HLA-DQA1 and -DQB1 Alleles Associated With Genetic Susceptibility to IDDM in a Black Population

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Transracial analysis provides a method of distinguishing primary associations between insulin-dependent diabetes mellitus (IDDM) and HLA class II alleles from those secondary to linkage disequilibrium. Blacks show DR-DQ relationships that are different from other races and are a useful group in which to investigate HLA-D region associations with IDDM. In this study, the frequencies of HLA-DQA1 and -DQB1 alleles in Afro-Caribbean IDDM and control subjects were compared. Alleles were identified with sequence-specific oligonucleotide probing. The DQA1 allele A3 was positively associated with IDDM (relative risk [RR] = 25.3, corrected P [P_c] $< 7.0 \times 10^{-6}$). The DQB1 alleles DQw2 and DQw8 were also positively associated (RR = 4.7, $P_c < 6.5 \times 10^{-3}$ and RR = 12.3, $P_c = 3.4 \times 10^{-3}$, respectively). The A1.2 and DQw6 alleles were negatively associated (RR = 0.16, $P_c < 3.5 \times 10^{-3}$ and RR = 0.15, $P_c = 2.4 \times 10^{-2}$, respectively). These findings were compared to data from other races. The positive associations with A3 and DQw2 are consistent with all racial groups investigated. The negative association with DQw6 is present in all racial groups in which it is a common allele. These findings suggest that DQ alleles, and hence DQ molecules, may directly affect predisposition to IDDM. *Diabetes* 40:748–53, 1991

Family and population studies have shown that at least one susceptibility locus for insulin-dependent diabetes mellitus (IDDM) is located in the HLA region (1). Characterization of these HLA susceptibility determinants has been complicated by the strong linkage disequilibrium that exists within the HLA complex (2). This makes it difficult to distinguish primary from secondary associations with disease.

Studies of whites indicate that a predisposing genetic factor is associated with each of the class II HLA-DRB1 alleles HLA-DR3 and HLA-DR4 (1). However, HLA-DRB1 alleles are unlikely to confer primary disease susceptibility (3). Attention has therefore focused on loci in linkage disequilibrium with HLA-DRB1, in particular on the HLA-DQB1 locus (4–7). The DQB1 allele DQw8 has been implicated as a primary susceptibility allele on DR4 haplotypes in whites (8). Involvement of both HLA-DQB1 and -DRB1 alleles cannot be excluded (9). More recently, associations with the HLA-DQA1 locus have been described (10), in particular with the A3 allele (11,12). However, the problem remains of how to determine whether such associations are primary or secondary to linkage disequilibrium with alleles at a locus that directly predisposes to disease.

One solution is to compare HLA associations with IDDM in different racial groups. Population-specific linkage-disequilibrium relationships have been demonstrated, and these result in race-specific HLA haplotypes. A primary susceptibility allele for IDDM should be associated with the disease regardless of its linkage-disequilibrium relationship with other alleles. If it is assumed that the disease has the same genetic basis in different racial groups, then a preliminary hypothesis is that primary disease associations should be common to all racial groups (13).

We have demonstrated that black subjects show DR-DQ relationships that are distinct from other races (14). They are thus informative in the study of MHC class II associations with disease. Serological HLA-DR typing shows positive associations between IDDM and HLA-DR3, -DR4, -DR7, and -DR9 and negative associations with HLA-DR2 and -DR5 in blacks (6). We have previously used restriction-fragment–length polymorphism analysis to define HLA-DQ associations with IDDM in a group of Afro-Caribbeans (6). In this study, we used sequence-specific oligonucleotide (SSO) probing to directly investigate disease associations with DQA1 and DQB1 alleles in the same population. Comparison

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of the associations detected with those found in other racial groups suggests further candidates for primary susceptibility alleles for IDDM.

