Asian Pacific Journal of Allergy and Immunology (1992) 10 : 151-158

SPECIAL ARTICLES

# Human Leukocyte Antigen (HLA) in Respiratory Allergy

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To the present authors, *respiratory allergy* denotes an immunological state acquired by a host as a consequence of contact with and sensitisation by allergens or antigens, and in whom subsequent interaction between the antigen and its specific humoral antibodies or specifically sensitised host cells may give rise to various clinical manifestations in respiratory organs, as an overt expression of respiratory allergic disorders.[1,2] IgE-mediated immediate hypersensitivity reactions (type I reactions) are the central component of immunopathogenesis of respiratory allergy in most instances.[3-5]

Available evidence indicates that genetic[6] as well as environmental factors[7] influence clinical expression of the atopy. For many years, it has been known that allergy tends to "run in families" and the primary basis for this familial aggregation is heredity.[8] Demonstration of immune response (Ir) and immune suppression (Is) genes within the major histocompatibility complex (MHC) stimulated research on the association of human leukocyte antigens (HLA) with numerous diseases.[9]

This review presents data concerning the role of HLA molecules in influencing the pathogenesis of allergic reactions and records possible association of these antigens in respiratory allergic conditions.

## Role of HLA in Type I Hypersensitivity Reactions

The three classes of type I hypersensitivity reactions (anaphylaxis, atopy and intolerance), although differing in the particulars of their manifestations, have a similar underlying mechanism. The initial phase of the mechanism (the "sensitisation phase") proceeds when antigen (allergen) enters the body and is picked up, processed and presented to T helper cells (Th cells) in the context of class II MHC molecules on the surface of an antigen-presenting cell (APC). Here, the HLA molecules play a critical role in presentation of the processed exogenous allergens (e.g. pollens) to the subset of T-lymphocytes through MHC-restricted interactions[10,11] and induce primarily antibody-mediated immediate hypersensitivity (Fig. 1). The allergen activated T helper cells produce lymphokines, which help to differentiate B-lymphocytes into antibody-producing plasma cells. The B-lymphocytes can also recognise the allergen *via* their surface receptors (IgM and IgD) and become transformed into plasma cells which produce antibodies of the IgE class specific to the sensitised allergen. These IgE antibodies bind to high affinity Fc receptors (Fc $\Sigma$ R) expressed on mast cells and basophils. Once the allergen binds with Fc-bound IgE antibodies on the surface of mast cells and basophils, they become activated, leading to the discharge of their mediators (histamine, heparin, prostaglandin D2, and the enzymes tryptase and acid hydrolases) contained in granules. These mediators are responsible for the clinical manifestation of allergic reactions. The lymphokines secreted from allergen-activated T helper cells participate in the activation of other inflammatory cells such as mast cells, neutrophils and eosinophils. Class II MHC molecules play an immunoregulatory role in this process. Some MHC

