HLA-DR2 in two sibships with insulin-dependent diabetes mellitus

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SUMMARY We report two families selected from 124 genotyped Caucasian insulin-dependent diabetes mellitus (IDDM) families because of unusual features. In both families, all offspring are affected and four out of six bear the allele HLA-DR2 which is an uncommon phenotype among diabetic patients. Onset before the age of 1 year in all the patients of one family, association with optic atrophy in the other, and the existence of pairs of affected sibs of different HLA types in both, are infrequent findings and support the evidence of heterogeneity in IDDM.

The HLA-DR2 allele is found at a significantly lower frequency in patients with insulin-dependent diabetes mellitus than in the random population. This has led to the suggestion that a protective factor might be associated with this marker. We have genotyped 124 Caucasian IDDM patients, 53 of whom were included in a previous publication. HLA typing for A, B, C, DR, and properdin factor B (BF) alleles and haplotype assignment have been described elsewhere. DR2 was found in 12 index cases (gene frequency 0-05 in patients, 0-13 in 106 controls, \( \chi^2 = 7-707, p<0-01, RR = 0-35 \)) in the following allelic combinations: DR2/DR3: three cases; DR2/DR4: three cases; DR2/DR1: three cases; DR2/DR7: two cases; DR2/DR5: one case. Thus, in six cases, DR2 was combined with neither DR3 nor DR4 which could possibly be an expression of heterogeneity of IDDM. Of these, two families showing other unusual features (all offspring affected and existence of pairs of sibs of different HLA types) were selected for this report.

**Case reports**

**FAMILY 1 (FIG 1)**
The mother was born in 1945. Onset of IDDM occurred at the age of 9 months following a smallpox vaccination. Her three children, born in 1972, 1975, and 1981, are diabetic. The onset of IDDM occurred in II.1 at the age of 7 months after a smallpox vaccination and in II.2 (not vaccinated) at the age of 10 months following a cranial trauma. II.3 became insulin-dependent at the age of 5 months after she had shown transient hyperglycaemic episodes from birth. HLA typing showed three genotypes in the children: bc, ac, and ad. Comparisons in pairs led to the observation of two haplidential situations (II.1, II.2 and II.1, II.3) and one non-identical (II.1, II.3). The DR2 allele is carried by the mother in combination with DR3 and by two of the children, in combination with DR1 in one and with DR4 in the other. Control of IDDM is excellent in all four patients, although there is no evidence of residual \( \beta \) cell function. Cytoplasmic islet cell antibodies (ICA) were detected in the mother's serum (duration of IDDM 34 years) but not in that of the children.

**FAMILY 2 (FIG 2)**
There was no family history of IDDM. The three children, born in 1960, 1964, and 1965, show an incomplete form of the Wolfram syndrome (IDDM, optic atrophy, diabetes insipidus, deafness) inherited as an autosomal recessive disease with complete penetrance) with the presence of IDDM and ocular
suggested in one family.\textsuperscript{8} However, as these patients were only typed for HLA-A and -B, a recombination at the DR locus of the sib with a different HLA type could not be excluded.

In both families presented, the HLA-DR2 allele did not contribute to a more favourable course of the disease, since similar clinical patterns were observed whether or not patients carried DR2.

Our observation correlates with that of Weitkamp\textsuperscript{9} who found less haplotype sharing in families with three or four affected sibs than in those with two affected sibs. This raises the question of more than one susceptibility locus,\textsuperscript{10,11} which could be more apparent in families with several affected subjects, and provides evidence suggesting genetic heterogeneity of juvenile onset IDDM.

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References


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