RESEARCH DESIGN AND METHODS

Thirty-seven IDDM patients and 82 healthy unrelated control subjects were studied. Informed consent of the patients was obtained. All subjects were of Afro-Caribbean black racial origin (predominantly Jamaican) and had resided in the United Kingdom since birth. No subject had any known white ancestry. The patients were recruited from diabetes clinics in London and the Midlands area of the UK. Control subjects were recruited from hospital staff, community centers, antenatal clinics, and hospital patients undergoing elective surgery in the Midlands. IDDM patients were diagnosed at <30 yr of age, were ketosis prone, and were absolutely dependent on insulin from the time of diagnosis. Control subjects had neither personal nor family history of diabetes.

Most patients and control subjects had already been serologically HLA-DR typed and studied by RFLP analysis with HLA class II probes as previously described (6). New recruits for this study were also investigated by these methods.

The second exons of the DQA1 and DQB1 genes were amplified by the polymerase chain reaction (15). The primers used are shown in Table 1. The sequences have been previously described: DQB1 primers were described in ref. 5; 26A and 27A are shorter versions of GH26 and GH27 (by omission of the restriction sites at the 5' ends; 16); and 27B was described in ref. 11. The DQA1 gene was first amplified with primers 26A and 27A, and 2 μl of the primary reaction mixture was then subjected to a second round of amplification with primers 26A and 27B. The DQB1 gene was first amplified with primers GLPDQB1 and GAMPDQXB2, and 2 μl of the primary reaction mixture was then amplified with GAMPDQXB2 and GLPDRB1. These double amplifications improved the intensity of the hybridization signal.

The primary reaction mixture contained 2 μg DNA (isolated from peripheral blood); 10 mM Tris-HCl; 50 mM KCl; 1.5 mM $MgCl_2$; 0.01% gelatin; 0.2 mM each of dATP, dCTP, dGTP, and dTTP; 15 μg · ml^{-1} of each primer; and 4 U *Taq* I polymerase (Perkin-Elmer/Cetus, Beaconsfield, UK) in a total volume of 100 μl. The secondary reaction mixture contained 2 μl of the primary reaction mixture in place of the genomic DNA. The reaction was incubated in a DNA thermocycler (Perkin-Elmer/Cetus) and subjected to a preliminary cycle of 92°C for 5 min, 55°C for 2 min, and 72°C for 3 min. Subsequent cycles were 92°C for 1 min, 55°C for 2 min, and 72°C for 2 min. The DQA1 gene was amplified in two stages of 25 cycles and the DQB1 gene in two stages of 35 cycles.

For SSO dot-blot analysis, 10 μl amplified DNA was denatured and dot blotted onto Hybond-N filters (Amersham, Aylesbury, UK) with a Hybridot apparatus (BRL, Paisley, UK). The DNA was fixed to the filters by exposure to UV light. The filters were prehybridized for 15 min at 34°C in a solution of 6× SSC (1× SSC, 0.15 M NaCl and 0.015 M sodium citrate), 5× Denhardt's solution, 0.5% sodium dodecyl sulfate (SDS), and 0.4 mg/ml denatured salmon sperm DNA. Filters were hybridized at 34°C overnight in 6× SSC and 0.1% SDS containing 0.2 μg radiolabeled SSO. SSOs were end labeled with [γ-^{32}P]ATP (Amersham) with T4 DNA kinase (Pharmacia, Milton Keynes, UK). After hybridization, filters were washed twice nonstringently in 6× SSC at room temperature and autoradiographed for 1 h at −70°C to assess the degree of amplification. Two stringent washes were subsequently performed at the DNA duplex dissociation temperature (17) in 6× SSC and 0.1% SDS for 15 min. Filters were then autoradiographed for 2–4 h. Assessment of the signals from a range of control cell line DNAs of known DQA1 and DQB1 alleles that were dotted onto each filter ensured that adequate washing had occurred.