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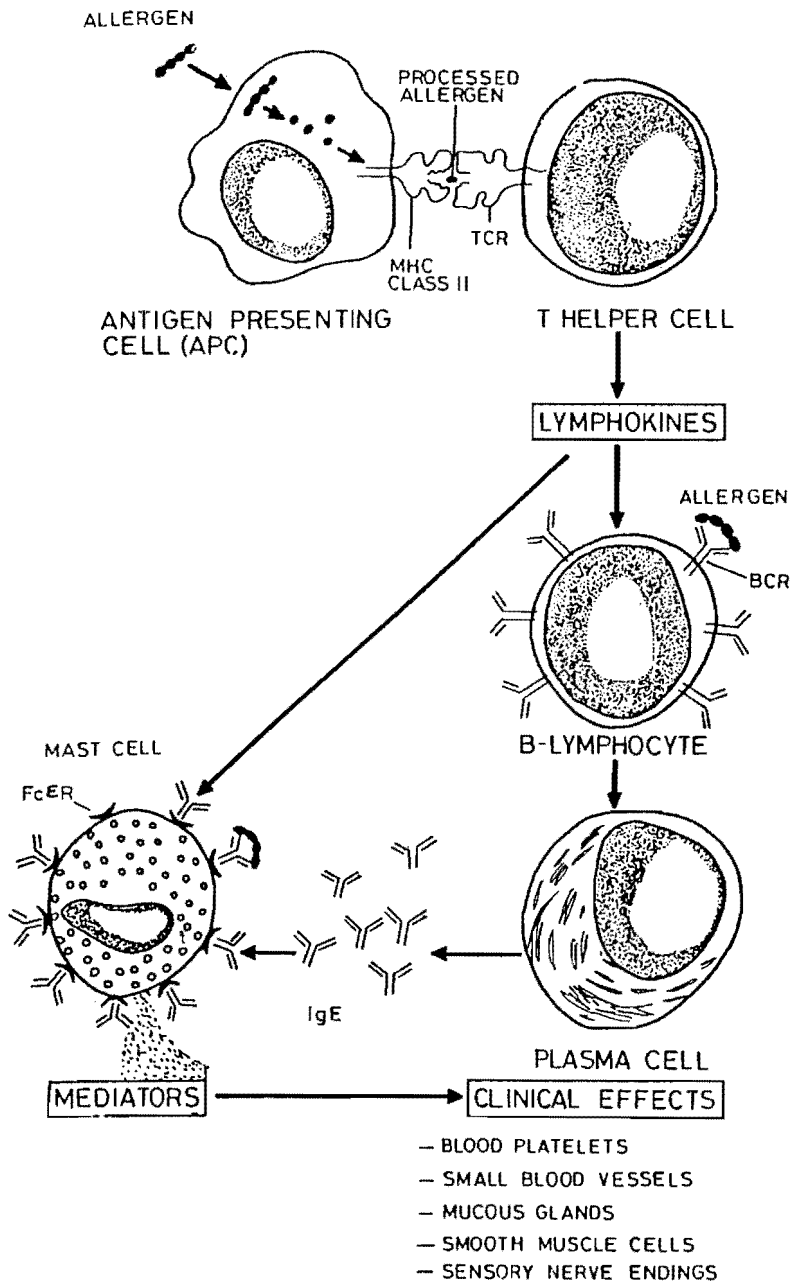


**Fig. 1.** The immunoregulatory role of HLA in type I hypersensitivity reaction. First exposure to an allergen activates both T–and B–lymphocytes. Plasma cells derived from allergen– activated B–lymphocytes secrete allergen–specific IgE antibodies. The IgE binds with surface high–affinity Fc receptors on mast cells and basophils to sensitise them, and becomes activated upon a second encounter with the same allergen. The mediators secreted by the activated mast cells and basophils initiate reactions responsible for the clinical effects. MHC, major histocompatibility complex; TCR, T–cell receptor; BCR, B-cell receptor; IgE, Immunoglobulin E; Fc Σ R, Fc receptor for IgE.

products, depending on the allele, promote efficient T-cell functions, while others produce a poor or no T-cell response and contribute towards susceptibility to or protection from the allergen.

### Genetic Control of Immune Response to Allergen

Following the demonstration of MHC-linked immune response (Ir) or immune suppression (Is) genes in animal models,[12-14] numerous studies have been conducted to explain the statistical association between HLA and diseases.[9] The existence of MHC-linked Ir or Is genes in humans also has been explained by using a series of antigens such as streptokinase and streptodornase,[15] influenza A,[16] vaccinia,[17] and tetanus toxoid.[18] However, studies on the cellular mechanisms of genetic regulation of immediate hypersensitivity reaction are limited. Sasazuki *et al.*[19] reviewed in 1983 the MHC-linked genetic control of hypersensitivity reaction to cedar pollen in patients with allergic rhinitis (cedar pollinosis). They described the HLA-B44-DRw6y-MB3-linked dominant gene (primary association was with MB3, now called DRw52, relative risk = 3.30, $p < 0.03$) that controls resistance to cedar pollinosis or nonresponsiveness to cedar pollen allergen. Another group of researchers reported a striking association between HLA-DR5 and IgG-antibody responsiveness to ragweed pollen allergen Amb a VI *(Ambrosia trifida)* in caucasoid patients with allergy.[20] Recently, O'Hehir *et al*[21] demonstrated the ability of non-stimulatory peptide analogue derived from influenza virus haemagglutinin to modulate T cell recognition of house dust mite, *Dermatophagoides* spp. The peptide inhibited the response of mite specific CD4+ T cell clones restricted by either the gene products of DRB1 (i.e. DR3, 5, 6) or DRB3 (DR52) genes. However, a clear association between HLA antigens and allergies has not been established. Probably several interacting factors may be involved in this lack of association :

