
Positive association between HLA-DRB1*07 and specific IgE responses to purified major allergens of *D. pteronyssinus* (Der p 1 and Der p 2)

Atopy was initially defined as a condition characterized by asthma, rhinitis, and eczema associated with an immediate skin test reaction to an allergen and a family history of allergy.¹ The definition of atopy has varied through the years, but central to its definition is the presence of a specific immunoglobulin (Ig)E response. The atopic state involves a specific IgE reaction and has a genetic basis. The phenotypes used to study the genetic components of atopy has varied from the triad of symptoms and skin test reactivity to that of a specific IgE response measured by skin test reactivity and/or presence of specific IgE levels and their affinity and capacity.^{2,3} The human leukocyte antigen (HLA) class II genetic polymorphisms have been suggested to be involved in the development of atopy.² As a result, many investigations to understand atopy have been directed toward studying the genetics of the specific IgE response specifically with regard to the HLA system.

The development of atopy involving the production of specific IgE is a complex process involving a variety of different steps influenced by genetic as well as environmental factors. Different genes, including those associated with the HLA system, in individuals with genetic heterogeneity influence the steps involved. The interpretation of the genetic analysis of atopy can be difficult because of the presence of multiple genes as well as the sample size, ethnic background of the subjects, and the number of variables investigated. Linkage disequilibrium to other genes in the same area may be a confounding factor. This may be a signif-

icant problem when comparing different populations. Environmental factors are many and include the amount of exposure to as well as the characteristics of the allergen, including its epitopes.

The two major types of the atopic phenotypes investigated genetically have been: 1) the measurement of a nonepitope-specific IgE responsiveness as defined by total serum IgE level and overall skin test reactivity, and 2) the epitope specific responses characterized by specific serum IgE levels and skin test reactivity. With these phenotypes the study of the genetics of atopy have been performed using the candidate gene and genome screen approaches.

Atopic individuals have higher total levels of IgE in circulation and the ability to develop multiple skin test reactions compared with their normal counterparts. These are not epitope-specific. This overall susceptibility seems to be associated and linked, using the candidate gene and genome screen approach, with several different genetic loci including those on chromosomes 5q, 11q, and 16q. They seem to involve cytokines, some of which are important in IgE isotype switching.²

A second type of inherited variation in IgE response involves the response to specific allergen epitopes. Many studies have shown that specific IgE production directed toward individual purified allergens usually measured by serum levels, in atopic individuals, are associated with particular HLA class II alleles. Elevated specific IgE to ragweed pollen allergens Amb a V in the early 1980s was demonstrated to be associated in individuals expressing

DRB1*1501 (DR2). Subsequent studies revealed other associations of immune responses to purified allergens with the HLA system (ie, Amb p V, Amb t V, and Amb a VI, DRB1*03 and DRB1*11 alleles and the immune response to *Lolium perenne* antigens, HLA-DR1 with Fed d I [cat] reactions, Ole e I [olive] with HLA-DR7 [DQ2], Par o I [*Parietaria*] with HLA-DRB1 [1101 to 1104] and Bet v I [birch] with HLA-DR3, DRB1).²

House dust mites, particularly *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, are important allergens and seem to be involved in the development of atopic rhinitis and asthma. As a result, their relationship to the HLA system has been studied. In this issue of the *Annals*, Dr. Kim et al⁴ report a positive association between HLA-DRB1*07 and to a lesser degree to HLA-DRB*13 and specific IgE responses to purified major allergens in *D. pteronyssinus* (Der p 1 and Der p 2) in a Korean population. A variety of findings have been reported by other investigators regarding the HLA system and mite sensitivity. Hu et al⁵ noted a negative association of HLA DPB1*0201 with mite sensitivity, but no significant association with HLA-DRB1, DQB1, and DQA1 in a Taiwan population. Lara-Marquez et al⁶ identified an association among the haplotype HLA-DRB1*1101, DQA1*0501, DQB1*0301, and atopic asthma that confers susceptibility to develop mite sensitive asthma in a Venezuelan mestizo population. Allele HLA-Cw7 was absent in the asthmatic patients studied and had higher frequencies in the atopic and nonatopic subjects. Thus, it may have a protective role for developing atopic asthma in the population studied. Stephan et al⁷ noted

linkage of mite-specific IgE response to HLA-DPB1, HLA-DRB1, and HLA-DQB1 in a German population. They suggest that their findings are consistent with the existence of one or more genes in the HLA class II region modifying the IgE immune response to common environmental allergens such as mites.

