Short Communications

Properdin Factor B in Black Type 1 (Insulin-Dependent) Diabetic Patients

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Summary. The properdin factor B(Bf) variant F1 was found in 20% of 70 black patients with Type 1 (insulin-dependent) diabetes compared with 7.3% of 165 control subjects, yielding a significant relative risk of 3.1. In addition, the BfF allele was negatively associated with Type 1 diabetes among blacks, resulting in a relative risk of 0.4. The data suggest that Type 1 diabetes in black Americans may be partially due to admixture of Caucasoid genes.

Key words: Properdin factor B, Type 1 diabetes, black Americans.

Type 1 (insulin-dependent) diabetes mellitus (IDDM) has been shown to be positively associated with HLA-B8, B15, B18, CW3, DR3, DR4, Dw3 and Dw4 in various racial and ethnic groups [3, 6, 8, 13, 15, 16, 23, 25]. In the majority of studies, the strongest associations have been with DR3, DR4, Dw3 and Dw4, while those with B-locus specificities appear to be secondary due to linkage disequilibrium with DR3 and DR4. In addition, Cudworth and Woodrow [6], Barbosa et al. [3] and Acton et al. [1] have suggested that an "IDDM susceptibility gene(s)" may be linked to the HLA region in Caucasoids. Similar findings seem to hold true for black Americans with Type 1 diabetes. Rodey et al. [21] and others [19, 29] demonstrated that such patients have significantly increased frequencies of the HLA antigens B8, B13, B15, DR3 and DR4 compared with healthy black control subjects.

Recently genetic markers on chromosome 6 other than HLA have been investigated for their potential association with Type 1 diabetes. Of these, properdin factor B (Bf) has been of particular interest. Through family studies, the Bf locus has been mapped at the

HLA region of chromosome 6, probably between the HLA-D/DR and the B loci [22]. In addition, it has been demonstrated that Bf is strongly associated with Type 1 diabetes in Caucasoid patients. Raum et al. [17, 18] found that 22.6% of the Type 1 diabetic patients had the BfF1 allele as opposed to 1.9% of the Caucasoid control subjects, giving a relative risk of 15.0. Similar trends were observed by Kirk et al. [11] and Dornan et al. [7], who found relative risks of 6.2 and 5.5, respectively, for Type 1 diabetes among BfF1 positive Caucasoids. This BfF1 association with Type 1 diabetes in Caucasoids has been found in populations from different geographical locations and ethnic origins. Associations with other Bf alleles have also been found. For instance, Cudworth et al. [5] found an increased association of the BfS allele in their population of Type 1 diabetic patients.

These data suggest that antigens of the major histocompatibility locus, certain alleles of the Bf system, and a 'diabetes susceptibility gene(s)' may be in linkage disequilibrium. In fact, a number of recent reports present data in support of linkage disequilibrium between BfF1 and HLA-B18 among Caucasoid diabetic patients [4, 7]. In addition, Cudworth et al. [5] found a significant increase of HLA-B8 and BfS in Type 1 diabetic patients.

At present, no information is available on the frequency of the Bf alleles in black Type 1 diabetic patients. Studies by Reitnauer et al. [19, 20] provide evidence that the occurrence of this disease in black Americans may be due to admixture of Caucasoid genes. Therefore, analysis of the Bf system in black Americans is of particular interest, since it may offer additional support to the admixture hypothesis. The purpose of this investigation was to look for the association of Bf in black patients with Type 1 diabetes from the southeastern United States.

Table 1. Distribution of Bf phenotypes in black Type 1 diabetic patients and control subjects

	Number (%) of patients with each phenotype							
	FF	FS	SS	FIS	FIF	FSI	SSI	FIFI
Black diabetic patients ^a (n = 70)	19 (27)	25 (36)	11 (16)	7 (10)	5 (9)	0 (0)	1 (1)	1 (1)
Black control subjects ^b (n = 165)	67 (41)	66 (40)	15 (9)	4 (2)	8 (5)	2 (1)	3 (2)	0 (0)

No significant deviation from distribution according to Hardy-Weinberg equilibrium:

^a $\sum \chi^2 = 2.35$; d.f. = 4

^b $\sum \chi^2 = 2.13$; d.f. = 4

Table 2. Bf gene frequencies in black Type 1 diabetic patients and control subjects

	Black control subjects (n = 165)	Black diabetic patients (n = 70)	Relative risk ^a	p
F	0.636	0.493	0.4	< 0.010
S	0.312	0.393	1.5	NS
FI	0.036	0.107	3.1	< 0.005
SI	0.015	0.007	—	—

^a Relative risks were estimated according to Woolf [28].