Eight SSOs complementary to DQA1 alleles and 15 complementary to DQB1 alleles were synthesized (Table 2). These enabled identification of 7 DQA1 alleles and 13 DQB1 alleles (Table 3). The nomenclature of Gyllensten and Erlich (18) was used for the DQA1 alleles and the nomenclature of Todd et al. (5) for the DQB1 alleles. World Health Organization nomenclature was also used for each allele (19). Probes were designed to allow unambiguous detection of pairs of DQA1 alleles and DQB1 alleles in both homozygous and heterozygous individuals. Thus, some alleles were recognized by ≥2 probes.

TABLE 1
Primer sequences

Primer	Sequence
DQA1 gene	
26A	5'-GGTGTAAACTTGTACCAG-3'
27A	5'-GGTAGCAGCGGTAGAGTTG-3'
27B	5'-GTAGAGTTGGAGCGTTTA-3'
DQB1 gene	
GLPDQB1	5'-GATTTCGTGTACCAGTTTAAGGGC-3'
GAMPDQXB2	5'-CCACCTCGTAGTTGTGTCTGCA-3'
GLPDRB1	5'-TTCTTCAATGGGACGGAGCG-3'

TABLE 2
Sequence-specific oligonucleotide probes used in detecting DQA1 and DQB1 alleles

Probe	Sequence	Amino acid positions
A1.1	5'-ATGAGGAGTTCTACGTG-3'	32–37
A1.2a	5'-AGATGAGCAGTTCTACG-3'	31–37
A1.2b	5'-CCTGGAGAGGAAGGAGA-3'	38–44
A1.3	5'-CCTGGAGAAGAAGGAGA-3'	38–44
A2	5'-TCTAAGTCTGTGGAACA-3'	50–55
A3	5'-TTCCGCAGATTTAGAAGATTT-3'	51–57
A4.1	5'-GTTTGCCTGTTCTCAGA-3'	47–52
A4.2	5'-TGGAGACGAGCAGTTCT-3'	30–36
B2	5'-GCTGGGGCTGCCTGCCG-3'	52–58
B4	5'-TGGAGGAGGACCGGGCG-3'	68–73
B5a	5'-GGCGGCCTGTTGCCGAG-3'	54–59
B5b	5'-CGTGCGGGGTGTGACCA-3'	23–29
B6	5'-GGCGGCCTGATGCCGAG-3'	54–59
B7a	5'-CGTGCGTTATGTGACCA-3'	23–29
B7b	5'-GGCCGCCTGACGCCGAG-3'	54–59
B8	5'-GGCCGCCTGCCGCCGAG-3'	54–59
B9	5'-GCGTGCGTCTTGTGACC-3'	23–28
B1.9a	5'-AGGGGCGGCCTGACGCC-3'	53–58
B1.9b	5'-AGGAGTACGTGCGCTTC-3'	35–40
B1.12	5'-GAGAGGAGGACGTGCGC-3'	34–39
B1.18	5'-CGTCTTGTAACCAGACA-3'	25–30
B1.19b	5'-CTTGTAACCAGATACATC-3'	26–31
B1.AZH	5'-GCGGCCTAGCGCCGAGT-3'	54–60

TABLE 3
Probe recognition of alleles

Allele	WHO nomenclature (19)	Probes recognizing allele
A1.1	DQA1*0101	A1.1
A1.2	DQA1*0102	A1.2a, A1.2b
A1.3	DQA1*0103	A1.3, A1.2a
A2	DQA1*0201	A2, A1.2b
A3	DQA1*0301	A3, A1.2b
A4.1	DQA1*0501	A4.1, A1.2a
A4.2	DQA1*0401	A4.2, A4.1
DQw2	DQB1*0201	B2
DQw4	DQB1*0402	B4
DQw5	DQB1*0501	B5a, B5b, B1.9b
DQw6	DQB1*0602	B6, B9
DQw7	DQb1*0301	B7a, B7b
DQw8	DQB1*0302	B8, B9
DQw9	DQB1*0303	B7b, B9
DQw1.AZH	DQB1*0502	B1.AZH, B5b, B1.9b
DQw1.9	DQB1*0503	B1.9a, B1.9b, B5b
DQw1.12	DQB1*0601	B1.12, B7a, B1.9a
DQw1.18	DQB1*0603	B6, B1.18
DQw1.19a	DQB1*0604	B5a, B1.18
DQw1.19b	DQB1*0604	B5a, B1.19b

WHO, World Health Organization.

