Rapid Publications

Genetic Susceptibility to Diabetes Mellitus: the Distribution of Properdin Factor B (Bf) and Glyoxalase (GLO) Phenotypes

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SUMMARY

The distribution of phenotypes controlled by two loci on chromosome 6 has been studied in a series of 239 patients with type 1 (insulin-dependent) and 297 patients with type 2 (non-insulin-dependent) diabetes mellitus. At the properdin factor B (Bf) locus there is a significant increase in the frequency of the *Bf*^{S1} and *Bf*^{F1} alleles for type 1 patients, and the combined increase in frequency of *Bf*^{S1} and *Bf*^{F1} in those patients is highly significant. The relative risk for F1 is 6.2 and for F1 and S1 combined is 5.3. These results confirm the association with F1 reported recently by Raum and co-workers in Boston. The two rare alleles *Bf*^{S1} and *Bf*^{F1} are in significant negative disequilibrium with HLA B8.

For the glyoxalase (GLO) locus there is a slight but nonsignificant increase in the frequency of the *GLO*^{2} allele, but a significant disturbance in the distribution of the GLO phenotypes for type 2 patients. These results for the GLO alleles may be due to stratification in our series of type 2 patients. Further studies are in progress to test this hypothesis. DIABETES *28*:949–951, October 1979.

Renewed attention has been given recently to the role of genetic factors in susceptibility to diabetes mellitus,[1–4] and this has received added impetus from the studies of the distribution of human leucocyte antigens (HLA) in diabetic patients. Several surveys[5–9] have shown a significant increase in some antigens, particularly HLA B8 and BW15 for Caucasian patients with type 1 (juvenile or insulin-dependent) diabetes mellitus, and the association is even stronger with HLA DW 3 and DW 4. Among Japanese patients with type 1 diabetes, there is an increased risk associated with HLA B12 or BW 22.[10,11] These associations with HLA antigens have not been observed for patients with type 2 (maturity-onset or non-insulin-dependent) diabetes mellitus. However, twin studies suggest that susceptibility to type 2 diabetes of the non-insulin-dependent type does have a strong genetic component.[12]

As part of the search for further associations between diabetes and other genetic markers, Raum et al.[13] recently reported a highly significant increase in the frequency of the F1 type in the properdin factor B (Bf) system in patients with juvenile diabetes. We also have similar evidence for a significant increase in the frequency of some phenotypes in the serum properdin factor B (Bf) system in patients with type 1 diabetes, and for an unusual distortion in the distribution of phenotypes in the glyoxalase (GLO) system in type 2 diabetes. Both the serum system Bf and the cell enzyme system GLO are controlled by loci close to HLA on the short arm of chromosome 6.[14,15] The locus for Bf is very close to that for HLA B, while that for GLO is between HLA D and the centromere. Cudworth et al.[1,16] previously reported an increase in *Bf*^{S} for type 1 diabetes, but so far there are no reports on the distribution of GLO types in either type 1 or type 2 diabetes.

PATIENTS AND METHODS

Blood samples were collected from patients with type 1 diabetes attending the Diabetic Clinic at the Royal Children's Hospital in Melbourne and from a further series attending the Diabetic Clinic at the Royal Southern Memorial Hospital, Melbourne. The majority of patients in the latter series were of the non-insulin-dependent type with age of onset 40 yr or over. A smaller number in this series were maturity-onset cases but were on insulin therapy, while a few cases in this older age group were type 1, fully insulin dependent. Control series of blood samples were obtained from nonselected blood donors attending the Blood Transfusion Service in Canberra and Sydney. Bf and GLO typing was performed using standard procedures.[17,18]

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TABLE 1
Bf types and gene frequencies in diabetes

Series	No. tested	Bf phenotypes								Percent gene frequencies			
		S	FS	F	S_1F	SF_1	SS_1	FF_1	F_1	Bf^S	Bf^F	Bf^{S1}	Bf^{F1}
Type 1 (IDDM)	239	163	38	3	1	25	6	2	1	82.6	9.8	1.5	6.1
Type 2 (NIDDM)	292	203	74	8	1	2	4	0	0	83.2	15.6	0.9	0.3
Controls	380	248	100	20	1	5	3	3	0	79.5	19.0	0.5	1.0

RESULTS

Bf types. Four Bf alleles segregated in the series studied and in the controls. Type 1 patients have a significant increase in the frequency of the rare alleles Bf^{S1} and Bf^{F1} when compared with the controls (for the two alleles combined χ^2 for type 1 versus controls = 22.8, $P \ll 0.001$). This increase in frequency of the rare alleles is not present in the type 2 patients.

