determination, or T cell assay are required for the effective immune intervention[49].

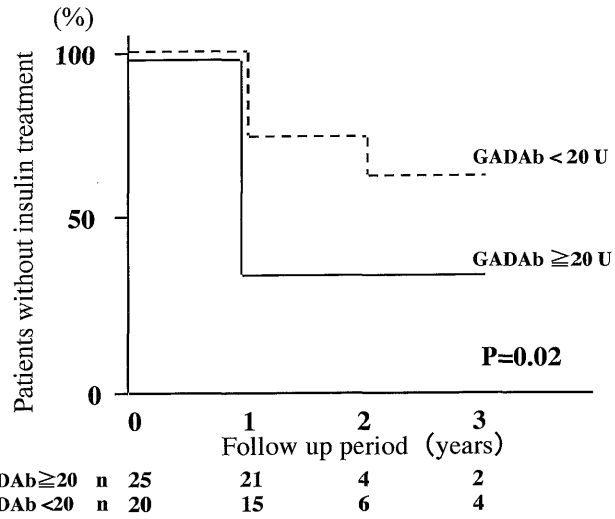

Figure 2. Life table analysis of the risk of insulin-requiring in GAD autoantibody-positive diabetic patients initially diagnosed as having type 2 diabetes. *Adapted from Takino et al, Diabet Med 19: 730-734, 2002*

Conclusion

Japanese type 1 diabetes has genetically and immunologically heterogenous mechanisms that result in different clinical course of β-cell destruction. A number of susceptibility genes and the different expression of anti-islet autoantibodies may influence the heterogeneity of disease phenotype such as early-onset versus adult-onset or abrupt-onset versus slow-onset. It is now possible to predict the ongoing β-cell destruction using combined measurement of autoantibodies to multiple islet autoantigens. A remarkable number of new agents for immunotherapy are being introduced into clinical practice. If a safe and effective therapy is identified, we should consider the use of agent for high risk individuals to prevent development of diabetes as well as for the patients with type 1 diabetes in adults who are often diagnosed as type 2 diabetes to preserve residual β-cell function.