(i) The concept that T-cell activation depends not only on the recognition of antigen by its antigen receptor (TCR) but also on the simultaneous recognition of MHC products.[22] Variation in the affinity of HLA molecule to the causative allergen due to the allergen's multiple epitopes and aggretopes could be the main factor for "disease heterogeneity" and "disease overlaping".

(ii) The existence of extreme polymorphism in MHC gene products leads to heterogeneity of the system, and population-dependent differences in MHC-linkage disequilibrium.

(iii) The intensity of allergen exposure and/or, increased exposure to new allergens due to rapid industrialisation and the resulting increase in atmospheric pollutants.

(iv) The possibility of multiple causative factors involved in the aetiology of allergic asthma such as variations in geographic region, season, climate, diet and infection.

### Heredity in Respiratory Allergy

Early studies have shown that asthma runs in families.[8] Coca and Cooke[23] in 1923 were among the first to demonstrate an important role of hereditary factors in allergy. They introduced the term atopy to define an inherited hypersensitivity state presenting the characteristic immediate type reaction, having circulating antibody, reagin, and manifesting peculiar clinical symptoms such as asthma, hay fever, etc. Greater concordance of asthma has been described in monozygotic as compared with dizygotic twin pairs.[24] The first detailed study demonstrating the role of heredity in bronchial asthma was published in 1916 by Cooke and Vander Veer.[25] They observed that 48% of 594 allergic patients had a family history of allergy, compared with only 14.5% of 76 control subjects, and that children with two allergic parents developed allergies more frequently (68%) than those with one allergic parent (51%). They concluded that allergy was inherited as an autosomal dominant trait. A hereditary prevalence study in an Indian population revealed that 81 of the 100 asthmatics had a positive family history of allergic diathesis in contrast to 36.6% of controls.[26] The most common allergic manifestations in their families were bronchial asthma (42%), seasonal and other rhinitis, (26%) and eczema (7%); the remaining 6% had other allergic disorders.

### HLA in Respiratory Allergy

There are several reports indicating the involvement of HLA-linked predisposing immunogenetic factors for governing susceptibility as well as non-responsiveness to the inhaled allergen. In the early 70s, studies concerning the genetic control of mouse IgE responses to low doses of complex protein antigens provided the rationale for HLA association studies with respiratory allergy.[27,28] Three lines of studies have been pursued in an attempt to understand the influence of HLA in respiratory allergic diseases. These include population, twin and family studies. Population studies have served to establish the prevalence, incidence and association of these diseases with HLA class I or class II antigens. On the other hand, studies on twins have been used to determine the relative influence of genetic and environmental factors on the development of the trait. Finally, the family studies have provided information about particular HLA-linked factors that may directly or indirectly be involved in governing susceptibility or resistance to atopic diseases.

### Population Studies

*MHC class I predisposition*

Studies suggesting an association of HLA class I antigens with respiratory allergy are summarised in

Table 1. The first report by Thorsby and his co-workers,[29] who described an insignificantly increased prevalence of a haplotype, A1-B8, in childhood asthmatic patients and significantly increased frequency of the same haplotype (4 out of 6 positive) in children with intrinsic asthma. This haplotype has also been shown to increase significantly in patients with extrinsic asthma coupled with other respiratory dysfunctions, such as IgA deficiency[30] and nasal polyp.[31] Similarly, an increased homozygosity of "public" specificity, HLA-Bw6, has been reported in patients with intrinsic asthma in two Western caucasian population groups, namely, English[32] and North Americans.[33]

Conflicting reports exist in the literature regarding the association of asthma with HLA class I antigens. Thurton *et al*[34] studied HLA antigens in three groups of asthmatic patients: (i) intrinsic asthma (n = 41); (ii) extrinsic atopic asthma (n = 40); and (iii) allergic bronchopulmonary aspergillosis (n = 41), and failed to find an association in any of them. Similarly, a study composed of a random group of *Alternaria*-sensitive (n = 100) and perennial non-allergic asthmatics (n = 87) also showed no association of HLA-A, -B and -C loci antigens.[35]