As shown in Table 1 both type 1 and type 2 patients show a small increase in the common Bf^S allele when compared with our normal controls, but the differences are nonsignificant. For both type 1 and type 2 patients there is a compensatory decrease in the frequency of the other common allele, Bf^F. This decrease is exaggerated in type 1 patients, and the difference from controls for Bf^F for these patients is highly significant ($\chi^2 = 21.5$, $P \ll 0.001$).

GLO types. The distribution of GLO phenotypes and the frequencies of the two GLO alleles is almost identical in patients with type 1 diabetes and in controls. For type 2 patients there is a decrease in the frequency of the GLO^1 allele, but the difference between the patients and controls is nonsignificant ($\chi^2 = 1.48$, $P = 0.2$–0.3). Type 2 patients, however, have an unusual distribution of GLO phenotypes. There is an excess of homozygous 2–2 individuals and a deficiency of heterozygotes compared with the number expected when the gene frequencies derived from the controls are applied to the patient series. Indeed, the type 2 series, when considered alone, is not in genetic equilibrium ($\chi^2 = 5.8$, $P = 0.02$)(Table 2).

DISCUSSION

These results confirm and extend the finding of Raum and his colleagues of a strong association between insulin-dependent diabetes and the F1 type in the Bf system, although in our own larger series, the level of association is not so high. The Boston study reported that 22.6% of their patients carry an F1 gene compared with 1.9% of their controls. In the Australian type 1 patients we have found 11.7% with an F1 gene and 0.6% and 2.1%, respectively, in type 2 patients and controls. We have also found a slight increase in the S1 gene. The relative risk in type 1 patients with F1 gene in the Bf system is 6.2, and for F1 and S1 combined it is 5.3.

TABLE 2
GLO types and gene frequencies in diabetes

Series	No. tested	GLO phenotypes			Percent gene frequencies	
		1-1	2-1	2-2	GLO^1	GLO^2
Type 1 (IDDM)	247	46	126	75	44.1	55.9
Type 2 (NIDDM)	292	58	121	113	40.6	59.4
Controls	382	72	195	115	44.4	55.6

Since type 1 diabetes is associated with an increase in the frequency of HLA B8 and BW15, it would not be surprising if there was also a change in frequency of Bf alleles, because the loci for HLA B and Bf are very close. Indeed, since it has been shown[19,20] for European and Icelandic populations that HLA B8 is in strong linkage disequilibrium with Bf^S, the frequency of Bf^S should be increased in type 1 diabetics. This was found to be true by Cudworth et al.,[16] and in the present series of type 1 patients there is a 3% increase in the frequency of Bf^S. We find a similar increase in Bf^S frequency, however, in type 2 patients. In neither series is this increase in the frequency of Bf^S significant.

Because Bf^{S1} and Bf^{F1} are associated significantly with type 1 diabetes, we have examined the linkage disequilibrium between HLA and Bf in our type 1 patients. Significant disequilibrium values occurred for HLA A1 with Bf^F and B35 with Bf^F. More interesting, however, is the finding that HLA B8 has significant negative disequilibrium values with Bf^{S1}, Bf^{F1}, and Bf^F.

Our series of type 1 patients shows the increase in HLA B8 frequency (48% versus 24%)[21] found in other studies of type 1 diabetes among Europeans. The negative disequilibrium values between HLA B8 and Bf^{S1} and Bf^{F1}, both of which also have significantly increased frequency among our type 1 patients, suggests that there is a diabetic susceptibility allele in linkage disequilibrium with HLA B8 in some cases and with Bf^{S1} and Bf^{F1} in others. The negative disequilibrium between HLA B8 and Bf^F probably reflects the known strong positive disequilibrium between B8 and Bf^S in normal European populations.

The lack of significant associations between alleles at either the Bf or GLO loci for type 2 patients is in agreement with previous studies, which have failed to show associations between HLA types and type 2 patients. Our own results indicate, however, a significant disturbance in the distribution of GLO phenotypes with an excess of 2–2 and deficiency of heterozygous 2–1 phenotypes. In the absence of evidence implicating other chromosome 6 markers in type 2 diabetes, the present results may be due to stratification in the series investigated here. Further studies are in progress to check the reproducibility of the disturbance in the distribution of GLO phenotypes, with adequate controls to eliminate confounding effects.

The genetic heterogeneity of diabetes is again demonstrated clearly in our studies of non-HLA loci on chromo-

some 6. The significant association between type 1 patients and some Bf phenotypes is not found in type 2 patients. In contrast, alleles at the other chromosome 6 locus, glyoxalase, show no significant difference from controls for either type 1 or type 2 diabetics.

We are extending these studies to diabetic patients in other parts of the Western Pacific to see if the results reported here are supported more generally.

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