HLA-A, -B, and -DR Associations in Type I Diabetes Mellitus with Onset After Age Forty

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SUMMARY

It remains to be convincingly demonstrated whether insulin-requiring, ketosis-prone, lean-at-onset, type I diabetics who develop their disease after age 40 have the same disease as the children with similar characteristics. To address this question, we examined the population HLA genetic associations of this group. One hundred forty white, insulin-using diabetics with onset of disease past age 40 yr and 268 normal white controls have thus far been analyzed for HLA type. In the group of patients who were lean-at-onset and/or ketosis-prone (N = 54), there was a significantly increased frequency of DR4 (RR = 4.63; $P < 0.01$) and significantly decreased frequency of DR2 (RR = 0.18; $P < 0.05$) after correction. DR4 was also significantly increased after correction (RR = 5.72; $P < 0.025$) in the subgroup who were both lean and ketosis-prone (N = 23). No significant differences in HLA-DR frequencies were found between the obese and not-ketosis-prone group (N = 69) and controls. No significant associations of HLA-A or -B antigens with either group were observed after correction for the number of antigens tested. To our knowledge, this is the first such study in the United States, and the first demonstrating that late onset diabetics who are lean-at-onset and/or ketosis-prone exhibit HLA-DR antigen associations which are similar to early onset cases. DIABETES *31*:122–125, February 1982.

The association of certain HLA antigens with insulin-dependent diabetes mellitus (IDDM) in patients less than age 40 yr at onset is now well recognized. Associations have been found with HLA antigens and IDDM in white (refs. 1 and 2 and reviewed in refs. 3 and 4), black[2,5–8], and Oriental[2,9–11] subjects. The observation that several high-risk alleles exist, together with evidence from linkage analysis in multiply affected families,[1,12–14] has led to the general belief that genes closely linked to the MHC region on chromosome number 6 may play an important role in the etiology of IDDM.

The consistent finding of no HLA association with those whose age of onset of diabetes was 40 yr or older[12,15,16] and who did not require insulin[5,15,17,18] has contributed to our understanding of IDDM and non-insulin-dependent diabetes mellitus (NIDDM) as two distinct disease entities. What remains uncertain is whether the IDDM individuals with onset past age 40 who have clinical features similar to earlier onset IDDM patients have the same HLA associations. Do both groups share a common genetic influence? Only a few reports directly address this question. In the paper of Cudworth and Woodrow,[18] a significantly increased frequency of B8 was found in a sample of white, British IDDM patients who were past age 30 at onset. Irvine et al.[19] found significantly increased frequencies of A1 and B8 in islet-cell antibody (ICAb) positive, white, British diabetic patients who were past age 40 at onset. Dausset et al.[20] reported significant increases in B8 and Bw15 in a subgroup of white, French ketosis-prone IDDM patients who were past age 40 at onset. Köbberling, et al.[21] found increases in the frequencies of A1, A2, B8, Bw15, and Cw3 and a decrease in the frequency of B7 in a sample of white, ketosis-prone, German IDDM patients who were past age 25 at onset, although the control frequencies and levels of significance were not given. All four studies demonstrate increased frequencies of B8 in late-onset IDDM samples. There have apparently been no studies replicating these findings in the U.S., and no reports have examined this relationship with respect to the DR antigens.

MATERIALS AND METHODS

Patients. One hundred forty unrelated, white, insulin-treated, type I diabetic patients whose age at onset of diabetes was 40 yr or older were phenotyped for HLA-A and -B antigens. An unselected subgroup of 123 patients was also

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phenotyped for HLA-DR antigens. All patients included in this study were seen at UAB's Diabetes Research and Training Center between June 1979 and June 1981. Over 70% of the patients were born in Alabama, 15% were born in the neighboring states of Tennessee, Georgia, Florida, and Mississippi, and less than 15% were born outside the southeastern United States. To our knowledge, none of the female patients had a history of gestational diabetes.