Turner *et al*[36] in 1977 reported differing frequencies of common HLA antigen combinations in some atopic syndromes. They found an increased prevalence of the HLA haplotype, A1-B8, and less frequent occurrence of the A3-B7 combination in allergic subjects presenting with eczema, than in those presenting with hay fever. Further A1-B8 was more frequent (36%) in cases of eczema complicated by asthma and/or hay fever, and least frequent (5%) in cases of hay fever alone, considerably above and below the frequency in the general population (17%). Blumenthal *et al*[37] in 1975 described high prevalence of HLA-DR2 in 204 unrelated individuals with ragweed sensitivity and significant positive correlation of IgE Ra5 immune response with the extended haplotype B7-DR2-SC31. March *et al*[38,39] reported a significant association between allergic skin test response to short ragweed pollen allergen Ra5 and HLA-B7. Subsequently, these investigators demonstrated significant IgG response towards an artificial immunisation (immunotherapy) of short ragweed allergen, Ra 5S (*Ambrosia artemisiifola)*[40,41] and to its homologue giant ragweed pollen allergen Ra 5G *(Ambrosia trifida),* which exhibited particularly striking association with HLA-Dw2 and DR2 in caucasoid populations.[42] The same group further demonstrated striking association between HLA-DR5 and IgG antibody responsiveness to Amb a VI (Ra6).[43]

*MHC class II predisposition*

Distribution of HLA class II antigens in patients with respiratory allergy has been studied in several population groups (Table 2). The earlier studies of Morris *et al* (1977)[44] showed a non-significant increase in the frequency of A1-B8 haplotype in extrinsic asthmatics and a non-significant decrease of B12 in intrinsic asthmatics in a caucasian population. Subsequently, they studied HLA-DR profile in three groups asthmatic patients ((intrinsic asthma, n = 33; extrinsic asthma, n = 34; *Aspergillus*-sensitive asthma, n = 36) and failed to find a definite association with HLA class II antigens. Incidentally, B12 was increased in the allergic asthmatics (46% *vs* 29% controls) and it is suggested that this allele may be associated with an ability to produce IgE antibodies. Further, antigens A3, B7, and DR2 showed a decreased frequency in intrinsic asthma (24, 12 and 9% *vs* 32, 26 and 24%, respectively, in controls). Finally, B8 and DR3, which showed a moderate increase in frequency in all these groups of asthmatics, occurred in five of the seven patients with low atopy by persisting antibodies to *Aspergillus fumigatus.*[45] Recently, the HLA-DR antigen profile of 12 aspirin-sensitive asthmatic patients (6 males, 6 females) of Western caucasian origin showed a statistically insignificant increase of blank alleles at the DR locus (DR-), raising the question of whether a correlation may exist with an as yet undefined DR antigen.[46]

A significant positive association between Chinese childhood asthma and HLA-DR2 and a negative association with HLA-DR4 has been reported.[47] The study included 176 asthmatic children with elevated total serum IgE levels, and positive skin test to crude house-dust mite and 231 unrelated healthy adults for HLA-D typing. While DR4 was much less frequent in patients than in controls (16.0% *vs* 32.4%), DQw2 occurred with much higher frequency in patients than in the control group (25.0% *vs* 13.0%). A recent report using oligonucleotide typing showed a decreased frequency of the DPB1* 0401 allele in patients with allergic asthma in a mulatto ethnic group prevalent in Cartagena, Colombia.[48] According to their study, DPB1*0401 could be acting as an immune suppressor (Is) gene that down-regulates the IgE respose to mites, suggesting that this gene could confer resistance to allergic asthma and other atopic diseases.