References

1. American Diabetes Association: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183-1197, 1997
2. Abiru N, Eisenbarth GS: Multiple genes/multiple autoantigens role in type 1 diabetes. *Clin Rev Allergy Immunol* 18:27-40, 2000
3. Kawasaki E, Eisenbarth GS: Multiple autoantigens in the prediction and pathogenesis of type I diabetes. *Diab Nutr Metab* 9:188-198, 1996
4. Tuomilehto J, Virtala E, Karvonen M, et al.: Increase in incedence of insulin-dependent diabetes mellitus among children in Finland. *Int J Epidemiol* 24:984-992, 1995
5. Matsuura N, Fukuda K, Okuno A, et al.: Descriptive epidemiology of IDDM in Hokkaido, Japan: the Childhood IDDM Hokkaido Registry. *Diabetes Care* 21:1632-1636, 1998
6. Field LL: Genetic linkage and association studies of Type I diabetes: challenges and rewards. *Diabetologia* 45:21-35, 2002
7. Awata T, Kanazawa Y: Genetic markers for insulin-dependent diabetes mellitus in Japanese. *Diabetes Res Clin* Pract 24 Suppl:S83-87, 1994
8. Awata T, Kuzuya T, Matsuda A, Iwamoto Y, Kanazawa Y: Genetic analysis of HLA class II alleles and susceptibility to type I (insulin-dependent) diabetes mellitus in Japanese subjects. *Diabetologia* 35:419-424, 1992
9. Kawabata Y, Ikegami H, Kawaguchi Y, et al.: Asian-specific HLA haplotypes reveal heterogeneity of the contribution of HLA-DR and -DQ haplotypes to susceptibility to type 1 diabetes. *Diabetes* 51:545-551, 2002
10. Bell GI, Horita S, Karam JH: A polymorphic locus near the human insulin gene is associated with insulin-dependent diabetes mellitus. *Diabetes* 33:176-183, 1984
11. Bennett ST, Lucassen AM, Gough SC, et al.: Susceptibility to human type 1 diabetes at IDDM2 is determined by tandem repeat variation at the insulin gene minisatellite locus. *Nat Genet* 9:284-292, 1995
12. Awata T, Shibasaki Y, Hirai H, et al.: Restriction fragment length polymorphism of the insulin gene region in Japanese diabetic and non-diabetic subjects. *Diabetologia* 28:911-913, 1985
13. Takeda J, Seino Y, Fukumoto H, et al.: The polymorphism linked to the human insulin gene: its lack of association with either IDDM or NIDDM in Japanese. *Acta Endocrinol (Copenh)* 113:268-271, 1986
14. Awata T, Kurihara S, Kikuchi C, et al.: Evidence for association between the class I subset of the insulin gene minisatellite (IDDM2 locus) and IDDM in the Japanese population. *Diabetes* 46:1637-1642, 1997
15. Marron MP, Raffel LJ, Garchon HJ, et al.: Insulin-dependent diabetes mellitus (IDDM) is associated with CTLA4 polymorphisms in multiple ethnic groups. *Hum Mol Genet* 6:1275-1282, 1997
16. Lowe RM, Graham J, Sund G, et al.: The length of the CTLA-4 microsatellite (AT)N-repeat affects the risk for type 1 diabetes. Diabetes Incidence in Sweden Study Group. *Autoimmunity* 32:173-180, 2000
17. Ihara K, Ahmed S, Nakao F, et al.: Association studies of CTLA-4, CD28, and ICOS gene polymorphisms with type 1 diabetes in the Japanese population. *Immunogenetics* 53:447-454, 2001
18. Ban Y, Taniyama M, Tozaki T, et al.: No association of type 1 diabetes with a microsatellite marker for CTLA-4 in a Japanese population. *Autoimmunity* 34:39-43, 2001
19. Kouki T, Sawai Y, Gardine CA, et al.: CTLA-4 gene polymorphism at position 49 in exon 1 reduces the inhibitory function of CTLA-4 and contributes to the pathogenesis of Graves' disease. *J Immunol* 165:6606-6611, 2000
20. Awata T, Kurihara S, Iitaka M, et al.: Association of CTLA-4 gene A-G polymorphism (IDDM12 locus) with acute-onset and insulin-depleted IDDM as well as autoimmune thyroid disease (Graves' disease and Hashimoto's thyroiditis) in the Japanese population. *Diabetes* 47:128-129, 1998
21. Abe T, Takino H, Yamasaki H, et al.: CTLA4 gene polymorphism correlates with the mode of onset and presence of ICA512 Ab in Japanese type 1 diabetes. *Diabetes Res Clin Pract* 46:169-175, 1999
22. Abe T, Yamaguchi Y, Takino H, et al.: CTLA4 gene polymorphism contributes to the mode of onset of diabetes with antiglutamic acid decarboxylase antibody in Japanese patients: genetic analysis of diabetic patients with antiglutamic acid decarboxylase antibody. *Diabet Med* 18:726-731, 2001
23. Ota M, Katsuyama Y, Mizuki N, et al.: Trinucleotide repeat polymorphism within exon 5 of the MICA gene (MHC class I chain-related gene A): allele frequency data in the nine population groups Japanese, Northern Han, Hui, Uygur, Kazakhstan, Iranian, Saudi Arabian, Greek and Italian. *Tissue Antigens* 49:448-454, 1997
24. Vitiani LR, Potolicchio I, D'Amato M, Baricordi OR, Sorrentino R: MICA exon 5 microsatellite typing by DNA heteroduplex analysis: a new polymorphism in the transmembrane region. *Tissue Antigens* 51:309-311, 1998
25. Mizuki N, Ota M, Kimura M, et al.: Triplet repeat polymorphism in the transmembrane region of the MICA gene: a strong association of six GCT repetitions with Behcet disease. *Proc Natl Acad Sci U S A* 94:1298-1303, 1997
26. Kawabata Y, Ikegami H, Kawaguchi Y, et al.: Age-related association of MHC class I chain-related gene A (MICA) with type 1 (insulin-dependent) diabetes mellitus. *Hum Immunol* 61:624-629, 2000
27. Yamada S, Motohashi Y, Yanagawa T, et al.: NeuroD/beta2 gene G-->A polymorphism may affect onset pattern of type 1 diabetes in Japanese. *Diabetes Care* 24:1438-1441, 2001
28. Pennline KJ, Roque GE, Monahan M: Recombinant human IL-10 prevents the onset of diabetes in the nonobese diabetic mouse. *Clin Immunol Immunopathol* 71:169-175, 1994
29. Wogensen L, Lee MS, Sarvetnick N: Production of interleukin 10 by islet cells accelerates immune-mediated destruction of beta cells in nonobese diabetic mice. *J Exp Med* 179:1379-1384., 1994
30. Ide A, Kawasaki E, Abiru N, et al.: Genetic association between interleukin-10 gene promoter region polymorphisms and type 1 diabetes age-at-onset. *Hum Immunol* 63:690-695, 2002
31. Hamaguchi K, Kimura A, Seki N, et al.: Analysis of tumor necrosis factor-alpha promoter polymorphism in type 1 diabetes: HLA-B and -DRB1 alleles are primarily associated with the disease in Japanese. *Tissue Antigens* 55:10-16, 2000
32. Awata T, Matsumoto C, Urakami T, et al.: Association of polymorphism in the interferon γ gene with IDDM. *Diabetologia* 37:1159-1162, 1994
33. Ide A, Kawasaki E, Abiru N, et al.: Polymorphism of the interleukine-18 gene is associated with a susceptibility to type 1 diabetes in Japanese population. *Diabetes Metab Res Rev* 18:S38 2002 (abstract)
34. Norman AW, Frankel JB, Heldt AM, Grodsky GM: Vitamin D deficiency inhibits pancreatic secretion of insulin. *Science* 209:823-825, 1980
35. Mathieu C, Laureys J, Sobis H, et al.: 1,25-Dihydroxyvitamin D3 prevents insulitis in NOD mice. *Diabetes* 41:1491-1495, 1992
36. Ban Y, Taniyama M, Yanagawa T, et al.: Vitamin D receptor initiation codon polymorphism influences genetic susceptibility to type 1 diabetes mellitus in the Japanese population. *BMC Med Genet* 2:7, 2001
37. Ide A, Kawasaki E, Abiru N, et al.: Stromal-derived factor-1 chemokine gene variant is associated with type 1 diabetes age-at-onset. *J Jpn Diab Soc* 45:S-189, 2002 (abstract)
38. Zimmet PZ, Tuomi T, Mackay IR, et al.: Latent autoimmune diabetes mellitus in adults (LADA): the role of antibodies to glutamic acid decarboxylase in diagnosis and prediction of insulin dependency. *Diabet Med* 11:299-303, 1994
39. Kobayashi T, Tamemoto K, Nakanishi K, et al.: Immunogenetis and clinical characterization of slowly progressive IDDM. *Diabetes Care* 16:780-788, 1993
40. Urakami T, Miyamoto Y, Fujita H, Kitagawa T: Type I (insulin-dependent) diabetes in Japanese children is not a uniform disease. *Diabetologia* 32:312-315, 1989
41. Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y: A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. Osaka IDDM Study Group. *N Engl J Med* 342:301-307, 2000
42. Leslie RD, Atkinson MA, Notkins AL: Autoantigens IA-2 and GAD in type 1 (insulin-dependent) diabetes. *Diabetologia* 42:3-14, 1999