The χ^2-test or Fisher's exact test was used as appropriate to identify significant differences in frequency of DR antigens and DQA1 and DQB1 alleles between the diabetic and control subjects. *P* values were corrected (P_c) for the number of comparisons made at each locus. Relative risk (RR) estimates were calculated by the method of Woolf with modification for small numbers (20). RR estimates for significant differences in frequency are given with 95% confidence intervals (CIs). The correlation coefficients for associations between serological HLA-DR types and DQA1 and DQB1 alleles were calculated from the formula $r = (\chi^2/n)^{1/2}$.

RESULTS

DR antigen frequencies in the IDDM patients and control subjects are shown in Table 4. Complete serological DR typing was available for only 70 of 82 control subjects. DR4 was significantly increased in frequency in the patient group and was rare in the control subjects (37.8 vs. 2.9%, RR = 16.9, CI = 4.4–65.3, $P_c < 10^{-4}$). DR3, DR7, and DR9 were not significantly increased in frequency in IDDM patients compared with control subjects. DR2 was significantly reduced in frequency in the IDDM subjects (5.4 vs. 28.6%, RR = 0.17, CI = 0.05–0.64, $P_c < 0.05$), and DR5 was not significantly reduced.

TABLE 4
DR antigen frequencies in black diabetic and control subjects

	Diabetic (*n* = 37)		Control (*n* = 70)		
	n	%	*n*	%	Relative risk
DR1	3	8.1	12	17.1	0.47
DR2	2	5.4	20	28.6	0.17 (0.05–0.64)*
DR3	14	37.8	19	27.1	1.6
DR4	14	37.8	2	2.9	16.9 (4.4–65.3)†
DR5	4	10.8	24	34.3	0.25
DRw6	6	16.2	21	30.0	0.48
DR7	11	29.7	10	14.3	2.5
DRw8	4	10.8	12	17.1	0.63
DR9	7	18.9	4	5.7	3.6
DRw10	0	0	1	1.4	0.62

Parentheses contain 95% confidence intervals. P_c, *P* value corrected for number of alleles compared.
*$P_c < 0.05$.
†$P_c < 10^{-4}$.

The frequencies of the DQA1 alleles identified in diabetic and control subjects are shown in Table 5. The frequency of the A1.2 allele was significantly decreased in the diabetic group compared with the control subjects (RR = 0.16, CI = 0.06–0.47, $P_c < 3.5 \times 10^{-3}$). The frequency of the A3 allele was significantly increased among diabetic subjects (RR = 25.3, CI = 9.2–69.3, $P_c < 7.0 \times 10^{-6}$).

The frequencies of the DQB1 alleles identified in diabetic and control subjects are shown in Table 6. DQw2 was significantly increased in the diabetic compared with the control group (RR = 4.7, CI = 2.0–10.7, $P_c < 6.5 \times 10^{-3}$). DQw8 was also significantly increased among diabetic subjects (RR = 12.3, CI = 3.1–48.6, $P_c = 3.4 \times 10^{-3}$). DQw6 was significantly decreased in the diabetic group (RR = 0.15, CI = 0.04–0.55, $P_c = 2.4 \times 10^{-2}$).

There were strong associations between DQA1 and DQB1 alleles and certain serological DR types. Table 7 shows the DQA1-DR and Table 8 shows the DQB1-DR relationships. The results shown are for 70 control subjects for whom full serological typing was available. A3 was associated with both DR4 and DR9 and A4.2 with both DR3 and DRw8. DRw6 was associated with both A1.2 and A1.3. DQw2 was associated with DR7 and DR9. DR3 was not significantly associated with DQw2 but was associated with DQw4. DQw7 was associated with both DR5 and DRw8.