**Twin Study**

Twins constitute the ideal study group for asthma since both hereditary and exogenous factors contribute to the development of allergic disease. The largest group, encompassing 7,000 twin-pairs was reported by Edfors-Lubs in 1971.[24] She found the prevalence of asthma to be 3.8 percent, but concordance among monozygotic twins was only one set in five compared to the dizygotic twins in which it was once in 20 pairs. This study also revealed that most allergic children were born in

**Table 1.** HLA class I antigen in patients with respiratory allergy.

| Study population | Patients | No. of patients | HLA | Reference |
|---|---|---|---|---|
| American caucasian | Extrinsic asthma | 41 | ↑ A2, ↓ B8 | Rachelefsky *et al* (1976) |
| | Hay fever | 41 | ↓ B5 | Bruce *et al* (1976) |
| | Intrinsic asthma | 39 | ↑ Homozygosity of Bw6 | Flaherty *et al* (1977) |
| English | Intrinsic asthma | 26 | 81% homozygous for HLA–Bw6 | Brostoff *et al* (1976) |
| | Eczema. Hay fever | – | ↑ A1/B8 and ↓ A3/B7 haplotypes in Eczema than Hayfever. | Turner *et al* (1977) |
| | Extrinsic asthmatics& Intrinsic asthmatics | 100 | Nonsignificant ↑ A1/B8 Nonsignificant ↓ B12 | Morris *et al* (1977) |
| | Intrinsic asthma<br>Extrinsic atopic asthma<br>Allergic bronchopulmonary aspergillosis | 41<br>40<br>41 | No association | Thurton (1979) |
| | Hay fever | 39 | No association | Gwynn and Mackintosh (1979) |
| Norwegian | Childhood asthmatics<br>Children with intrinsic asthma | 35<br>4 | Nonsignificant ↑ A1/B8<br>↑ A1/B8 | Thorsby *et al* (1971) |
| Danish | Extrinsic asthmatic children with IgA deficiency. | 37 | Significant ↑ A1/B8 | Ostergaard and Erickson (1979) |
| Asian Indian | Atopic allergy | – | No association | Dasgupta *et al* (1977) |
| Others | Extrinsic asthmatic children with nasal polyps | 29 | Significant ↑ A1/B8 | Moloney and Oliver (1980) |
| | Alternaria–sensitive adthmatics<br>Perennial non–allergic asthmatics | 100<br>87 | No association | Flaherty *et al* (1980) |

**Table 2.** HLA class 2 antigens in patients with respiratory allergy.

| Study population | Patients | No. of patients | HLA | References |
|---|---|---|---|---|
| American caucasians | Aspirin sensitive asthma | 12 | insignificant ↑ DR- (blank) | Jones *et al* (1984) |
| English | Intrinsic asthma | 33 | ↓ A3/B7/DRw2 | |
| | Extrinsic asthma | 34 | ↑ B12 | |
| | Aspergillus sensitive asthma | 36 | No association | Morris *et al* (1980) |
| Mullatto of Columbia | Allergic asthma | 43 | ↓ DPB1*0401 | Caraballo *et al* (1991) |
| Chinese | Asthmatic children | 176 | ↓ DR4, DQw2 | Hsieh *et al* (1991) |
| Thai | Chronic obstructive pulmonary disease | | ↓ DR7 | Chandanayingyong *et al* (1988) |
| Others | Ragweed sensitivity individuals | 204 | ↑ DR2 | Blumenthal *et al* (1975) |

families in which neither parent was allergic (67%). No HLA association studies with atopic allergy in twins are available in the literature.

### Family Studies

Several investigators have studied families with allergic conditions, with a view to define the involvement of genetic factors in allergy. One of the earliest was a compilation of 594 allergic patients by Cooke and Vander Veer (1916)[25] who reported that at least 48.4 percent of these patients gave a positive family history of allergy. One fourth of these families had both a parent as well as a child affected with asthma and in addition there were 14 families that had at least two or more siblings affected with asthma, thus implicating family transmission of the disease in 25 percent of their total sample. On the other hand, in a family study with small sample size, no direct evidence was found for linkage of a hypothetical asthma locus with HLA or for a significant association of asthma with any HLA haplotype.[49]

A study involving immune responsiveness (IgE-mediated skin sensitivity, IgG antibody production, and lymphocyte response) to four different highly purified pollen allergens (Antigen E, Ra3 and Ra5 from short ragweed, *Ambrosia elatior;* Group I allergen from rye grass, *Lolium perenne)* in 13 families failed to demonstrate any evidence of an association between specific familial HLA haplotypes and specific immune response.[50] Another investigation on 98 members belonging to 17 families with hay fever revealed no significant correlation between hay fever, total or specific IgE and a certain HLA antigen and/or a haplotype.[51]

