Correspondence Section

Linkage disequilibrium prevents precise definition of susceptibility determinants for idiopathic nephrotic syndrome

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Clark et al. (Clin. Sci. 1990; 78, 391-7) [1] have recently demonstrated positive associations between HLA-DR7, HLA-DQw2 and steroid-sensitive nephrotic syndrome (SSNS). Their conclusions, however, that the DR7 DRβ chain and the DQw2 DQβ chain may determine SSNS susceptibility over-interpret the presented data.

Distinct effects of DR7 and DQw2 were inferred from the positive associations of the two markers with SSNS, while the disease was not significantly associated with the DR3-DQw2 haplotype. A synergistic effect between DR7 and DQw2 is suggested by examination of the frequencies of DR7 and DR3 haplotypes in SSNS subjects. DR7-DQw9 and DR3-Dw2 haplotypes occurred together in the patients more frequently than expected by chance (6 observed versus 2.1 expected, \( \chi^2 = 7.24, P < 0.01 \)). A three-way interaction between the two haplotypes and SSNS might be tested by log-linear analysis of the raw data [2]. DR7-DQw2/DR3-DQw2 heterozygotes were not observed more frequently than expected in SSNS patients (7 observed versus 5.5 expected, \( \chi^2 = 0.43 \)), consistent with both disease susceptibility factors occurring on the DR7-DQw2 haplotype.

In spite of the strong associations described, linkage disequilibrium prevents clear identification of the susceptibility factors. The DQw2-associated factor could be any DQ-linked allele common to both the DR3-DQw2 and DR7-DQw2 haplotypes which does not occur on the DR7-DQw9 haplotype. If DQw2 is an SSNS susceptibility determinant, A2 would be an intuitively obvious candidate for synergism, since A2 and DQw2 encode DQα and DQβ chains which associate to form a single DQ molecule.

Linkage disequilibrium within the major histocompatibility complex shows racial variation [5]. Disease associations which are not consistent in all races are likely to be secondary to linkage disequilibrium between the marker gene and a distinct susceptibility allele. SSNS in the Japanese is not associated with DR7 and DQw2 [6], suggesting that either the disease differs between races, or that DR7 and DQw2 are markers for closely linked, undefined disease susceptibility alleles.

If sufficient SSNS subjects of Negroid origin could be recruited, DR7-associated disease susceptibility might be studied further. A subset of Negroid DR7-positive haplotypes carry the A3 allele of the DQA1 gene characteristic of Caucasian DR4-positive haplotypes rather than the A2 allele [5]. The DRB1 and DQB1 alleles on this haplotype are identical to those on the Caucasian DR7 haplotype. If all Negroid DR7-positive haplotypes are positively associated with SSNS, regardless of the DQA1 allele, the DQA1 gene would be unlikely to determine disease susceptibility. A difference in the DQA1 allele which correlated with a difference in disease susceptibility would support A2 as a determinant of SSNS. Trans-racial gene mapping has already proved useful in mapping disease susceptibility genes for Type 1 diabetes mellitus.

REFERENCES


