Letter to the Editor

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The HLA Component of Type I Diabetes

To the Editor:

The conclusion of the paper by Lie et al. (1999), that the involvement of the DR-DQ genes alone does not fully explain the HLA component of insulin-dependent diabetes mellitus (IDDM), is not a new result. More importantly, the proposed approach is not reliable to pinpoint an etiological locus.

It was shown >15 years ago that the haplotypes carrying DR3 (and consequently DRB1*03-DQA1*0501-DQB1*0201) were distributed significantly differently in patients and controls (Contu et al. 1982; Thomson et al. 1988). In Contu et al. (1982), 50% of IDDM DR3 haplotypes are DR3 BfF1 B18 versus 18% for DR3 control haplotypes.

Robinson et al. (1993), as indicated by Lie et al. (1999), also reached the same conclusion by considering the segregation of DR3 alleles from homozygous parents to affected sib pairs. The nonrandom DR3 transmission they observed clearly demonstrates that not all DR3 haplotypes are at same risk. They estimated a proportion of 49% high–IDDM-susceptibility DR3 haplotypes.

In addition, the fact that the DR3DR4 individuals have a greater risk of developing IDDM than DR3DR3 individuals clearly shows that the susceptibility is not simply due to a double dose of identical sequence(s), as suggested by Todd et al. (1987), but instead to the complementation of at least two different sequences at two different loci (Clerget-Darpoux et al. 1991).

Furthermore, as discussed by the authors, "the association of a marker with disease does not necessarily reflect its proximity to the etiological locus" (Lie et al. (1999, p. 798). Indeed, the strength of allelic association between several loci does not necessarily depend on their map order. This is particularly true in the major histocompatibility complex region, in which allelic associations have probably been created during invasions, migrations from small villages to large cities (mixture of heterogeneous populations), and large epidemics (selection of protective gametes). For example, there are allelic associations between class I and class II genes or, as reported by the authors, between DQ CAR and D6S2223 but not between TAP and LMP, which are more tightly linked.

Consequently, the conclusion that "the most likely location of the proposed and novel type 1 diabetes involved gene in linkage disequilibrium with D6S2223 would be telomeric of HLA-F in the vicinity of D6S2223" (Lie et al. (1999, p. 798) ignores these considerations and cannot be reached confidently from the findings reported.

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