

A Study of HLA Antigen Distribution in Families with Atopic Dermatitis

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Seventeen children presenting with atopic dermatitis were HLA typed together with their parents and siblings. A total of 89 individuals was studied. No close link between HLA antigen distribution and clinical expression of atopy was demonstrated, and 14 HLA identical but disease-free siblings were identified. An increase in the A1 B8 haplotype was observed in the families as a whole by comparison with a large control series.

Key words: antigens; atopy; haplotype; HLA; IgE.

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It is well established that the atopic state is in part genetically determined, but factors determining clinical expression of atopy are far from clear. Environmental factors including early exposure to food antigens are considered by some to play an important part but the object of this study was to determine whether or not HLA antigen distribution played a significant role in clinical expression of respiratory, cutaneous, or combined symptoms of atopic disease. Although work has been done previously on HLA distribution and clinically affected individuals with atopic disease no study has to our knowledge compared the HLA distribution in family members with and without symptoms and signs of atopy. The object of this study was therefore to determine by a family study the significance of HLA antigen distribution in families one of whom had clinical signs of atopy. An ancillary aspect of the study was to determine IgE levels in all family members and relate this to HLA antigens.

MATERIAL AND METHODS

A total of 89 individuals from 17 families have been HLA typed. At the time of study 20 individuals had active symptoms and signs of atopy; eight had pure cutaneous atopy with eczema as the only clinical manifestation of the atopic state, three had active asthma, one had severe allergic rhinitis and eight had combined cutaneous and respiratory symptoms. A further 27 had a past personal history of respiratory, cutaneous, or combined atopic symptoms. Two sets of twins (both non-identical) were included in the study.

Families were selected on the basis of a child aged between 4 and 10 years with moderately severe symptoms of atopy attending the Royal Hospital for Sick Children, Glasgow, who had one or more sibs, and parents all willing to give a 5-10 ml blood sample on one occasion. No grandparents or more distant family members were asked to take part in the

study. A full explanation of the study was given to all parents and informed consent obtained. The blood samples were then collected on a home visit which was found to be the simplest method of seeing entire families on one occasion.

10 ml of fresh venous blood were collected into universal containers containing TC199 tissue culture medium and where possible an additional 2-4 ml of blood was put in a dry container for serum studies. HLA typing was then performed using standard techniques

(2). Serum IgE levels were estimated by radioimmunoassay.

RESULTS

Table 1 details the genotypic information on the families involved in the study. The significant points which arise from the study of these families are that there are 14 HLA identical siblings free of either present signs or a past history of atopy, suggesting that the association between HLA and atopy is not

Table 1
Family studies—HLA genotypes

	A Series		B Series		Genotypes	
Family 1						
Father	1	2	5	12	a/b	2, 12/1, 5
Mother	2	9	12	(12)	c/d	2, 12/9, (12)
Children					ad; ac; ad; ac	
(in birth order)						
Family 2						
Father	2	9	7	?	a/b	9, 7/2, ?
Mother	2	9	w40	13	c/d	9, w40/2, 13
Children					ad; ad; ac	
Family 3						
Father	2	w31	7	12	a/b	2, 12/w31, 7
Mother	1	9	5	8	c/d	1, 8/9, 5
Children					ac; ac; ac; ac	
Family 4						
Father	1	11	7	8	a/b	1, 8/11, 7
Mother	2	3	12	w35	c/d	2, 12/3, w35
Children					ac; bd; bd; bc; bd	
Family 5						
Father	2	(2)	w35	w21	a/b	2, w35/(2), w21
Mother	3	(3)	7	w35	c/d	3, 7/(3), w35
Children					ac; ac; ac	
Family 6						
Father	2	9	7	w35	a/b	2, w35/9, 7
Mother	2	9	w35	w40	c/d	2, w35/9, w40
Children					bc; ad; bc; ad	
Family 7						
Father	1	3	7	8	a/b	1, 8/3, 7
Mother	3	11	12	27	c/d	11, 27/3, 12
Children					bc; ac; ad	

	A Series		B Series		Genotypes	
Family 8						
Father	2	w31	27	w22	a/b	w31, 22/2, 27
Mother	29	w31	13	w35	c/d	29, w35/w31, 13
Children						ac; ad; ac
Family 9						
Father	1	28	8	14	a/b	1, 8/28, 14
Mother	2	26	12	13	c/d	2, 12/26, 13
Children						ad; bc
Family 10						
Father	2	w31	5	14	a/b	2, 5/w31, 14
Mother	2	3	7	14	c/d	2, 14/3, 7
Children						ac; ac
Family 11						
Father	1	2	7	8	a/b	1, 8/2, 7
Mother	3	(3)	7	w40	c/d	3, 7/(3), w40
Children						(ND); ac; bc; ac; ac
Family 12						
Father	2	(2)	7	18	a/b	2, 7/2, 8
Mother	1		8	(14)	c/d	1, 8/1, 4 or 1, 8
Children						bc; bc; bc; ac; ac; ac
Family 13						
Father	3	9	18	27	a/b	3, 18/9, 27
Mother	2	26	5	18	c/d	26, 5/2, 18
Children						bc; ac; ac
Family 14						
Father	1	—	8	—	a/b	1, 8/? (1, 8)
Mother	1	28	5	14	c/d	28, 5/1, 14
Children						ac
Family 15						
Father	2	(2)	12	17	a/b	2, 12/(2), 7
Mother	2	9	7	w40	c/d	2, w40/9, 7
Children						ac; ad; ad; ac; ad
Family 16						
Father	2	3	12	(12)	a/b	2, 12/3, (12)
Mother	2	11	7	12	c/d	2, 12/11, 7
Children						ad
Family 17						
Father	1	29	12	w40	a/b	1, w40/29, 12
Mother	3	9	8	37	c/d	9, 8/3, 37
Children						bc; cd

