

Genetic Susceptibility for Ocular Cicatricial Pemphigoid

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Ocular cicatricial pemphigoid (OCP) is a systemic auto immune disease that produces chronic cicatrizing conjunctivitis, and, eventually (if not treated with systemic immunomodulatory drugs) corneal scarring and neovascularization. We have identified the target auto antigen for this disease (see next month's Laboratory report at this Web Site), and we have investigated the possibility that, as in so many other auto immune diseases, OCP is associated with a "genetic susceptibility."

Blood samples were obtained from 20 randomly selected unrelated caucasian patients with OCP and from their immediate family members. Control cells for subtypes for HLA-DQw3 (the gene associated with OCP discovered in preliminary studies by us) were obtained from the Tenth International Histocompatibility Workshop, and additional control cells for subtyping by RFLP were from healthy normal caucasian individuals who carried serologically determined HLA-DR4, DR5, and DQw3 genes. Haplotype assignments were made from family studies, including the RFLP variance and complotypes. All patients had definitively-proven (by immunohistochemical analysis of biopsied, inflamed, conjunctiva) OCP.

The most striking increase compared with overall controls was noted in a HLA-DQw3 gene, unassociated with any extended haplotype. On analysis by restriction fragment length polymorphism in genomic DNA, the HLA-DQw3 gene seen in our OCP patients was, in every instance, HLA-DQw7. (DQB1*0301). The frequency of HLA-DQB1*0301 in patient haplotypes compared with overall normal DR4 and DR5 DQw3-varying haplotypes was statistically significantly increased ($P < 0.003$, relative risk = 9.6).

In a separate, additional study published in the *Proceedings of the National Academy of Science* (Volume I, Page 7747-7751, 1994), we found a significant statistical association of HLA-DRB1*04 ($P=0.005$) with OCP compared to controls, in addition to the DQB1*0301 association.

It is clear from our studies that HLA-DQB1*0301 is a marker of both oral and ocular forms of ocular cicatricial pemphigoid, and our analysis of the amino acid sequence of the DQB1 alleles present in oral pemphigoid and in ocular cicatricial pemphigoid suggest that amino acid residues at position 57 and position 71-77 may be markers for the disease.