The familial occurrence of atopy, defined by skin prick test responses and serum immunoglobulin E titers to common inhaled allergens (mixture of purified and dialysed allergens like timothy-grass pollen, coxsfoot-grass pollen, cat dander, dog dander, willow pollen, birch pollen, oak pollen, *Alternaria, Cladosporium,* and *Aspergillus)* was studied in 239 members of 40 nuclear and three extended families.[52] In each extended family, atopy was transmitted through affected individuals in a vertical pattern clearly suggesting autosomal dominant inheritance. This conclusion was supported by the findings of 31 out of 47 (66%) offspring of marriages between atopic and unaffected parents, being atopic. Using molecular genetic lingkage analysis, these investigators confirmed that the transmission of atopy was linked with a maximum load score of 5.58 to a DNA polymorphism defined by p-lambda MS.51, which confirms

dominant inheritance and assigns the gene locus to chromosome 11.[53] A recent study of HLA haplotype segregation in 20 families with multiple cases of allergic asthma suggested the existence of an HLA-linked recessive gene controlling the IgE immune responsiveness to mite allergens *(Dermatophagoides farinae)* and conferring susceptibility to allergic asthma.[54]

## CONCLUSION

The definitive factors that enhance IgE responsiveness in atopic individuals are still not known. Familial aggregation, implying a genetic predisposition, is a long-established feature of atopy. Studies on the involvement of HLA-linked factors influencing either the clinical expression of disease or total production of serum IgE have not provided any concrete association. This might be due to the involvement of several interacting factors including environmental ones. Nevertheless, HLA antigen analysis in families with respiratory allergy has demonstrated increased or decreased incidence of particular HLA antigens/haplotypes, thus suggesting the existence of MHC-linked Ir and Is genes to allergen, that confer susceptibility and/or protection to IgE-mediated immediate hypersensitivity reactions.

