Proceedings of the National Science Council, ROC
Part B: Life Sciences
Vol. 19, No. 2, 1995. pp. 73-79

HLA DQA1 Genotypes and Its Interaction with HLA DQB1 in Chinese IDDM Living in Taiwan

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(Received August 19, 1994; Accepted January 23, 1995)

ABSTRACT

To study the role of the HLA DQA1 gene and its interaction with DQB1 in the susceptibility of IDDM, subjects with insulin-dependent (type 1) diabetes mellitus and non-diabetic unrelated controls were recruited from a Chinese population living in northern Taiwan. HLA DQA1 exon 2 was enzymatically amplified by polymerase chain reaction. HLA DQA1 alleles were diagnosed by dot blotting and hybridization with 11 sequence-specific oligonucleotide probes. Among all the DQA1 alleles, DQA1*0301 and DQA1*0501 were more frequent while DQA1*0102, DQA1*0103 and DQA1*0601 were less frequent in Chinese with IDDM than in controls. Among the DQA1 genotypes, only DQA1*0301/0301 and DQA1*0301/0501 were associated with increased risk to IDDM while DQA1*0301/0601 and DQA1*0102/0103 were protective against IDDM in our population. As the cell surface HLA DQ molecules were formed from each DQA1 and DQB1 alleles either in cis- or trans-position, the numbers of susceptible HLA DQ$\alpha\beta$ heterodimers were then derived from the genotypes of HLA DQA1/DQB1 in each person. The numbers of the possible diabetogenic DQ$\alpha\beta$ dimers correlated with the degree of risk to IDDM ($r = 0.92$) but were not statistically significant ($p > 0.05$). Subjects with absence of diabetogenic HLA DQ molecules were resistant to developing IDDM while subjects with two or more forms of diabetogenic DQ molecules were associated with increased risk to IDDM. In conclusion, both DQA1 and DQB1 genes, which determine the formation of susceptible DQ$\alpha\beta$ heterodimers, were significantly associated with IDDM in Chinese subjects living in Taiwan.

Key Words: Chinese; HLA-DQ heterodimer; insulin-dependent diabetes mellitus (IDDM); Taiwan.

I. Introduction

As with many other autoimmune diseases, insulin-dependent diabetes mellitus (IDDM) is associated with particular HLA alleles/haplotypes in different ethnic populations (Tiwari and Terasaki, 1985; Jenkins *et al.*, 1990). Class II HLA molecules are highly polymorphic $\alpha\beta$ heterodimers which are encoded by the respective A and B genes for HLA-DR, -DQ, and -DP (Svejgaard *et al.*, 1983; Korman *et al.*, 1985). Among them, HLA-DQ molecules, in which both α and β chains are highly polymorphic, are the most influential markers for IDDM susceptibility (Trucco and Duquesnoy, 1986; Trucco and Dorman, 1989; Erlich *et al.*, 1991). Recent studies in several groups have revealed that susceptibility to IDDM is better defined by a combination of HLA DQA1 and DQB1 alleles (Nepom *et al.*, 1987; Khalil *et al.*, 1990; Rønningen *et al.*, 1991a; Khalil *et al.*, 1992; Gutierrez-Lopez *et al.*, 1992; Cavan *et al.*, 1993). These data support the hypothesis that the potential antigen binding sites located near amino acid position 52 of the HLA DQα chain and the 57th amino acid residue of the HLA DQβ chain might be very important in the presentation of

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antigen peptides to T cells, which is thought to be critical for IDDM susceptibility (Brown *et al.*, 1988; Trucco and Dorman, 1989; Trucco, 1992).

We previously characterized the HLA-DQB1 gene in a Chinese population living in Taiwan and confirmed a strong association between HLA DQB1 and IDDM (Chuang *et al.*, 1994). However, the HLA DQβ-57 was insufficient to explain the incidence of IDDM in several different populations, even in the Chinese populations inhabiting different areas (Bao *et al.*, 1989; Chuang *et al.*, 1994). Some other genetic and/or environmental factors should help explain the role of HLA DQβ-57. In this study, we further characterized the HLA-DQA1 gene and assessed the role of HLA DQA1 and its interaction with HLA-DQB1 in the pathogenesis of IDDM in Chinese population living in Taiwan.

