

A family study of allergy: Segregation with HLA but not with T-cell receptor genes

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The mode of inheritance of allergic disease is unclear. Several studies examining the genetic linkage to atopy have failed to show a codominant, recessive, or dominant mode of inheritance.¹ Other studies have suggested autosomal dominance as the mechanism and have suggested that the gene is on chromosome 11q.¹ Genetic epidemiologic studies have also attempted to relate specific allergen responsiveness to HLA type, and evidence supports the view that in general HLA-DR rather than HLA-DP or -DQ gene products are involved in allergen recognition.¹ Most recently, the linkage between specific IgE reactions to highly purified allergens and the T-cell receptor V- α/δ and V- β genes, localized on chromosomes 14 and 7, respectively, has been investigated by two separate groups with the "sibling pair" method.² No linkage of IgE serotypes to T-cell receptor (TCR)- β genes was detected, but significant linkage to TCR- α/δ genes was seen in both family groups.

CASE REPORT

We have studied a family (Fig. 1) in which four (D, E, F, G) of the five siblings have a strong allergy to peanuts and several other allergens. The aim of the study was to determine whether either peanut-specific allergy or more general allergy, noted in all siblings, involved shared TCR- α , TCR- β , or HLA haplotypes.

Skin tests were performed on the forearm with allergen extracts (ryegrass pollen, Bermuda grass pollen, *Alternaria* spp., *Cladosporium herbarum*, *Penicillium* spp., house dust, *Dermatophagoides pteronyssinus*, *D. farinae*,

Abbreviation used

TCR: T-cell receptor

cat fur, dog fur, nut mix, peanut, and egg; Hollister-Stier, Bayer Diagnostics, Sydney, Australia). Histamine acid phosphate (10 mg/ml) was used as a positive control, and albumin-saline solution was used as a negative control. A wheal diameter of 3 mm or greater at 15 minutes was interpreted as a positive result. RASTs to measure specific IgE reactivities were carried out on patients' sera with allergen disk (egg white, milk, wheat, soya bean, almond, Brazil nut, hazelnut, peanut, walnut, cashew, banana, shrimp, bakers' yeast, cat epithelium, *D. pteronyssinus*, ryegrass pollen, plantain pollen, *C. herbarum*, *Alternaria alternata*) obtained from Pharmacia (Uppsala, Sweden). HLA-A and -B typing was performed with the standard microtoxicity assay, and HLA-DR typing was carried out by polymerase chain reaction with sequence-specific oligonucleotides.³ TCR V- α/δ and TCR V- β 6.7 oligonucleotide primers were synthesized according to previously published sequences.^{4,5} These oligonucleotides were used as primers in polymerase chain reactions, with DNA template prepared from peripheral blood, to determine TCR alleles.

In this family the mother (A) aged 49 years had no evidence of any allergies, either clinically or serologically, or as determined by skin prick test. The father (B) aged 54 years had a clinical history of allergy and positive responses to extracts of *D. pteronyssinus* on skin prick tests and RAST. Four of the five children (D, E, F, and G) aged 27, 26, 22, and 21 years, respectively had allergies to a large number of different allergens, in particular, severe allergy to peanuts but also to true nuts. These patients also had strong positive responses to skin prick tests and RASTs with several other allergens including several food substances, *D. pteronyssinus*, and ryegrass pollen. The fifth child (C) aged 28 was only allergic to cat fur dander. The fact that the children had greater reactivities in terms of the intensity of their symptoms and the number of different allergens recognized (skin prick test, RAST) compared with either parent sug-

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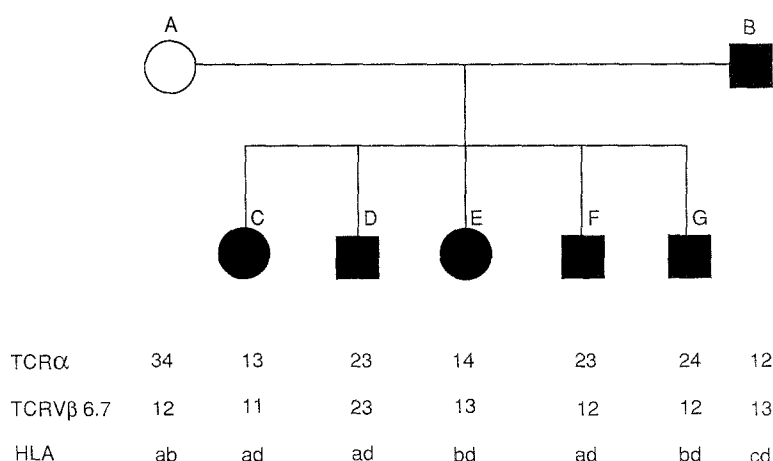


FIG. 1. Composite figure showing family tree and individual member genotype analysis for TCR V- α/δ , TCR V- $\beta_{6.7}$, and HLA alleles. For example, patient E had TCR V- α/δ allele 4 and TCR V- $\beta_{6.7}$ allele 1 from the mother and TCR V- α/δ allele 1 and TCR V- $\beta_{6.7}$ allele 3 from the father, respectively. The paternal haplotype shared by all the children was HLA A2, B13, DR4.

gest that genetic factors from *both* parents contribute to the childrens' more allergic condition.

DISCUSSION

If we consider the four siblings with peanut allergy (D, E, F, and G) with sibling D the index case, one sibling pair shared 0, one pair shared 1, and one pair shared 2 TCR- α haplotypes, respectively. Thus for this family there was no excess sharing of both haplotypes, and so the results argue against any linkage at the TCR- α locus. However, with the small number of individuals, we cannot rule out the presence of a linkage to the TCR- α locus with a susceptibility gene, which has high frequency in the community. In general, these results argue against any linkage to the TCR- α locus. Similarly, with the TCR- β locus and peanut allergy, all the sibships shared one TCR- β haplotype but none shared both, arguing against a linkage to this locus. With HLA (A, B, DR) all sibships shared one paternal DR4 haplotype, one shared two, and none shared zero. These results suggest that peanut allergy in the four affected siblings and allergy in general in all five siblings segregates with a paternal HLA allele but not with TCR- α or TCR- β alleles.

In studies of atopy it is quite uncommon to find

individuals with positive responses to only a single allergen. What is generally more common, and within families, is that affected siblings have different spectrums of allergen reactivities. Thus the relationship between any TCR allele and any specific IgE serotype is likely to vary according to which specific IgE serotype one selects. In our single family, the sibling-pair results obtained varied with the specific IgE serotype selected, with the exception of HLA.

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