### REFERENCES


1. Bovornkitti S, Pushpakom R, Maranetra N, Charoenratanakul S. Common pulmonary allergic disorders in Southeast Asia. In : Sharma OP, ed. Lung disease in the tropics. New York : Marcel Dekker, 1991 : 383-97.
2. Bovornkitti S, Tuchinda M. Respiratory allergy and Immunoglobulin E. Intern Med 1991; 7 : 129-31.
3. Durham SR. Leukocyte activation following IgE dependent mechanisms in bronchial asthma. Clin Rev Allergy 1989; 7 : 49-72.
4. Platts-Mills TAE, deWeck AL. Dust mite allergens and asthma- a worldwide problem. J Allergy Clin Immunol 1989; 83 : 416-27.
5. Chapman MD. Mite allergens and asthma. Curr Op Immunol 1990; 2 : 523.
6. Hopp RJ, Townley RG. Genetics of asthma. In : O'Byrne PM, ed. Asthma as an inflammatory disease. New York : Marcell Dekker, 1990.
7. Anderson HR, Bailey PA, Cooper JS, Palmer JC. Influence of morbidity, illness label and social, family and health service factors on drug treatment of childhood asthma. Lancet 1981; 2 : 1030-2.
8. Schwartz M. Heredity in bronchial asthma. Acta Allergol 1959; 5 (Suppl. 2) : 1-128.
9. Tiwari JL, Terasaki PI. HLA and disease association. New York : Springer-Verlag, 1985.
10. Schwartz RH. T-lymphocyte recognition of antigen in association with gene products of the major histocompatibility complex. Ann Rev Immunol 1985; 3 : 237-361.
11. Schwartz RH. The interaction of antigen and the histocompatibility molecule during T-cell activation. Prog Clin Biol Res 1985; 172B : 333-41.
12. McDevitt HO, Benacerraf B. Genetic control of specific immune responses. Adv Immunol 1969; 11 : 31.
13. McDevitt HO,Chinitz A. Genetic control of the antibody response : relationship between immune response and histocompatibility (H-2) type. Science 1969; 163 : 1207-8.
14. Benacerraf B, McDevitt HO. Histocompatibility-linked immune response genes. Science 1972; 175 : 273-9.
15. Greenberg LJ, Gray ED, Yunis EJ. Association of HL-A5 and immune responsiveness *in vitro* to streptococcal antigens. J Exper Med 1975; 141 : 935-43.
16. Spencer MJ, Cherry JD, Terasaki PI. HLA antigens and antibody response after influenza A vaccination. Decreased response associated with HLA type w16. New Engl J Med 1976; 294 : 13-6.
17. deVries RRP, Kreeftenberg HG, Loggen HG, vanRood JJ. *In vitro* immune responsiveness to vaccinia virus and HLA. New Engl J Med 1977; 197 : 629-6.
18. Sasazuki T, Kohno Y, Iwamoto I, Tanimura M, Naito S. Association between an HLA haplotype and low responsiveness to tetanus toxoid in man. Nature 1978; 273 : 359-60.
19. Sasazuki T, Nishimura Y, Muto M, Ohta N. HLA linked genes controlling immune response and disease susceptibility. Immunol Rev 1983; 70 : 51-75.
20. Marsh DG, Freidhoff LR,Ehrlich-Kantzky E, Bias WB, Roebber M. Immune responsiveness to *Ambrosia artemisiifolia* (short ragweed) pollen allergen Amb a VI (Ra6) is associated with HLA-DR5 in allergic humans. Immunogenetics 1987; 26 : 230-6.
21. O'Hehir RE, Busch R, Rothbard JB, Lamb JR. An *in vitro* mode of peptide mediated immunomodulation of the human T cell response to *Dermatophagoides* spp. (housedust mite). J Allergy Clin Immunol 1991; 87 : 1120-7.
22. van Eden W, deVries RRP, van Rood JJ. The genetic approach to infectious disease, with special emphasis on the MHC. Dis Markers 1983; 1 : 221-42.
23. Coca AF, Cooke RA. On the classification of the phenomena of hyperresponsiveness. J Immunol 1923; 8 : 163-72.
24. Edfors-Lubs M. Allergy in 7000 twin pairs. Acta Allergol 1974; 26 : 249-85.
25. Cooke RA, Vander Veer A. Human sensitization. J Immunol 1916; 1 : 201-305.
26. Mullick RNB, Mullick SB. Heredity in bronchial asthma and other allergic diathesis. J Ind Med Assoc 1987; 85 : 44-47.
27. Levine BB, Vaz NM. Effect of combinations of inbred strain, antigen and antigen dose on immune responsiveness and reagin production in the mouse. Int Arch Allergy Appl Immunol 1970; 39 : 156-71.
28. Vaz NM, Levine BB. Immune responses in inbred mice to repeated low doses of antigen: relationship to histocompatibility (H-2) type. Science 1970; 168 : 852-4.
29. Thorsby E,Engeset A, So L. HL-A antigens and susceptibility to disease. A study of patients with acute lymphoblastic leukemia, Hodgkin's disease and childhood asthma. Tissue Antigens 1971; 1 : 147-52.
30. Ostergaard PA, Ericksen J. Association between HLA-A1/B8 in children with extrinsic asthma and IgA deficiency. Eur J Pediat 1979; 131 : 263-70.
31. Moloney JR, Oliver TD. HLA antigens, nasal polyps and asthma. Clin Otolaryngol 1980; 5 : 183-9.

32. Brostoff J, Mowbray JF, Kapoor A, Hollowell SJ, Rudolf M, Saunders KB. Eighty percent of patients with intrinsic asthma are homozygous for HLA-w6: Is intrinsic asthma a recessive disease? Lancet 1976; 2 : 872-3.

33. Flaherty DK, Geller M, Bach FH, Reed CE. Frequency of W4 and W6 antigens in perennial, nonallergic asthmatics. J Allergy Clin Immunol 1977; 60 : 236-7.

34. Thurton CWG, Morris L, Buckingham JA, Lawler SD, Turner-Warwick M. Histocompatibility antigens in asthma : population and family studies. Thorax 1979; 34 : 670-9.