Classification. The criteria for dividing patients into subgroups were ketosis-proneness and body weight at onset of diabetes. Ketosis-proneness was defined as a history of ketoacidosis and/or a history of concurrently positive urine sugar and urine ketones. "Lean at onset" was defined as a weight less than or equal to 120% of the ideal body wt. estimates of the Society of Actuaries.[22] Those greater than 120% of ideal body wt. at onset were defined as obese. Information concerning these characteristics was obtained by interview and review of medical charts. Four subgroups were defined on the basis of these criteria: lean and ketosis-prone (N = 23), lean and not-ketosis-prone (N = 17), obese and ketosis-prone (N = 14), and obese and not-ketosis-prone (N = 69). Because of the small numbers of patients in the first three subgroups, they were pooled as a lean and/or ketosis-prone group (N = 54) for comparing the frequency of HLA-A and -B antigens. The mean age at onset was 52.55 ± 1.15 yr for the lean and/or ketosis-prone group, and 52.65 ± 0.94 yr for the obese and not-ketosis-prone group. The male:female ratio was approximately 1.5:1 in the lean and/or ketosis-prone group and 1:1.8 in the obese and not-ketosis-prone group. Only four patients had coexistent autoimmune diseases, including one with Addison's disease, one with Graves' disease, one with pernicious anemia and one with both Hashimoto's thyroiditis and idiopathic thrombocytopenic purpura. All four patients with known coexistent autoimmune diseases were in the lean and/or ketosis-prone group.

Controls. The control sample for the HLA-A and -B comparisons consisted of 268 healthy, unrelated, white subjects with no history of diabetes among first degree relatives. An unselected subgroup of 123 controls was also typed for HLA-DR antigens. Over 60% of the controls were born in Alabama, 20% were born in the neighboring states, and less than 20% were born outside the southeastern United States. A fasting blood sugar was examined on all the controls and no abnormal results were found.

Typing techniques. HLA-A and -B antigens were determined by the standard microdroplet cytotoxicity test as described by Terasaki and McClelland[23] and refined by Mittal et al..[24] Antisera were obtained from the serum screening program of the Tissue Typing Laboratory at UAB's Diabetes Research and Training Center, from the NIH, by exchange with other investigators, and from Dr. Paul Terasaki at UCLA. The HLA antigens analyzed include 16 specificities at the A locus and 20 specificities at the B locus.

HLA-DR typing was performed by the microdroplet cytotoxicity test on lymphocytes enriched with B-cells. Separation of B-cells was carried out by the nylon wool column technique.[25] Antisera detecting six specificities at the DR locus were obtained from Dr. Paul Terasaki.

Analysis. Comparisons of the HLA antigen frequencies between patient groups and controls were made using 2 × 2 contingency tables. The relative risks were estimated by Woolf's odds ratio.[26] The statistical significance of association was tested by conventional chi-square analysis. The P values were corrected for the number of antigens tested (P × 42).

RESULTS

Comparisons of the HLA-A, -B, and -DR antigen frequencies between the two patient groups and controls are given in Tables 1–3. In the lean and/or ketosis-prone group, significantly increased frequencies before correction were found for A29 (RR = 3.14, $P < 0.05$), Aw33 (RR = 9.05, $P < 0.05$), and DR4 (RR = 4.63, $P < 0.0005$), while the frequencies of DR2 (RR = 0.18, $P < 0.001$) and DR7 (RR = 0.30, $P < 0.025$) were decreased. After correction for the number of antigens tested, only the increase in DR4 and the decrease in DR2 remained significant. The frequencies of B8 and B15 were increased in the lean and/or ketosis-prone group (B8, RR = 1.21; B15, RR = 1.54), although not significantly different from controls.

In the obese and not-ketosis-prone group, increased frequencies were found for B7 (RR = 2.21, $P < 0.005$) and DR4 (RR = 2.47, $P < 0.025$). A decreased frequency was found for B15 (RR = 0.16, $P < 0.005$). When the P values were corrected for the number of antigens tested, none of the associations was significant.

The lean and/or ketosis-prone group was divided into three subgroups for comparisons of the DR frequencies. As shown in Table 4, statistically significant differences between patient subgroups and controls were found for DR2, DR4, and DR7 antigens. The DR2 antigen was completely absent in the lean and ketosis-prone subgroup (N = 23, RR = 0.00, $P < 0.005$). The relative risk of DR2 was also decreased in the lean and not-ketosis-prone subgroup (RR = 0.48, $P > 0.05$) and the obese and ketosis-prone subgroup (RR = 0.17, $P > 0.05$), although the differences were not statistically significant. The DR4 antigen was sig-

