

From Sapporo Municipal General Hospital, Department of Pathology,
Hokkaido University School of Medicine, Sapporo, and Department of
Pathology, Asahikawa Medical College, Asahikawa, Japan.

INHERITANCE OF ASTHMA IN FAMILIES AND ITS LINKAGE TO HLA HAPLOTYPES

By

Y. WAGATSUMA, H. YAKURA, E. NAKAYAMA, A. WAKISAKA,
M. AIZAWA, M. MIYATA, R. MATSUYAMA, M. SATO
& K. ITAKURA

From early studies, there is strong evidence that genetic factors operate in each of the major allergic manifestations. Recently, several attempts have been made to analyze the genetic factors involved in allergy by using major histocompatibility antigens as genetic markers. Two main approaches have been used for the investigation: (1) population studies of highly allergic individuals; (2) studies in allergic families.

Thorsby & Lie (11) have reported an association of the HLA haplotypes 1-8 and 2-BB with severe childhood asthma. Marsh et al. (7) have found evidence of a highly significant association between possession of the B7 cross-reacting group and IgE and IgG antibody responses to a minor ragweed pollen allergen Ra5. These two studies are among the first approaches.

On the other hand, Levine et al. (5) have demonstrated linkage between HLA haplotype and sensitivity to antigen E within a family. More recently, Blumenthal et al. (3) have also shown linkage between an Ir gene for antigen E (IrE) and the B locus of HLA in a large three-generation family comprising 57 members. However, Marsh et al. (6) were unable to find a significant correlation of allergy with HLA,

and Bias & Marsh (2) commented upon several points of the studies of Levine et al. (5) and Blumenthal et al. (3).

At the present time, problems concerning the participation of an HLA-linked Ir gene to allergy are not completely settled.

In order to see whether an HLA-linked gene (e.g. disease susceptibility gene or immune response gene) is involved in the pathogenesis of asthma, we investigated an association between clinical asthma and HLA haplotypes in four families.

MATERIAL AND METHODS

Thirty-one members belonging to four families in which asthma occurred in more than three members, and in which there were at least three children, were studied in terms of clinical symptoms, serum IgE levels and HLA haplotypes. The patients with asthma were diagnosed at the Allergy Outpatient Clinic, Sapporo Municipal General Hospital. The diagnosis was established by clinical history and by intradermal and provocation tests using commercial allergen preparations (12). These included six pollen allergens of white birch, white oak, orchard grass, timothy, wormwood and short ragweed, two mold allergens of *Candida albicans* and *Alternaria* (Hollister-Stier Laboratories, Los Angeles), and an extract of house dust (Torii Co., Tokyo).

Total serum IgE levels and specific IgE levels to various allergens were measured by Phadebas RIST and RAST (Pharmacia, Sweden), respectively (14, 15).

HLA typing was performed by the two-stage microlymphocytotoxicity test of Amos (1). At least two well-defined antisera were used to determine the following 23 HLA specificities (13):

A locus: A₁, A₂, A₃, A₉, A₁₀, A₁₁, A₂₈ and A_{W19} (not subdivided).

B locus: B₅, B₇, B₈, B₁₂, B₁₃, B₁₄, B₂₇, B_{W15}, B_{W16}, B_{W17}, B_{W21}, B_{W22J}, ('Sa 1'; Japanese specific variant of B_{W22}), B_{W55} and B_{W40}.

Assignment of haplotypes was based on inheritance patterns within the family.

RESULTS

Two representative families are presented.

Fig. 1 and Table 1 show data on the pedigree, HLA typing and clinical examinations of the NU family. In this family, three of the four family members with HLA haplotype A₉, x of the propositus (# 1) have been diagnosed as asthmatic.