The frequencies of certain DR-DQ haplotypes were significantly different in the diabetic compared with the control group. The haplotypes were determined from the DR-DQ associations determined in the control group (Tables 7 and 8) and not from family studies.

DR7,A3,DQw2 haplotypes were significantly increased in the diabetic group (7 of 11 DR7+ diabetic patients vs. 1 of 10 DR7+ control subjects; RR = 10.6, CI = 1.6–73, *P* = 0.034). DR7,A2,DQw2 haplotypes were neutral (5 of 11 DR7+ diabetic patients vs. 9 of 10 DR7+ control subjects; RR = 0.13, NS). One DR7+ diabetic patient was a DR7,A3,DQw2/

TABLE 5
DQA1 allele frequencies in black diabetic and control subjects

	Diabetic (*n* = 37)		Control (*n* = 82)		
	n	%	*n*	%	Relative risk
A1.1	4	10.8	30	36.6	0.28
A1.2	4	10.8	37	45.1	0.16 (0.06–0.47)*
A1.3	2	5.4	6	7.3	0.83
A2	5	13.5	12	14.6	0.79
A3	30	81.1	11	13.4	25.3 (9.2–69.3)†
A4.1	15	40.5	27	32.9	1.4
A4.2	4	10.8	23	28.0	0.34

Parentheses contain 95% confidence intervals. P_c, *P* value corrected for number of alleles compared.
*$P_c < 3.5 \times 10^{-3}$.
†$P_c < 7.0 \times 10^{-6}$.

TABLE 6
DQB1 allele frequencies in black diabetic and control subjects

	Diabetic (n = 37)		Control (n = 82)		
	n	%	n	%	Relative risk
DQw2	26	70.3	27	32.9	4.7 (2.0–10.7)*
DQw4	3	8.1	15	18.3	0.44
DQw5	4	10.8	23	28.0	0.34
DQw6	2	5.4	26	31.7	0.15 (0.04–0.55)†
DQw7	6	16.2	32	39.0	0.32
DQw8	10	27.0	2	2.4	12.3 (3.1–48.6)‡
DQw9	2	5.4	0	0	11.6
DQw1.18	2	5.4	4	4.9	1.2
DQw1.19a	0	0	13	15.9	0.07
DQw1.19b	2	5.4	1	1.2	3.8
DQw1.9	1	2.7	3	3.7	0.93
DQw1.AZH	0	0	2	2.4	0.43
DQw1.12	0	0	1	1.2	0.72

Parentheses contain 95% confidence intervals. P_c, P value corrected for number of alleles compared.
*$P_c < 6.5 \times 10^{-3}$.
†$P_c < 2.4 \times 10^{-2}$.
‡$P_c < 3.4 \times 10^{-3}$.

DR7,A2,DQw2 heterozygote. DR5,A3,DQw2 was also positively associated with IDDM (3 of 4 DR5$^+$ diabetic patients vs. 3 of 24 DR5$^+$ control subjects; RR = 14.3, CI = 1.9–110, P = 0.04). DR3,A4.1,DQw2 haplotypes were positively associated with IDDM (14 of 14 DR3$^+$ diabetic patients vs. 7 of 19 DR3$^+$ control subjects; RR = 48.3, CI = 5.1–458, $P = 2.8 \times 10^{-4}$). DR3,A4.2,DQw4 haplotypes were significantly reduced in frequency (0 of 14 DR3$^+$ diabetic patients vs. 12 of 19 DR3$^+$ control subjects; RR = 0.02, CI = 0.002–0.2, $P = 2.8 \times 10^{-4}$). DR4,A3,DQw8 was not significantly increased in the diabetic group (10 of 14 DR4$^+$ diabetic patients vs. 1 of 2 DR4$^+$ control subjects, NS), but only small numbers of DR4$^+$ subjects were available for analysis.