TABLE 1
Comparisons of HLA-A locus antigen frequencies between late-onset diabetics and controls

HLA antigen	Normal controls (N = 268)	Lean and/or ketosis prone (N = 61)		Obese and not-ketosis-prone (N = 75)	
	(%)	(%)	RR*	(%)	RR*
A1	35.8	32.8	0.87	28.0	0.70
A2	47.8	52.5	1.21	56.0	1.39
A3	27.2	27.9	1.03	20.0	0.67
A11	11.2	6.6	0.56	16.0	1.51
Aw23	6.3	1.6	0.25	4.0	0.62
Aw24	14.9	13.1	0.86	18.7	1.31
A25	4.9	3.3	0.66	5.3	1.11
A26	5.2	1.6	0.30	5.3	1.02
A28	11.6	6.6	0.54	8.0	0.66
A29	3.4	9.8	3.14†	2.7	0.79
Aw30	5.6	9.8	1.84	1.3	0.23
Aw31	3.7	6.6	1.81	2.7	0.71
Aw32	3.7	3.3	0.87	5.3	1.45
Aw33	0.4	3.3	9.05†	2.7	7.32
Aw34	0.4	0.0	0.00	0.0	0.00
Aw36	1.1	0.0	0.00	0.0	0.00

* Relative risk estimated by Woolf's odds ratio.
† $P < 0.05$ before correction.

TABLE 2
Comparisons of HLA-B locus antigen frequencies between late onset diabetics and controls

HLA antigen	Normal controls (N = 268) (%)	Lean and/or ketosis-prone (N = 61) (%)	RR*	Obese and not-ketosis-prone (N = 75) (%)	RR*
B7	21.7	16.4	0.73	37.3	2.21†
B8	21.3	24.6	1.21	20.0	0.93
B13	4.1	4.9	1.21	1.3	0.32
B14	8.2	11.5	1.45	4.0	0.47
B15	14.9	21.3	1.54	2.7	0.16†
B17	11.2	4.9	0.41	9.3	0.82
B18	8.6	11.5	1.38	6.7	0.76
Bw22	5.2	1.6	0.30	9.3	1.87
B27	7.5	6.6	0.87	5.3	0.70
Bw35	19.4	9.8	0.45	18.7	0.95
B37	2.2	0.0	0.00	0.0	0.00
Bw38	3.7	0.0	0.00	4.0	1.08
Bw39	3.0	4.9	1.68	4.0	1.35
B40	14.6	19.7	1.44	12.0	0.80
Bw44	23.1	32.8	1.62	29.3	1.38
Bw45	1.1	0.0	0.00	1.3	1.19
Bw49	2.6	4.9	1.93	5.3	2.11
Bw50	1.5	3.3	2.24	0.0	0.00
Bw51	6.3	6.6	1.04	9.3	1.52
Bw52	2.2	0.0	0.00	1.3	0.59

* Relative risk estimated by Woolf's odds ratio.
† $P < 0.05$ before correction.

nificantly increased in the lean and ketosis-prone subgroup (RR = 5.72, $P < 0.0005$), the lean and not-ketosis-prone subgroup (RR = 4.36, $P < 0.005$), and the obese and ketosis-prone subgroup (RR = 3.46, $P < 0.05$). The strongest DR4 association was in the lean and ketosis-prone subgroup, which remained significant after correction ($P < 0.025$). The DR7 antigen, which was detected in 31 out of 123 controls, was significantly decreased in the lean and ketosis-prone subgroup (RR = 0.13, $P < 0.05$), although not significantly after correction. The relative risk for DR7 was also decreased in the lean and not-ketosis-prone subgroup (RR = 0.19, $P > 0.05$).

TABLE 3
Comparisons of DR locus antigen frequencies between late onset diabetics and controls

HLA antigen	Normal controls (N = 123) (%)	Lean and/or ketosis-prone (N = 54) (%)	RR*	Obese and not-ketosis-prone (N = 69) (%)	RR*
DR1	13.8	9.3	0.64	21.7	1.73
DR2	30.9	7.4	0.18†	27.5	0.85
DR3	32.5	38.9	1.32	26.1	0.73
DR4	13.8	42.6	4.63†	27.5	2.37‡
DR5	4.9	7.4	1.56	4.4	0.89
DR7	25.2	9.3	0.30‡	17.4	0.62

* Relative risk estimated by Woolf's odds ratio.
† $P < 0.05$ after correction.
‡ $P < 0.05$ before correction.