However, Holloway et al⁸ found no evidence for a significant association between HLA-DRB1, DQB1, and DPB1 genotypes and atopy in families with house-dust mite sensitivity. They suggest that HLA class II restriction does not play a major role in the development of the IgE response to domestic house dust allergens in the British population. In a similar population, Howell et al⁹ also found no significant associations between HLA-DR expression and DRB1 genotype with allergens such as Der p 1 and Der p 2 or atopy. Hizawa et al,¹⁰ as part of the Collaborative Study on the Genetics of Asthma, evaluated the linkage of *D. pteronyssinus*-specific IgE response with polymorphic markers on chromosome 6p21 (HLA-D region) in Caucasian families by the transmission/disequilibrium test. They demonstrated that genes in the HLA-D region might influence the expression of Der p-specific IgE responsiveness. Their article demonstrates the complexity of genetic regulation of Der p-specific IgE responsiveness by HLA-D genes, suggesting that non-HLA loci and environmental factors are also important for the development of Der p-specific IgE responsiveness.

In addition to the specific IgE immune responses, the T cell responses have also been investigated regarding HLA restriction. O'Brien et al¹¹ studied associations between allergic sensitivity to Der p 1 and HLA-DPB1 genotypes in a British population. Although allergic patients did not differ from controls in DPB1 allelic distribution, there was a correlation of DPB1*11011 with strongly reactive T cell proliferative response to Der p 1 and high titer specific IgE to *D. pteronyssinus*. In another study of cellular reactivity, they found no correlation between the Der p 2 T cell epitopes

recognized and the presence of particular HLA-DQ antigens.¹² Okano et al¹³ studied the T cell epitopes of mite Der p 2 and noted restriction by HLA-DRB1*1502 and HLA-DRB1*0405, suggesting that these T cell epitopes might be important for the onset of house-dust mite allergen in Japanese population. Their data seemed to suggest that antigen recognition of T cells as well as other unknown factors, which promote TH₂ rather than TH₁ responses, might be important for the onset of house-dust mite allergy.

Higgins et al¹⁴ analyzed HLA class II restriction of the T cell clones and found that the T cell epitope residual 110 to 131 was restricted by HLA-DRB1*0101. In contrast, peptide Der p 1 110 to 119 was recognized in association with HLA-DPB1*0402. They also demonstrated the ability of cloned T cells to proliferate to the peptide Der p 1 107 to 119 presented by HLA-DPB1*0401, HLA DPB1*0402, and HLA-DPB1*0501 expressing accessory cells. This illustrated the heterogeneity of the restriction specificity of this region of Der p 1. If these findings are adequately replicated, they may be helpful in the designing of peptide-based immunotherapy for the management of immune responses. At the present time, the exact relationship between the HLA system and the immune response as measured by specific IgE production and T cell responses to mite allergens is not clear.

The significant HLA association noted for purified allergens is compatible with the codominant expression of major histocompatibility-linked Ir genes.¹⁵ Up to the present time, no consistent findings have been reported for mites and the HLA system. One of the major problems of studying mite sensitivity is that it is a relatively complex allergen with multiple epitopes. It is unlikely that any unique HLA-D genetic sequence will be identified only among subjects responding to a particular allergen or epitope. The HLA system is necessary, but not sufficient by itself to result in an immune response to a particular allergenic epitope. The atopic model suggests that there are

many other steps in addition to the HLA system, which are needed to develop a specific IgE response. Huang et al¹⁵ reported genetic linkage of T cell receptor α/δ complex to specific IgE response. Family studies, in general, have failed to demonstrate a high heritability for the specific immune responses to a particular allergen. This suggests that environmental factors are also important for the expression of specific immune responses. Currently, considerable uncertainty exists as to the exact role a particular HLA class II genetic polymorphism has in the development of atopic conditions. Regardless, there can be little doubt that HLA genes have a crucial role in the development of the specific IgE response. As a result of improved methodology being used to investigate the genetics of complex disease, we can expect to see rapid advances, which will result in a better understanding of the genetics of specific immune responses to allergens and their relationship to atopic disease.

MALCOLM N. BLUMENTHAL, MD
Minneapolis, MN

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