Letters to the Editor

Several HLA Haplotypic Factors for Both Type 1 (Insulin-Dependent) and Type 2 (Non-Insulin-Dependent) Diabetes

Sir,

HLA-B15, B8 and B18 are associated with Type 1 (insulin-dependent) diabetes susceptibility gene(s) [1]. These associations are secondary to a stronger DR3 and DR4 association [2]. BfF1 has also been reported to be increased in Type 1 diabetes [3, 4]. Different HLA markers may be linked to Type 1 diabetes susceptibility in different populations: DRw8 in Japanese [5], B18 in Southern Europeans [6]. Moreover, BfF1 is peculiarly increased in the normal Spanish population [7]. On the other hand, Type 2 (non-insulin-dependent) diabetes has not been found to be associated with HLA factors except perhaps in a few cases [8]. We have mapped susceptibility genes within the HLA region in a sample of Spanish diabetic patients using available HLA markers.

Ninety-seven Type 1 and 113 Type 2 patients were typed for HLA-A, B, C and DR [9, 10] and 61 Type 1 and 101 Type 2 diabetic patients were also typed for Bf [11]. Criteria for classification were those established by the National Diabetes Data Group [12]. HLA and Bf frequencies found in the patients were compared with those found in normal subjects [7, 11]. The *p* values given are with Yates' correction and multiplied by the number of tested antigens when more than 20 were considered.

In the Type 1 patients we found that: (a) B8 (16.5%) and B15 (7.2%) frequencies were not increased; (b) B18 was increased (30.9%; $p < 0.01$); (c) DR3 (64.9%; $p < 0.0005$) and DR4 (51.4%; $p < 0.0005$) were also increased; (d) DR2 (10.8%; $p > 0.05$) was not significantly decreased; (e) DR5 (8.1%; $p < 0.005$) and DR7 (16.2%; $p < 0.005$) were significantly decreased; (f) BfF1 gene frequency (0.2) was increased ($p < 0.001$; normal BfF1 frequency is 0.05 in 330 Spaniards [11]); (g) early onset < 10 years and DR4 showed significant association ($p < 0.0005$). BfF1 relative risk (12.6; $p < 0.0005$) was similar to DR3 relative risk (12.7; $p < 0.0005$), and B18 and DR3 relative risks rose when these antigens were associated to BfF1 and lowered when they were not (B18-BfF1: 6.5; $p < 0.05$; B18-non-BfF1: 1; NS), (DR3-BfF1: 19.3; $p < 0.0005$; DR3-non-BfF1: 2.9; NS).

In our Type 2 diabetic sample we found an increase in DR3 (44.4%; $p < 0.05$). Interestingly DR3 tended to be associated by itself (without B18 and BfF1) in this particular Spanish Type 2 diabetic sample because the relative risks were higher for DR3-non-B18 (8.9; $p < 0.01$) and DR3-non-BfF1 (7.3; $p < 0.01$) than for DR3 (5.2; $p < 0.05$).

Our results on DR typing in Type 1 diabetes agree with those found by others in Caucasoids [6, 13]. The significant decrease in DR5 and DR7 in our sample supports the view that DR2, DR5 and DR7 are all secondarily decreased in different populations. B8 and B15 are not increased in our sample because in the Spanish population DR3 is linked to B18 and DR4 is not in linkage disequilibrium with B15 [7]. From our previous results [7] and those of this study, we conclude that the haplotype B18-Cw5-BfF1-DR3 carries Type 1 diabetic factors in our population and that cross-overs through generations have isolated those factors within the BfF1-DR3 segment.

DR3-non-BfF1 and non-B18 was increased in our Type 2 diabetic patients. This may be an indication that this particular DR3 does not belong to the B18-Cw5-BfF1-DR3 haplotype or the Type 1 diabetic haplotype. These findings support the view that there may be several closely linked factors or genes within an HLA haplotype, all of which could be necessary for the development of insulin dependence. Absence of one or several HLA diabetic factors may lead to the develop-

ment of Type 2 diabetes [8]. It may be that in a particular Type 2 diabetic sample one could find an isolated B18 (non-BfF1 [8]) relatively raised and in another sample an isolated DR3 (non-BfF1, non-B18) could be found relatively raised (see present data).

Yours sincerely,

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