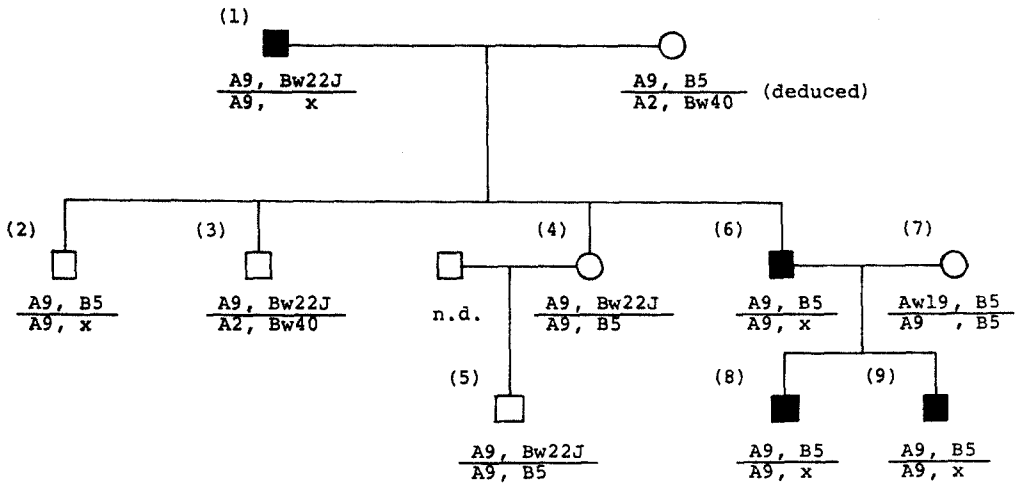


Fig. 1.

Family NU. Patients with asthma are represented as solid squares. Asthma-associated haplotype is A9, x. n.d. = not done.

None of the three subjects with the other haplotype A9, Bw22J of the propositus have asthma.

Fig. 2 and Table 2 represent the data of the SH family. Of the blood relatives of the propositus (# 1), four out of five individuals with A2, x have asthma. None of the two subjects

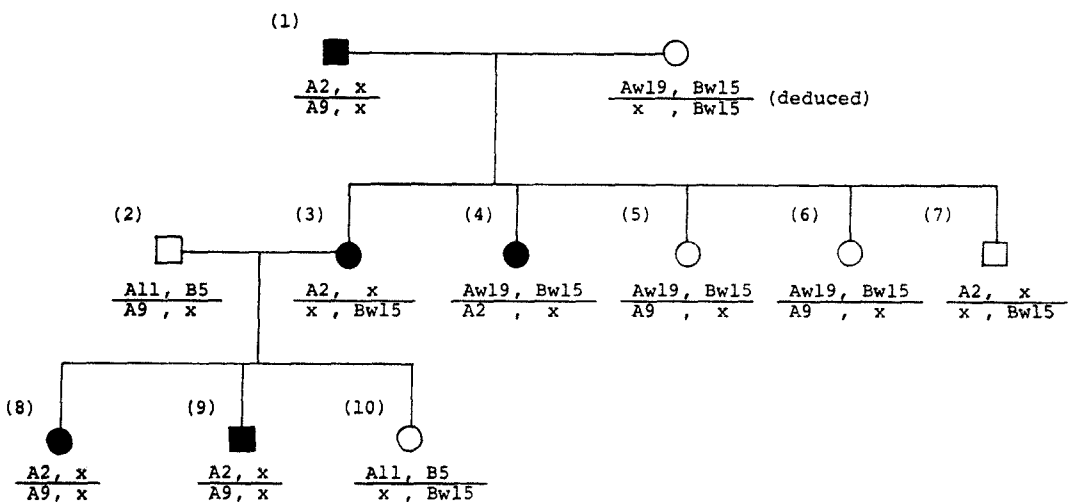


Fig. 2.

Family SH. Patients with asthma are represented as solid squares or circles. Asthma-associated haplotype is A2, x.

TABLE I
Clinical and Immunological Data of NU Family.

Subject	Symptoms of asthma	Etiology of asthma*	Asthma-associated HLA haplotype A9, x	IgE (U/ml)	WB*	RAST** O	WW	SR
1	+	n.d.	+	n.d.	o	1	o	o
2	—		+	81		n.d.		
3	—		—	122		n.d.		
4	—		—	n.d.	o	1	o	o
5	—		—	65	o	o	o	o
6	+	HD, C	+	4200	o	o	o	o
7	—		—	1500	o	o	o	o
8	+	HD, C, SR, O	+	n.d.	o	1	o	o
9	+	HD, SR	+	2300	o	o	o	o

* Allergens: HD: house dust, C: *Candida albicans*, SR: short ragweed, O: orchard grass, WB: white birch, WW: wormwood.