DISCUSSION

This study supports the involvement of the A3 allele in susceptibility to IDDM. A previous study showed that the IDDM-predisposing black DR7 haplotype carried the A3 allele, whereas the neutral white DR7 haplotype carried the A2 allele. The DRB1 and DQB1 genes were identical (11). Population analysis showed that only A3$^+$ DR7 haplotypes were associated with IDDM in blacks, and A2$^+$ DR7 haplotypes were neutral. In addition, a subset of black DR5 haplotypes carrying the A3 allele were positively associated with the disease. The A3 allele was also found on the predisposing black DR9,DQw2 haplotype.

A3 has also been significantly positively associated with IDDM in North Indian Asians (21), Japanese (12), and whites (22). A3 thus shows a consistent positive association with disease in all races studied and so may contribute to DR4-associated susceptibility.

However, other data indicate that the presence of A3 alone is not adequate to confer susceptibility to IDDM. DR4,DQw7 haplotypes that are negatively associated with the disease in whites carry the A3 allele (8). In Japanese, DR4,DQw8 haplotypes carry the A3 allele and are neutral (7,12,23). If A3 is a susceptibility allele, then its effect must be modified on these haplotypes.

The A1.2 allele was negatively associated with IDDM in blacks. In this race, the A1.2 allele was found on DR2,DQw6 haplotypes that were negatively associated with the disease and on DRw6,DQw1.19 haplotypes that were not significantly reduced in frequency in the diabetic group. There is no significant association between A1.2 and IDDM in North Indian Asians (21). These inconsistent transracial findings indicate that the association with A1.2 is probably secondary to linkage disequilibrium with a primary disease-susceptibility allele.

DQw2 was positively associated with IDDM and is found on DR3 (DRw17), DR7, DR9, and a subset of DR5 haplotypes in blacks. In this race, only the DQw2$^+$ subset of DR3 (DRw17) haplotypes was positively associated with IDDM; DR3 (DRw18),DQw4 haplotypes were negatively associated. This may indicate that DQw2 is the DR3-associated susceptibility allele and that DQw4 is protective (24). DR3 (DRw17),DQw2, and DR3 (DRw18),DQw4 haplotypes are also different at the DRB1 and DQA1 loci (25), however, and it is possible that these differences are important.

TABLE 7
Associations between DQA1 alleles and serological DR types

	DQA1 allele/DR type					
Specificity	++	+−	−+	−−	r	P
A1.1,DR1	12	12	0	46	0.63	$<10^{-6}$
A1.1,DRw6	8	16	13	33		NS
A1.2,DR2	19	11	1	39	0.66	$<10^{-6}$
A1.2,DR5	10	20	14	26		NS
A1.2,DRw6	13	17	8	32	0.25	<0.05
A1.3,DRw6	4	1	17	48	0.30	<0.025
A2,DR7	9	2	1	58	0.83	$<10^{-6}$
A3,DR4	2	9	0	59	0.40	$<10^{-3}$
A3,DR5	4	7	20	39		NS
A3,DR9	4	7	0	59	0.57	$<10^{-5}$
A4.1,DR3	8	17	11	34		NS
A4.1,DR5	15	10	9	36	0.37	$<5 \times 10^{-3}$
A4.2,DR3	12	9	7	42	0.44	$<5 \times 10^{-4}$
A4.2,DRw8	10	11	2	47	0.53	$<10^{-5}$

Values are number of control subjects for whom serological DR types were available (n = 70) in each category of DQA1,DR association.

TABLE 8
Associations between DQB1 alleles and serological DR types

	DQB1 allele/DR type					
Specificity	++	+−	−+	−−	r	P
DQw2,DR3	8	16	11	35		NS
DQw2,DR7	10	14	0	46	0.57	$<10^{-5}$
DQw2,DR9	4	20	0	46	0.34	$<5 \times 10^{-3}$
DQw4,DR3	12	1	7	50	0.70	$<10^{-6}$
DQw5,DR1	12	4	4	50	0.68	$<10^{-6}$
DQw5,DR5	7	9	17	37		NS
DQw6,DR2	16	6	4	44	0.66	$<10^{-6}$
DQw6,DR5	8	14	16	32		NS
DQw7,DR4	2	28	0	40		NS
DQw7,DR5	17	13	7	33	0.40	$<10^{-3}$
DQw7,DRw8	12	18	0	40	0.52	$<10^{-4}$
DQw8,DR4	1	1	1	67	0.48	$<10^{-4}$
DQw1.19a,DRw6	9	1	12	48	0.53	$<10^{-5}$

Values are number of control subjects for whom serological DR types were available (n = 70) in each category of DQB1,DR association.