43. Verge CF, Gianani R, Kawasaki E, et al.: Prediction of type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. *Diabetes* 45:926-933, 1996
44. Sera Y, Kawasaki E, Abiru N, et al.: Autoantibodies to multiple islet autoantigens in patients with abrupt onset type 1 diabetes and diabetes diagnosed with urinary glucose screening. *J Autoimmun* 13:257-265, 1999
45. Kawasaki E, Yamaguchi Y, Nagataki S: Insulitis in an autoimmune-mediated patient originally classified as having type 2 diabetes. *Diabetes Care* 22:541-542, 1999
46. Abiru N, Takino H, Yano M, et al.: Clinical evaluation of non-insulin-dependent diabetes mellitus patients with autoantibodies to glutamic acid decarboxylase. *J Autoimmun* 9:683-688, 1996
47. Kobayashi T, Nakanishi K, Murase T, Kosaka K: Small doses of subcutaneous insulin as a strategy for preventing slowly progressive β-cell failure in islet cell antibody-positive patients with clinical features of NIDDM. Diabetes 45:622-626, 1996
48. Takino H, Yamasaki H, Abiru N, et al.: Antibodies to GAD in Japanese patients classified as Type 2 diabetes at diagnosis. High titre of GAD Ab is a predictive marker for early insulin treatment-report of west Japan (Kyushu, Yamaguchi, Osaka) study for GAD Ab(+) diabetes. *Diabet Med* 19:730-734, 2002
49. Kawasaki E, Abiru N, Ide A, et al.: Epitope analysis of GAD65 autoantibodies predicts the risk for insulin requirement in LADA. *Diabetes Metab Res Rev* 18:S38, 2002 (abstract)
50. Nishino M, Ikegami H, Kawaguchi Y, et al.: Polymorphism in gene for islet autoantigen, IA-2, and type 1 diabetes in Japanese subjects. *Hum Immunol* 62:518-522, 2001
51. Iwata I, Nagafuchi S, Nakashima H, et al.: Association of polymorphism in the NeuroD/BETA2 gene with type 1 diabetes in the Japanese. *Diabetes* 48:416-419, 1999