HLA and Complement Genetic Markers in Diabetic Retinopathy

Dear Sir,

In a recent publication Dornan et al. [1] reported an association between HLA-DR4 and retinopathy in Type 1 (insulin-dependent) diabetic patients and concluded that genetically determined factors appeared to influence susceptibility to retinopathy. We have also examined the relationship between HLA and retinopathy in a smaller series of patients with Type 1 diabetes with onset before the age of 40 years and duration >10 years. Patients were divided into three groups; those with no retinal changes, those with background retinopathy and those with severe retinopathy (proliferative changes or vascular changes requiring laser therapy). HLA antigens, properdin factor B(Bf) and complement C4 allotypes were determined in these patients.

Table 1 shows the frequencies of HLA-B8, B15, DR3, DR4 and the complement variant C4B2.9 in the three patient groups examined. Although B15 and DR4 are more frequent in patients with severe retinopathy, the differences were not statistically significant. The rare factor B allele BfF1 was equally prevalent among the patients with and without retinopathy. On the other hand, the C4B allele C4B2.9 was present in 28% with severe retinopathy and only in 10% of patients with no retinopathy (NS). This variant is nearly always found on a DR4 haplotype and is also associated with rheumatoid arthritis.

Table 1. Selected HLA antigens, complement C4B2.9 and retinopathy

	No retinopathy	Minimal retinopathy	Severe retinopathy
	<i>n</i> = 15	<i>n</i> = 12	<i>n</i> = 22
B8	6 (40%)	4 (33%)	8 (36%)
B15	2 (13%)	5 (42%)	9 (41%)
	<i>n</i> = 11	<i>n</i> = 10	<i>n</i> = 17
DR3	7 (64%)	8 (80%)	10 (59%)
DR4 ^a	4 (36%)	5 (50%)	12 (71%)
	<i>n</i> = 10	<i>n</i> = 11	<i>n</i> = 18
C4B2.9 ^b	1 (10%)	2 (18%)	5 (28%)

^a Fisher's exact probability for this distribution $p = 0.22$; ^b Fisher's exact probability for this distribution $p = 0.61$

A Theory of Insulin-Receptor Interactions

Dear Sir,

It has been pointed out to me by Dr. Quast (Freiburg) that the model I have proposed for insulin binding and negative cooperativity, and which was recently published in *Diabetologia* 23: 386–390, in fact leads to positive cooperativity. This is due to an oversight on my part with Figure 5 where the isomerization step indicated for the bivalent receptor in the doubly-liganded form should also be permitted for the singly-liganded form of the hormone receptor complex. If this is not allowed then of course one obtains a preferential "loading" of doubly-liganded receptors in the isomerized form in a way dependent on the ratio of the equilibrium constants of isomerization and receptor-bound hormone association; this can only lead to positive coopera-

tivity. Although isomerization of the two liganded forms of the receptor to a similar state was discussed in the text, this was not evident in Figure 5. I apologize for this oversight and hope it will not cause any confusion.

Based upon glycosylated haemoglobin estimations, there was no significant difference in diabetic control in patients with DR4 compared with those without DR4 (mean value 13.5% versus 12.2%).

Studies of HLA and microvascular complications in Type 1 diabetes have produced conflicting results [2]. In our patients, as in other studies, the major risk factor influencing the prevalence of retinopathy is the duration of diabetes. Hence any additional genetic influence is likely to be difficult to detect. Bodansky and Wolf [3] emphasized the multiple factors contributing to retinopathy and Barbosa and Ramsay [4] have summarised some of the logistic requirements for future population studies on this question.

Yours sincerely,

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References

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