DQw2 is rare in Japanese (7,12,23) but is positively associated with IDDM in North Indian Asians (21,26) and whites (22). In these races, as in blacks, DQw2 is also found on the neutral DR7,A2,DQw2 haplotype. This suggests that DQw2 itself cannot be the DR3-associated susceptibility allele unless there is a protective element on the neutral DR7 haplotype. Data from the Afro-Caribbeans suggest that the A2 allele might be a protective element, because DR7,DQw2 haplotypes carrying the A3 allele in this race confer susceptibility.

DQw4 was not significantly reduced in frequency in black IDDM patients. DQw4 is positively associated with IDDM in Japanese (7,12,23). Black and Japanese DQw4 second-exon sequences differ by a single nucleotide (27) that changes an arginine to a leucine at position 23, so direct comparison is not valid. However, it is unclear whether this small difference would have functional relevance. The role of DQw4 in susceptibility to IDDM in blacks thus remains uncertain.

The frequency of DQw8 was significantly increased in the black diabetic subjects compared with control subjects. This has also been demonstrated in whites (8) and North Indian Asians (21), and it has been suggested that DQw8 is the primary DR4-associated susceptibility factor (8). In Japanese, however, DQw8 is not positively associated with IDDM, even though it is present in 12–20% of healthy control subjects (7,12,23). This finding has several alternative explanations: the appropriate environmental factor may be lacking in Japanese, there may be a protective factor on Japanese DR4,DQw8 haplotypes, or the association with DQw8 seen in whites may be a result of linkage disequilibrium with another allele at a primary susceptibility locus.

DQw6 was significantly negatively associated with IDDM in blacks and was found on DR2 and DR5 haplotypes. This negative association has also been demonstrated in whites (28) and Japanese (23). In North Indian Asians, however, DQw6 is rare, and DQw1.18 (rare in blacks) is negatively associated with the disease (21,26). DQw6 and DQw1.18 differ by a single codon at position 30 in their first domain-coding sequences (5). It is thus possible that their β-chains may have similar functions.

The DQw6 and DQw1.18 alleles both encode Asp-57$^+$ DQ β-chains. It has been suggested that such Asp-57 positivity confers a direct protective effect against IDDM (5,29). However, the existence of predisposing Asp-57$^+$ DQ β-chains in Japanese makes this unlikely (23).

Transracial analysis indicates that susceptibility to IDDM is associated with alleles of both the DQA1 and DQB1 genes. This is consistent with the current model for a class II molecule that indicates that both the α- and β-chains are involved in formation of the putative antigen-binding cleft (30). In addition, it has been demonstrated that the specificities of both the DQ α- and β-chains affect T-lymphocyte activation (31).

Data from blacks suggest that the DQA1/B1 combination A3,DQw2 may be important in determining IDDM susceptibility (32). This combination exists on susceptibility haplotypes carrying three different DRB1 specificities: DR5, DR7, and DR9. The encoded molecule may be an example of a DQ structure that has a direct role in the pathogenesis of IDDM. This might be via increased efficiency of binding and presentation of diabetogenic peptides to T lymphocytes. Such hypotheses cannot be tested until the functional role of HLA class II molecules in IDDM is defined.

In conclusion, the data from blacks presented here, in combination with data from other races, support a role for the DQ molecule in susceptibility to IDDM. However, the DQ molecule is unlikely to be the only determinant of susceptibility. Further transracial studies of additional and/or alternative candidates are required.

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