NS = not significant

Table 3. Selected^a phenotypic relative risks for Bf in black Type 1 diabetic patients (n = 70) and control subjects (n = 165)

Genotype	Relative risk ^b	p
FF	0.5	< 0.05
FS	0.7	NS
SS	1.9	NS
FIS	4.5	< 0.025

^a Subjects with other genotypic frequencies were too few and therefore relative risks were not calculated.

^b Relative risk estimated according to Woolf [28].

NS = not significant

Materials and Methods

Populations Studied

Serum samples from 70 black Type 1 diabetic patients and 165 healthy black control subjects from the southeastern United States were typed for properdin factor B. All diabetic patients were under the age of 40 years at onset of diabetes, insulin dependent and ketosis prone. The control sample included normal individuals without any form of diabetes, a normal fasting blood glucose and no history of diabetes of any type in their first degree relatives. All patients and control subjects were at least third generation American with no history of HLA-associated disease.

Methods

The serum samples were subjected to agarose gel electrophoresis according to the method of Teisberg [26]. The samples were electrophoresed for 1½ h and subsequently immunofixed with Bf antisera (Atlantic antibodies) according to the method of Alper and Johnson [2]. The gels were stained with 0.1% Coomassie brilliant blue R250. The comparisons of Bf were made by use of the chi-square. The *p* values were determined from a cumulative distribution of chi-square table. A probability level of 0.05 was considered significant. The relative risks were estimated using Woolf's odds ratio method [28], in which individuals positive for a particular phenotype were compared with those negative for that Bf phenotype.

Results

As shown in Table 1, the observed distribution of the Bf phenotypes for black control subjects and patients is in agreement with the expected Hardy-Weinberg distribution. The Bf gene frequencies for the black control subjects (Table 2) are similar to those in the Negroid population reported by Mauff et al. [14] ($\chi^2 = 6.96$; df = 6). The BfF1 allele was detected in 20% of the black diabetic patients compared with 7.3% of the control patients. This allele is significantly increased among black Type 1 diabetic patients ($p < 0.005$) and gives a relative risk of 3.1 (Table 2). When comparing black patients with the corresponding controls, BfFIS is significantly increased ($p < 0.025$), and the relative risk for developing Type 1 diabetes in black individuals with this phenotype is 4.5 (Table 3). The BfF allele is negatively associated among black subjects with Type 1 diabetes (71.4%, compared with 86.7% in control subjects; $p < 0.010$), giving a relative risk of 0.4 (Table 2). In addition, the significant (uncorrected) decrease of BfFF individuals among black diabetic patients ($p < 0.050$) results in a relative risk of 0.5 (Table 3).

Discussion

This is the first report of Bf and its associations among black diabetic patients. The genetic association of BfFI with Type 1 diabetes found in Caucasoids [7, 11, 18, 27] also occurs in black patients. The black diabetics have an increased frequency of the BfFIS genotype, as do Caucasoids with Type 1 diabetes [7]. In addition, we found a significantly decreased association of BfF with Type 1 diabetes in black subjects, as seen in Caucasoid diabetic patients [7]. However, at this time our sample of patients is not large enough to determine the mode of inheritance of this disease.

Studies have shown that there is a decreased incidence of Type 1 diabetes in American black subjects compared with American Caucasoids [12]. In addition, Type 1 diabetes has been shown to be rare in

black Africans [9, 10, 24]. Therefore, it has been suggested that racial admixture may account for the incidence of Type 1 diabetes among black Americans, although environmental factors may also be involved. Reitnauer et al. [19] and others [21, 29] found that the HLA antigens associated with Type 1 diabetes in black subjects are similar to those observed in Caucasoids with Type 1 diabetes. We found that the genetic associations of the Bf markers are similar for the diabetic samples of both races. At this time, there is no evidence that Bf is directly involved with the aetiology of Type 1 diabetes. Therefore, these genetic similarities add support to the hypothesis that the increased incidence of Type 1 diabetes in black Americans compared with black Africans may be partially due to racial admixture of Caucasoid genes.

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