** RAST: o: negative, 1: borderline, 2: clear positive, 3: strong positive, 4: highly positive.
n.d. = not done.

TABLE 2
Clinical and Immunological Data of SH Family.

Subject	Symptoms of asthma	Etiology of asthma*	Asthma-associated HLA haplotype A2, x	IgE (U/ml)	WB*	RAST** O	WW	SR
1	+	unidentified	+	100	0	0	0	0
2	—		—	830	3	0	0	0
3	+	WB, HD	+	510	0	0	0	0
4	+	WB, O	+	880	0	0	0	0
5	—		—	1800	0	2	0	1
6	—		—	83	0	1	1	1
7	—		+	73	0	1	0	0
8	+	WB, O, HD, ALT	+	1700	0	2	1	1
9	+	WB, O, WW	+	375	0	0	0	0
10	—		—	800	0	0	0	0

* See legend of Table 1. ALT: Alternaria.

** See legend of Table 1.

TABLE 3
Association Between Clinical Asthma and HLA Haplotypes.

Family	No. of relatives	Asthma-associated haplotype	Patients with asthma-associated haplotype	Patients with other haplotype of the propositus
NU	8	A9, x	3/4	0/3
SH	9	A2, x	4/5	0/2
SU	6	Aw19, B5	2/2	1/3
OH	8	x, Bw15	1/2	1/3
Total	31		10/13 (76.9 %)*	2/11 (18.2 %)

* χ^2 with Yates' correction = 7.58, $P < 0.01$.

with the other haplotype have asthma. There seems to be no clear association between asthma and the results of RIST and RAST in both families.

The results of HLA typing in four families are totalled in Table 3. Ten of thirteen individuals with putative asthma-associated HLA haplotypes had asthma (76.9 per cent). Two of the eleven with other haplotypes had asthma (18.2 per cent). These data show a close genetic linkage between the HLA system and the development of asthma ($P < 0.01$). RIST and RAST showed no such correlation in four families.

DISCUSSION

The biological mechanisms underlying the correlation between histocompatibility antigens and diseases have been discussed and reviewed by some investigators (4, 8, 9, 10). Immune response (Ir) genes linked to HLA are at the present time the most potent candidates among the factors responsible for the associations. Several studies on ragweed hay fever (3, 5) have given supporting evidence to the participation of an HLA-linked Ir gene in diseases, although there is some criticism of these analyses (2).

The present study demonstrates a statistically significant

linkage between asthma and HLA haplotypes ($P < 0.01$). This implies that in asthma there might be a disease susceptibility gene locus closely linked to the HLA system. There are some discordant cases, e.g. # 2 in family NU and # 7 in family SH. These could be explained by (a) lack of appropriate environmental exposure, (b) lack of complete penetrance of the gene, (c) participation of other genes unlinked to HLA, and (d) recombination between HLA and a disease susceptibility gene, although there is no direct evidence to support these explanations.

In order to obtain conclusive results concerning the participation of an HLA-linked gene in allergy, intensive and extensive studies, including antibody responses, HLA-D typing, and possibly typing of other markers on chromosome 6, might be necessary.

SUMMARY

Four families in which asthma occurred in more than three members, and in which there were at least three children, were studied in terms of clinical symptoms, serum IgE levels determined by RIST and RAST, and HLA haplotypes. No association between clinical asthma and serum IgE level was found, but a close association between asthma and a particular HLA haplotype in a family was demonstrated. It was therefore postulated that a disease susceptibility gene closely linked to an HLA gene complex may play a role in the development of asthma.

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Authors' address:

Dr. Hidetaka Yakura
 Department of Pathology
 Hokkaido University School of
 Medicine
 Sapporo 060
 Japan

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