Affected child or children, genotype in italics thus: *ac*.

Antigens deduced from family studies are bracketed thus: (2).

Uncertain or "blank" antigens are included (— or ?).

ND = not done.

Children's genotypes in birth order, starting with eldest.

close. This is well illustrated in family no. 11 where the proband is A1 A3: B7 B8. One sibling with no past history or present signs of atopy has identical HLA antigens as also does one member of the pair of twins in this family who has a past history of atopic eczema in infancy. The other twin, a child with active atopic dermatitis at the time of study, has the distribution A2 A3: B7.

A further point emerging from this study, and which will merit further investigation, is a tendency to B locus antigen identity between parents. In seven families, B locus antigens were shared by both parents, and in three, the parents each had an identical haplotype. The occurrence of the A1, B8 haplotype in one parent and the A2, B12 in the other was also noted in three other families. It is possible that these observations are related to the occurrence of homozygosity in offspring for an "atopic" gene, not necessarily present within the major histocompatibility complex, but it would require further similar studies to confirm this. The association is not a direct one between HLA homozygosity and atopy, since only two of the afflicted children inherited identical parental haplotypes (Family 17).

Comparing haplotypes in this study with those from large control groups it will be seen that there is a 40% incidence of A2, B12 and 30% incidence of A1, B8 haplotypes. No particular haplotypes with reduced frequency were noted during this study. A1, B8 haplotypes were found in three families showing pure cutaneous symptoms, two with pure asthma and three with combined cutaneous and respiratory lesions.

Estimation of serum IgE levels was carried out in 42 individuals. Only in those children with both asthma and eczema were very high levels of circulating IgE (over 4000 units/ml) found. In children with pure eczema the log mean IgE level was 605 units/ml. In four relatives with no past or present history or symptoms of atopy a serum IgE level of over 400 units/ml was recorded. Identification of

specific antigens against which IgE is being manufactured by the radioallergosorbent test (RAST) was not performed in this study.

DISCUSSION

These results indicate that there is not a close relationship between HLA tissue type and a predisposition to atopy. Furthermore, there would not appear to be any close association between the clinical expression of atopy and specific HLA antigens. This study is, to our knowledge, the only one reported in which family groups have been studied rather than individual patients with atopic disease, and the existence within the families studied of 14 siblings sharing HLA identical haplotypes with diseased patients, but no clinical evidence of disease, is the most convincing evidence yet reported against a direct association between HLA and atopy.

In six families (Nos. 1, 2, 4, 6, 12 and 15) the chromosomes inherited by the affected child or children have been inherited separately by unaffected siblings indicating that neither chromosome may be specifically implicated in the production of the disease state. On the other hand, the number of HLA identical (for A and B) unaffected siblings of affected patients also suggests that homozygosity for a gene or genes linked to HLA is not involved.

The high incidence of the A1, B8 haplotype in our series has also been reported by Turner (7), who found a 37% incidence of this grouping in children with eczema complicated by respiratory symptoms compared with a 17% incidence in a control population from the Bristol transplantation registry. Patients with hay fever alone had, by contrast, a reduced incidence of this haplotype (5%). No unaffected family members were included in this latter study. Our own observations on a population drawn from the West of Scotland suggest that the haplotype A1, B8 may be associated with an increased tendency to immune hyper-reactivity. Coeliac disease and dermatitis

herpetiformis are also associated with increased incidence of A1, B8 and are relatively common in the Scottish population. A study of A1, B8 incidence relative to the incidence of atopy, coeliac disease and dermatitis herpetiformis might well clarify this point.

It is difficult at this stage to identify whether the rather unusual haplotype distribution reported here is a reflection of a normal population distribution in the West of Scotland, or whether the high incidence of certain diseases is directly attributable to the presence of these particular haplotypes and the relevant linked immune response genes.

Elevated serum IgE levels were found in all patients with clinical evidence of atopy at the time of venesection. The highest levels, found in children with combined respiratory and cutaneous symptoms, confirms several previous studies (1, 3, 4, 5). Children with pure cutaneous atopy had elevated IgE levels and a small proportion (8%) of symptom-free relatives has serum IgE levels two standard deviations or more above the mean for the group. No association between HLA type and level of total serum IgE emerged from this study, but in view of the reports on ragweed pollen antibodies and HLA type, it is possible that a study of specific IgE formation by the RAST technique could yield useful information (6).

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