II. Materials and Methods

Eighty-nine subjects with type 1 diabetes mellitus (IDDM) were recruited at the Diabetic Clinic of the National Taiwan University Hospital (Taipei, Taiwan). The patients were diagnosed as IDDM according to the previously published criteria (National Diabetes Data Group International Workgroup, 1979), and their clinical characteristics and the beta cell function test have been described previously (Chuang *et al.*, 1994). Fourty-four non-related healthy subjects served as controls. They had no family history of diabetes and were recruited from among those who had been hospitalized for physical check-ups.

Genomic DNA was extracted from peripheral blood leukocytes (Baas *et al.*, 1984). Exon 2 of the HLA-DQA1 gene was enzymatically amplified by polymerase chain reaction (PCR) (Saiki *et al.*, 1988) using sequence-specific primers (GH26 and GH27) (Bugawan *et al.*, 1988). An amplification without target DNA was always included to check for contamination. DNA from cells with known HLA-DQA1 alleles was also amplified and used as a control in typing. Aliquots of the amplified DNA were checked to see if the amplification worked well. Non-radioactive oligotyping for HLA DQA1 was performed by use of eleven HRP-labeled sequence-specific oligoprobes (SSO). The details of the hybridization and detection protocols followed the methods published previously (Bugawan *et al.*, 1988; Khalil *et al.*, 1990). The stringency of hybridization and washing was adjusted to obtain accurate signal patterns for the DNA from the control cells. The hybridized probes were then detected with the ECL gene detection system (Amersham). Signals were captured on X-ray film after 30 seconds to 5 min of exposure. For reprobing, membranes were treated according to the manufacturer's recommendation.

The number of susceptible DQαβ heterodimers in each person was derived from HLA DQA1/DQB1 genotypes according to previous reports (Rønningen *et al.*, 1991b; Khalil *et al., 1992; Lipton et al.*, 1992).

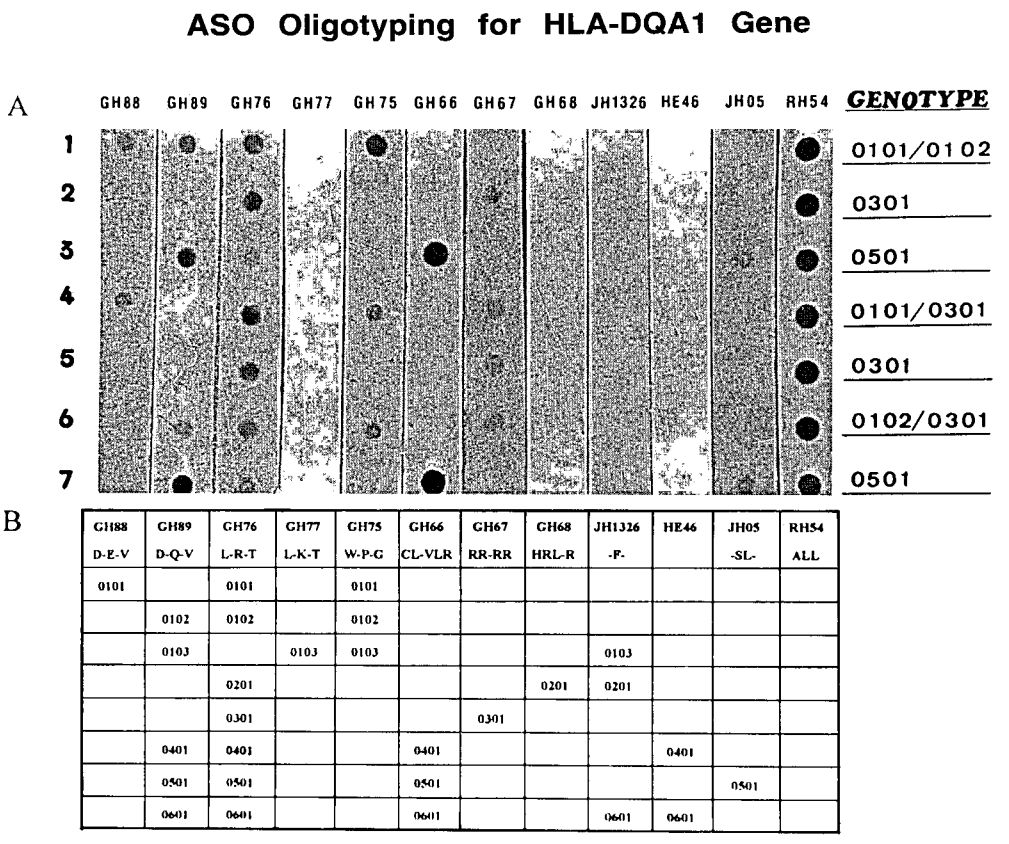
1. Statistical Analyses

For each allele or genotype, no matter whether structural or functional, a chi-square test or Fisher's exact probability test was used where appropriate to compare the differences in the frequencies between the IDDM and control groups. Relative risk (RR) was calculated according to Woolf (Woolf, 1955) and Haldane's modification (Haldane, 1956). The etiologic fraction (EF, %) and prevented fraction (PF, %), the attributable risk percentage of each marker, were also analyzed (Rimm *et al.*, 1980). As none of the analyses were for multiple comparisons, a 0.05 significant level was applied without any correction.

