

EDITORIAL

HLA immunogenetics and specific IgE responses to allergens

It is now well established that the major cause of asthma, hay fever and eczema in children and young adults is atopic allergy, a disorder characterized by persistent immunoglobulin E (IgE) responses to extrinsic protein allergens. The phenotype is multivariate, including total and specific IgE titres, skin-prick tests, medical history and provocation tests of bronchial reactivity. An arbitrarily broad definition of atopy includes nearly 40% of the population [1] and up to 10% of the population of Western European countries suffers from asthma. Not surprisingly, genetic analysis has been difficult and contradictory, despite ample evidence for heritability.

Currently, worldwide searches are underway for loci regulating the IgE response, with particular interest centring on the β subunit of the high affinity IgE receptor located on chromosome 11q [2–8]. However, genetic epidemiological studies in atopic subjects have also demonstrated several significant associations between particular human leucocyte antigen (HLA) class II phenotypes and allergic IgE (and IgG) responses to environmental allergens. These investigations are taken a stage further in the study by Young *et al.* [9] reported in the current issue of this journal.

The HLA class I (A, B and C) and class II (DR, DQ and DP) genes are located on chromosome 6p and as expressed as highly polymorphic glycoproteins on the cell surface, function in the presentation of endogenous (class I gene products) and exogenous peptides (class II gene products) to cytotoxic and helper T lymphocytes respectively. Because of the pivotal role of the HLA class II molecules in particular in regulating the immune response, combined with their extensive polymorphism, it is not surprising that particular HLA class II alleles have been implicated in susceptibility to a wide range of diseases known to have an immunological basis. Atopic allergy is no exception. Initial studies of the possible role of HLA class II polymorphism in atopy, dating from the early 1980s onwards, concentrated on pollen allergens and it has been clearly demonstrated that elevated IgE production to ragweed (*Artemisia artemisiifolia*) pollen allergens *Amb a* V, *Amb t* V, *Amb p* V and *Amb a* VI occurs in individuals expressing DRB1*1501 (DR2)-associated haplotypes [10–13]. Further studies have established population associations between DRB1*03 and DRB1*11 alleles and immune responses to rye grass (*Lolium perenne*) antigens [14,15]. In addition, it has now been established that HLA-DRB1, DRB3 and DRB5

gene products are able to restrict the recognition of house dust mite (*Dermatophagoides* spp.) determinants [16,17] in line with population associations demonstrated in the Eleventh International Histocompatibility Workshop (IHW) [18].

However, all of the above studies were based on unrelated clinically atopic individuals. The study by Young *et al.* [9] in this issue is the first major study to investigate HLA class II DR and DP associations with IgE responses to six major aeroallergens in a large number of nuclear and extended families recruited through allergy or asthma clinics. This approach is valuable since sib-pair tests for genetic linkage may be performed in addition to a search for HLA class II population associations. Four hundred and thirty-one subjects in 83 families were studied and HLA-DRB1 and DPB1 allele frequencies were determined by DNA typing, using the now well established, accurate and sensitive procedures for polymerase chain reaction (PCR) DNA amplification, combined with sequence specific oligonucleotide probe (SSOP) typing of PCR products. Since there was no difference in the frequency of HLA-DR or the five most common DP alleles between the study subjects and two control populations (one control group typed for DR, the other for DP), all allele frequency comparisons were made between reactive and non-reactive subjects in the test population. The six purified allergens used for the determination of specific IgE responses were *Der p* I and *Der p* II (from the house dust mite), *Alt a* I (from the mould *Alternaria alternata*), *Can f* I (from the dog), *Fel d* I (from the domestic cat) and *Phl p* V (from the timothy grass, *Phleum pratense*).

In summary, a limited number of weak associations between HLA-DR alleles and IgE responses to the common test allergens was observed, namely HLA-DRB1*04 with *Alt a* I and *Phl p* V, HLA-DRB1*01 with *Fel d* I (the strongest association) and HLA-DRB1*03 with *Der p* II. Of these associations, those of HLA-DRB1*04 and *Alt a* I and HLA-DRB1*01 with *Fel d* I were supported by excess sharing of the HLA haplotype concerned in affected sibling pairs, demonstrating the advantage of studying multicase nuclear and extended families in HLA and disease association studies. In addition, Young *et al.* [9] also performed logistic regression analysis to control for individual reactions to more than one antigen and thus showed that the apparent association of IgE response to *Phl p* V with DRB1*04

was due to the presence of many individuals showing an IgE response to both *Alt a I* and *Phl p V*.

Despite the low odds-ratios for the associations concerned (the rule rather than the exception in studies of HLA and disease), the results represented by Young *et al.* [9] confirm that HLA-DR alleles do modify an individual's ability to mount an IgE response to particular aeroallergens. Confirmation of the population associations by excess sharing of the HLA haplotypes in affected sib-pairs is a valuable addition to the literature. However, the authors did not include HLA-DQ genotyping in their study (HLA-DQ lies between the DR and DP sub-regions), and thus weak HLA-DQ associations with specific IgE responses may have been overlooked. In addition, while it is true that DQ alleles show extremely strong linkage disequilibrium with DR alleles such that significant HLA-DQ associations may be detected by HLA-DR typing, certain DR alleles are associated with more than one DQ allele. Thus, DQ typing would allow more accurate characterization of specific IgE response-associated HLA haplotypes. Stronger associations between a specific IgE response and HLA-DQ rather than HLA-DR may also be revealed by such approach. This has been a common finding in HLA-associated susceptibility to autoimmune diseases, including coeliac disease [19] and insulin-dependent diabetes mellitus [20]. Such studies of complete HLA class II haplotypes in atopic individuals will undoubtedly follow.