35. Flaherty DK, Geller M, Surfus JE, Leo GM, Reed CE, Rankin J. HLA antigen frequencies and natural history in *Alternaria* sensitive perennial nonallergic asthmatics. J Allergy Clin Immunol 1980; 66 : 408-16.

36. Turner MW, Brostoff J, Wells RS, Stokes CR, Soothill JF. HLA in eczema and hayfever. Clin Exper Immunol 1977; 27 : 43-47.

37. Blumenthal M, Awdeh Z, Alper C, Yunis E. Ra5 immune responses, HLA antigens and complotypes. J Allergy Clin Immunol 1975; 75 : 155A.

38. Marsh DG, Bias WB, Hsu SH, Goodfriend L. Association of HL-A7 cross-reacting group with a specific reaginic antibody response in allergic man. Science 1973; 179 : 691-3.

39. Marsh DG, Bias WB, Santilli J, Schacter B, Goodfriend L. Ragweed allergen Ra5: a new tool in understanding the genetics and immunochemistry of immune response in man. Immunochemistry 1975; 12 : 539-43.

40. March DG, Hsu SH, Roebber M, *et al.* HLA-Dw2: a genetic marker for human immune response to short ragweed pollen allergen Ra5. I. Response resulting primarily from natural antigenic exposure. J Exper Med 1982; 155 : 1439-51.

41. Marsh DG, Meyers DA, Freidhoff LR, *et al.* HLA-Dw2: a genetic marker for human immune response to short ragweed pollen allergen Ra5. II. Response of following ragweed immunotherapy. J Exper Med 1982; 155 : 1452-63.

42. Roebber M, Klapper DG, Goodfriend L, Bias WB, Hsu SH, Marsh DG. Immunochemical and genetic studies of Amb t.v. (Ra 5G), and Ra 5 homologue from giant ragweed pollen. J Immunol 1985; 134 : 3062-9.

43. Marsh DG, Freidhoff LR, Ehrlich-Kantzky E, Bias WB, Roebber M. Immune responsiveness to *Ambrosia artemisiifolia* (short ragweed) pollen allergen Amb a VI (Ra6) is associated with HLA-DR5 in allergic humans. Immunogenetics 1987; 26 : 230-6.

44. Morris MJ, Vaughan H, Lane DJ, Morris PJ. HLA in asthma. Mongr Allergy 1977; 11 : 30.

45. Morris MJ, Faux JA, Ting A, Morris PJ, Lane DJ. HLA-A, B and C and HLA-DR antigens in intrinsic and allergic asthma. Clin Allergy 1980; 10 : 173-9.

46. Jones DH, May AG, Candemi JJ. HLA-DR typing of aspirin sensitive asthmatics. Ann Allergy 1984; 52 : 87-9.

47. Hsieh KH, Shieh CC, Hsieh RP, Liu WJ. Association of HLA-DQw2 with Chinese childhood asthma. Tissue Antigens 1991; 38 : 181-2.

48. Caraballo L, Marrugo J, Jimenez S, Angelini G, Ferrara GB. Frequency of DPB1*0401 is significantly decreased in patients with allergic asthma in a mulatto population. Human Immunol 1991; 32 : 157-61.

49. Brady RE, Glovsky MM, Opelz G, Terasaki P, Malish DM. The association of an HLA Asthma associated haplotype and immediate hypersensitivity in familial asthma. J Immunogenetics 1981; 8 : 509-17.

50. Black PL, Marsh DG, Jarrett E, Delespesse GJ, Bias WB. Family studies of association between HLA and specific immune responses to highly purified pollen allergens. Immunogenetics 1976; 3 : 349-68.

51. Geller-Bernstein C, Keret N, Zamir R, *et al.* HLA antigens A, B, C and DR in nayfever families of similar environmental conditions. Exper Clin Immunogenet 1984; 1 : 66-9.

52. Cookson WOCM, Hopkins JM. Dominant inheritance of atopic immunoglobulin E responsiveness. Lancet 1988; 1 : 86-8.

53. Cookson WOCM, Sharp PA, Faux JA, Hopkins JM. Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q. Lancet 1989; 1 : 1292-4,

54. Caraballo LR, Hernandez M. HLA haplotype segregation in families with allergic asthma. Tissue Antigens 1990; 35 : 182-6.