III. Results

1. HLA-DQA1 Alleles and Genotypes in Normal Chinese and IDDM Subjects

The oligotyping of the HLA-DQA1 gene was done by hybridization with a combination of 11 sequence-specific oligonucleotides, as is shown in Fig. 1. Table 1 shows the HLA-DQA1 allele frequencies of the IDDM patients and of the controls. Alleles not carrying Arg at position 52 of DQα, the nR alleles, were significantly associated with resistance to IDDM with a relative risk (RR) of 0.28 and prevented fraction of 32.8%. On the contrary, alleles carrying Arg at position 52 of DQα, the R alleles, were associated with increased risk to IDDM (RR = 3.53 and etiologic fraction = 58.0%). Detailed comparison of the frequency of each allele revealed five different alleles (DQA1*0102, 0103, 0301, 0501 and 0601) which were different among the normal and IDDM. The frequencies of DQA1*0301 and 0501 were significantly increased in IDDM patients when compared to the control subjects. On the contrary, the frequencies of DQA1*0102, 0103, and 0601 were significantly decreased among the patients. It is interesting to note that DQA1*0601, an $Arg52^+$-containing allele, was associated with resistance to IDDM. Genotypes containing both R alleles of DQA1 were significantly increased in IDDM subjects while the combination containing a single or nR alleles conferred IDDM protection (Table 2). Among the R/R combinations, DQA1*0301/0301 and 0301/0501 were the most sig-



GH88 D-E-V	GH89 D-Q-V	GH76 L-R-T	GH77 L-K-T	GH75 W-P-G	GH66 CL-VLR	GH67 RR-RR	GH68 HRL-R	JH1326 -F-	HE46	JH05 -SL-	RH54 ALL
0101		0101		0101							
	0102	0102		0102							
	0103		0103	0103				0103			
		0201					0201	0201			
		0301				0301					
	0401	0401			0401				0401		
	0501	0501			0501					0501	
	0601	0601			0601			0601	0601		

Fig. 1. Oligotyping of the HLA DQA1 gene. Exon 2 of the HLA-DQA1 gene was amplified from genomic DNA (0.5-1 μg) with primers (GH26, GH27) and spotted onto nylon membrane. The blot was hybridized with 11 different HRP-labeled sequence-specific oligonucleotides, and the signals were recognized by an ECL system. Diagnosis of genotypes was accomplished by means of the combination of positive dots as demonstrated (A). The reference pattern for diagnosis of genotypes of HLA DQA1 is shown in (B).

Table 1. Distribution of HLA-DQA1 Alleles in IDDM and Normal Subjects Among Chinese Living in Taiwan

Allele	IDDM (N=178) N	%	Normal (N=88) N	%	Relative risk	p	EF (%)	PF (%)
nR alleles	34	19.1	40	45.5	0.28	0.000		32.8
DQA1*0101	13	7.3	8	9.1	0.79	NS		
DQA1*0102	14	7.9	19	21.6	0.31	<0.005		14.9
DQA1*0103	4	2.2	12	13.6	0.15	<0.0005		11.6
DQA1*0201	3	1.7	1	1.1	1.49	NS		
R alleles	144	80.9	48	54.5	3.53	0.000	58.0	
DQA1*0301	77	43.3	24	27.3	2.03	<0.01	21.9	
DQA1*0401	1	0.6	0	0.0	1.49	NS		
DQA1*0501	64	36.0	13	1.1	3.24	<0.0005	2.4	
DQA1*0601	2	1.1	11	12.5	0.08	<0.0001		11.5

R: Arg at position 52 of DQα chain.
nR: non-Arg at position 52 of DQα chain.
NS: non-significant.

nificant genotypes predisposing to IDDM. However, the combination of DQA1*0301/0601 was associated with protection against IDDM (RR=0.07 and PF=12.6%, p=0.09). Although there were no single genotypes of nR/R at a significant level, the total value of the risk for this genotype was associated with protection against IDDM (RR=0.34, p=0.007). More significantly, the genotypes of nR/nR were associated with stronger protection against IDDM (RR=0.27, p=0.047). Among them, DQA1*0102/0103 was the only significant genotype associated with protection against IDDM (Table 2).