Secondly, it is informative to set the results of this large study alongside those obtained in the Eleventh IHW [18], which is, to date, the largest study of the type, although based on unrelated atopic individuals. This is particularly important since three of the allergens used in Young's study [9] (*Der p I*, *Alt a I* and *Fel d I*) were also included in the Eleventh IHW study [18]. Interestingly, while the association between HLA-DRB1*01 and IgE response to *Fel d I* was the strongest association seen in Young's study, supported by haplotype sharing in affected sib pairs, no associations between *Fel d I* responses and HLA-DRB*01 were seen in any of the 13 population groups examined in the Eleventh IHW. This was despite the fact that the highest rate of IgE responsiveness towards any of the eight allergens tested in the IHW (*Lol p V*, *Amb a V*, *Par o I*, *Bet v I*, *Cry j I*, *Fel d I*, *Alt a I* and *Der p I*) was towards *Fel d I*. The latter study included several caucasoid study groups, including US, Swedish, Italian and Germanic caucasoid populations, with the last group showing a weak positive association with DRB1*15 and a negative association with DRB1*14, not significant in multiple regression analysis. This difference between the two studies may be due to differing levels of exposure to the sensitizing allergen in the populations studied, perhaps reflecting British fondness for the domestic cat!

A comparison of Young's data showing an association between *Alt a I* IgE responsiveness and HLA-DRB1*04 with data from the IHW is also interesting. In the IHW study, similar HLA-DRB1*04 associations were seen in unrelated Bulgarian and Israeli atopic subjects. Conversely, associations with HLA-DRB1*14 were seen in US caucasoid and Swedish individuals. These apparently conflicting findings may be elucidated by further studies of complete HLA class II haplotypes in atopic individuals in these populations. For example, the same DQB1 alleles can be found on some HLA-DRB1*04 and DRB1*14 haplotypes. Finally, HLA associations with *Der p I* responsiveness are worthy of comment. While Young *et al.* [9] failed to find any positive or negative associations with any of the HLA-DR or DP alleles tested for, positive associations with HLA-DRB1*04 and DRB1*03 were seen in the Eleventh IHW in Swedish and Italian subjects respectively, although no DR associations were seen in US caucasoids. HLA-DP associations were not examined in the IHW study, but the possible role of HLA-DPB1 alleles in IgE responsiveness to *Der p I* has been a matter of some excitement since a negative association between the DPB1*0401 allele and allergic asthma was reported in a Colombian mulatto study population [21]. This finding was substantiated by a more recent report that a component of the T-cell repertoire reactive with *Dermatophagoides* spp. determinants in atopic individuals is HLA-DP restricted [22]. The same study also identified the epitope in the *Der p I* allergen recognized by HLA-DP. A further study has also reported a negative association between HLA-DPB1*0401 and aspirin tolerant and intolerant asthmatics in both German and British subjects [23]. The role of HLA-DP alleles in IgE responsiveness to *Der p I* determinants in population studies and the identification of these DP-associated epitopes is currently the object of much study and further results are awaited with great interest. Initial indications are that particular *Der p I* epitopes may be recognized by multiple HLA-DPB1 alleles with further heterogeneity in the HLA class II restriction of the same regions of the *Der p I* allergen.

Thus, while there is still considerable conflict in the literature concerning the exact HLA class II associations with IgE responsiveness to particular allergens (the DRB1*15 associations with responsiveness to *Amb a V* is still the only consistent association seen in several studies [10,18]), it is clear that such HLA associations do occur. Positive associations between specific IgE responsiveness and HLA class II alleles are consistent with the concept of strong CD4+ helper T cell (TH-2) responses to immunodominant regions of processed allergenic antigen, regulating IgE-mediated hypersensitive responses. Negative HLA class II associations may reflect weak processed antigen presentation by the expressed class II molecule in

question, lack of T-cell recognition or responsiveness, or recognition by 'suppressor' T-cells. However, a third mechanism may also be important. During fetal development, the T-cell repertoire may be influenced by the HLA haplotype of each individual [24]. Studies in mice support this concept, as do the small number of family studies reported in man, especially those comparing identical twins [25,26] and the T-cell receptor (TcR) repertoire has a direct influence on the type and strength of immunological responsiveness to a variety of antigens [27-31]. Skewing of the expressed TcR repertoire within the CD4 and CD8 T-cell subsets may result from interaction of these subsets with HLA class II and I molecules respectively during development [32]. The degree and significance of these HLA-mediated effects on TcR repertoire in T-cell mediated diseases remains controversial.

In conclusion, the role of HLA polymorphism in the generation of specific IgE responsiveness to allergens, although real, is still far from clear. The study now reported in this journal [9] represents a further advance in that IgE responses to six common Western European aeroallergens was investigated in a large panel of selected families, allowing more rigorous genetic analysis to be performed, using DNA-based methods for HLA typing—now a requirement for any serious study of this nature. It is surely right that the collaborative studies of HLA and allergy to be performed in the 12th International Histocompatibility Workshop will also be based upon multicase nuclear and extended families. Ideally these studies should include complete HLA haplotype characterization in affected and unaffected individuals, so that the effects of linkage disequilibrium, so peculiar to the HLA system, can be confounded, allowing the full potential of these studies to be realized. Finally, a role for polymorphism of the HLA class I genes should not be totally overlooked, since the natural immune response to inhaled soluble protein antigens has now been shown to involve both MHC class I-restricted CD8+ and class II-restricted CD4+ T-cells in an experimental animal model [33].

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