TABLE 4
Comparisons of DR locus antigen frequencies between subgroups of late onset diabetics and controls

HLA antigen	Normal controls (N = 123) (%)	Lean and ketosis-prone (N = 23) (%)	RR*	Lean and not-ketosis-prone (N = 17) (%)	RR*	Obese and ketosis-prone (N = 14) (%)	RR*
DR1	13.8	8.7	0.59	5.9	0.39	14.3	1.04
DR2	30.9	0.0	0.00†	17.7	0.48	7.1	0.17
DR3	32.5	47.8	1.90	29.4	0.86	35.7	1.15
DR4	13.8	47.8	5.72‡	41.2	4.36†	35.7	3.46†
DR5	4.9	4.4	0.89	5.9	1.22	14.3	3.25
DR7	25.2	4.4	0.13†	5.9	0.19	21.4	0.81

* Relative risk estimated by Woolf's odds ratio.
† $P < 0.05$ before correction.
‡ $P < 0.05$ after correction.

DISCUSSION

The finding of previously reported HLA associations with early onset IDDM cases in a sample of late onset cases with similar characteristics would suggest that both groups share at least one common genetic influence in the etiology of their disease. The data from population studies during the past decade indicate that the HLA-A and -B antigens associated with IDDM often differ between racial and ethnic groups. However, the results of the 1980 International Histocompatibility Workshop[2] reveal significantly decreased frequencies of DR2 and significantly increased frequencies of DR4 in all early onset IDDM populations studied.

The HLA-B locus antigens most commonly found associated with early onset and late onset IDDM in Caucasian populations have been B8 and B15. Although the frequencies of these antigens were increased in the lean and/or ketosis-prone group, these findings were not significant. The lack of any significant differences with respect to the -B antigens could reflect small sample size.

The HLA-DR2 and DR4 associations of the late-onset, lean and/or ketosis-prone group found in this study are similar to the previously reported associations of HLA-DR with early-onset IDDM. Comparisons of the HLA-DR frequencies between the different subgroups of lean and/or ketosis-prone patients (Table 4) demonstrate that the strongest associations occur in the lean and ketosis-prone subgroup. The complete absence of DR2 in this subgroup suggests that the hypothesized protective effect of DR2 in the development of IDDM persists throughout life. The increase of DR4 in the lean and ketosis-prone subgroup (RR = 5.7), which was significant after correction, demonstrates that the genetic susceptibility to IDDM associated with the D/DR locus is not restricted to those under age 40.

The previously reported association with DR3 was not observed in the lean and/or ketosis-prone group, although an increase was seen in the subgroup who were both lean and ketosis prone. The reason for this lack of association with DR3 is uncertain. Some investigators have advanced a two diabetogenic allele hypothesis based initially on the observation that the risk for B8/B15 heterozygotes appeared to be higher than the risks for B8/B8 and B15/B15 homozygotes.[27–29] As HLA-DR data became available, analogous arguments were made for a distinction between DR3 and

DR4 forms of IDDM.[2,30] The DR3 form (type 1b) is proposed to be primary autoimmune in nature, while the DR4 form (type 1a) is proposed to be virally induced.[31,32] DR3 is associated with a number of autoimmune diseases[33–36] that frequently occur with IDDM.[37] Since our sample included only four patients with known coexistent autoimmune diseases, it is possible that our sample is comprised primarily of type 1a diabetics, which might be expected to have a DR4, and not a DR3, association. Alternatively, the lack of significant association with DR3 may reflect a characteristic of the Caucasian population in this geographic area and/or small sample size.

No HLA association was observed in the obese at onset and not-ketosis-prone group after correction. We feel that most of these patients represent insulin-treated, non-insulin-dependent diabetics. The slight increase in DR4 may represent contamination by IDDM patients.

In conclusion, the results of the present study suggest that the influence of HLA-associated genes in insulin-requiring, ketosis-prone, lean at onset, primary diabetes in patients who develop their disease after age 40 is similar to that found in patients below age 40 with similar characteristics. It still remains an open question which factors influence the age at onset. It may be that individuals who develop IDDM after age 40 are identical to those with earlier onset except that they escaped an environmental trigger earlier in life.

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