2. HLA-DQαβ Heterodimers and IDDM

The distribution of the possible susceptible HLA DQαβ heterodimers in both IDDM and normal subjects is shown in the Table 3. Each person has the potential to produce 0, 1, 2, or 4 susceptible forms of active DQ heterodimers. The control subjects displayed a trend towards a lower number of sus-

Table 2. Distribution of HLA-DQA1 Genotypes in IDDM and Normal Subjects Among Chinese Living in Taiwan

Genotype	IDDM (N=89) N	%	Normal (N=44) N	%	Relative risk	p	EF (%)	PF (%)
R/R	60	67.4	12	27.3	5.52	0.000	55.2	
0301/0301	14	15.7	1	2.3	8.03	0.044	13.9	
0301/0401	1	1.1	0	0				
0301/0501	34	38.2	3	6.8	8.45	0.000	33.6	
0301/0601	1	1.1	6	13.6	0.07	0.009		12.6
0501/0501	9	10.1	1	2.3				
0501/0601	1	1.1	2	4.5				
nR/R	24	27.0	23	52.3	0.34	0.007		34.7
0101/0301	4	4.5	4	9.1				
0101/0501	4	4.5	0	0				
0101/0601	0	0	2	4.5				
0102/0301	8	9.0	6	13.6				
0102/0501	3	3.4	3	6.8				
0102/0601	0	0	1	2.3				
0103/0301	2	2.2	3	6.8				
0103/0501	2	2.2	3	6.8				
0103/0601	0	0	1	2.3				
0201/0501	1	1.1	0	0				
nR/nR	5	6.7	8	18.2	0.27	0.047		13.3
0101/0102	3	3.4	1	2.3				
0101/0201	2	2.2	0	0				
0102/0102	0	0	1	2.3				
0102/0103	0	0	5	11.4	0.04	0.006		10.9
0102/0201	0	0	1	2.3				

R: Arg at position 52 of DQα chain.
nR: non-Arg at position 52 of DQα chain.

ceptible DQ$\alpha\beta$ heterodimers, and the IDDM subjects towards a higher number of susceptible heterodimers. Absence of any susceptible form of DQ heterodimers was associated with protection against IDDM (RR = 0.21, p = 0.001). One susceptible form of DQ$\alpha\beta$ heterodimer from a combination of double heterozygotes of HLA DQA1 and DQB1 genes was neutral in IDDM susceptibility/protection. However, the presence of 2 or more forms of susceptible DQ heterodimers was associated with increased risk to IDDM (RR = 2.57 and 22, respectively). The degree of the relative risk to IDDM correlated with the numbers of the diabetogenic HLA DQ molecules, although it was not statistically significant (r = 0.92, p > 0.05).

IV. Discussion

Several studies on the HLA class II genes have identified the specific susceptibility alleles of HLA DQA1 and DQB1 genes in different ethnic populations (Nepom *et al.*, 1987; Khalil *et al.*, 1990; Renningen *et al.*, 1991b; Khalil *et al.*, 1992: Gutierrez-Lopez *et al.*, 1992; Cavan *et al.*, 1993), including Chinese (Ju *et al.*, 1991; Penny *et al.*, 1992; Wang and He 1993; Hu *et al.*, 1993). Since the populations of Chinese are heterogeneous, the specific alleles associated with IDDM susceptibility are different among the populations from different areas. In this study, we hve shown that both DQA1*0301 and 0501 alleles were incresed while DQA1*0102, 0103 and 0601 alleles were decreased in IDDM patients. The positive as-

Table 3. HLA-DQ Heterodimer in IDDM and Normal Subjects in Taiwan

Possible HLA-DQ combination at alpha + beta	No. of diabetogenic heterodimers	IDDM (N=57) n	%	Normal (N=44) N	%	Relative risk	p
nR/nR + D/D	0	1	1.8	1	2.3		
or R/nR + D/D		4	7.0	8	18.2		
or nR/nR + nD/D		2	3.5	0	0.0		
or R/R + D/D		2	3.5	7	15.9		
or nR/nR + nD/nD		1	1.8	6	13.6		
[subtotal]	0	10	17.5	22	50.0	0.21	0.001
R/nR + nD/D	1	8	14.0	10	22.7	0.56	NS
R/R + nD/D	2	23	40.4	6	13.6	4.28	0.007
or R/nR + nD/nD		5	8.8	6	13.6		
[subtotal]	2	28	49.1	12	27.3	2.57	0.043
R/R + nD/nD	4	11	19.3	0	0.0	22.00	0.006

R (Arg) alleles: DQA1 locus with $Arg52^+$. They are DQA1*0301, 0401, 0501, 0601.
nR: alleles: DQA1 locus with $Arg52^-$. They are DQA1*0101, 0102, 0103, 0201.
D (Asp) alleles: DQB1 locus with $Asp57^+$. They are DQB1*0301, 0303, 0401, 0402, 0503, 0601, 0602, 0603.
nD alleles: DQB1 locus with $Asp57^-$. They are DQB1*0201, 0302, 0501, 0502, 0504, 0604, 0605.

sociation of DQA1*0301 and 0501 with IDDM was similar to that observed in Caucasians (Khalil *et al.*, 1990; Cavan *et al.*, 1993). However, this association was not homogeneous in Chinese populations from different areas. Namely, only DQA1*0301 was found to have increased in a study at Beijin (Wang *et al.*, 1993), and only DQA1*0501 was found to have increased in study at Hong Kong (Penny *et al.*, 1992). Negative association of DQA1*0102 and 0103 with observed in a Chinese population in Taiwan (present study) as well as in Caucasians (Khalil *et al.*, 1990; Cavan *et al.*, 1993) but was not observed in Chinese living in Hong Kong and Beijin (Penny *et al.*, 1992; Wang *et al.*, 1993). Interestingly, the frequency of DQA1*0601 was relatively high in the Chinese populations in Taiwan (present study) and Beijin (Wang *et al.*, 1993) as compared to that in Caucasians (Khalil *et al.*, 1990). DQA1*0601, although carrying Arg at position 52 of the DQα chain, was found to offer protection from IDDM. These data strongly argue against HLA DQA1 alone being sufficient to confer IDDM susceptibility.

Since the single amino acid changes at position 57 of the DQβ chain (Chuang *et al.*, 1994) and the amino acid changes at position 52 of DQα (this study) were not sufficient to account for the susceptibility to IDDM in Taiwan, the interaction of both DQA1 and DQB1 alleles to form functional DQ$\alpha\beta$ heterodimers was the most likely risk determinant for IDDM. In this study, we showed that the relative risk to IDDM was associated with the number of susceptible DQ$\alpha\beta$ heterodimers with a relative risk of 22 when the number of susceptible heterodimers was 4. This level of RR was highest as compared to the relative risk due to any other single parameter in our series, including DQA1 alleles and genotypes, DQB1 alleles and genotypes. Thus, our data support the HLA DQ$\alpha\beta$ heterodimer hypothesis for IDDM susceptibility.

In summary, distinct DQA1 alleles and genotypes were associated with IDDM in a Chinese population in Taiwan. Formation of the functional DQ$\alpha\beta$ heterodimer molecules, through the combination of DQA1 and DQB1 gene products, played a significant role in the pathogenesis of IDDM.

Acknowledgments

This work was supported by grants from the National Science Council, the Republic of China (NSC-81-0412-B002-42 and NSC-82-0412-B002-122-H12).

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人類白血球抗原DQA1基因型及與DQB1基因型對台灣地區中國人胰島素依賴型糖尿病之影響

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摘　要

爲了解人類白血球組織抗原DQA1基因及其與DQB1基因之交互作用，在胰島素依賴型糖尿病所扮演的角色，89名胰島素依賴型糖尿病病人與44名正常人接受本研究。人類白血球組織抗原DQA1基因型是利用聚合酶鏈合成反應(polymerase chain reaction)及特異序列寡核苷酸(sequence-specific oligonucleotide)之雜合方法鑑定。在中國人胰島素依賴型病患，DQA1*0301及0501對偶基因較爲常見，而DQA1*0102，0103及0601對偶基因較爲少見；在DQA1基因型中，以DQA1*0301/0301及0301/0501兩型較易發生胰島素依賴型糖尿病，而DQA1*0101/0103及0301/0601則有保護作用。細胞表面的DQ分子是由DQA1/DQB1基因來決定，而所產生的致病分子DQ α β之數目與胰島素依賴型糖尿病的相對危險性有密切關連。結論：DQA1基因和DQB1基因決定致病的DQ α β分子，兩者均與台灣地區中國人之胰島素依賴型糖尿病的發生有關。