

Genetic influences of chromosomes 5q31-q33 and 11q13 on specific IgE responsiveness to common inhaled allergens among African American families

Nobuyuki Hizawa, MD,^a Linda R. Freidhoff, MS,^a Eva Ehrlich, MS,^a Yen-Feng Chiu,^b David L. Duffy, MD,^{c,d} Carsten Schou, PhD,^e Georgia M. Dunston, PhD,^f Terri H. Beaty, PhD,^c David G. Marsh, PhD,^{a†} Kathleen C. Barnes, PhD,^a Shau-Ku Huang, PhD,^a and the Collaborative Study on the Genetics of Asthma (CSGA)^g Baltimore and Bethesda, Md, Queensland, Australia, Hörsholm, Denmark, and Washington, DC

Background: We have recently conducted a genome-wide screening for genes influencing *Dermatophagoides pteronyssinus*-specific IgE responsiveness as a part of the Collaborative Study on the Genetics of Asthma (CSGA), which showed evidence for linkage in some regions, including chromosomes 5q31-q33 and 11q13 in African American families.

Objectives: To clarify relative contributions of these regions to atopy in the same African American population, we have conducted further genetic linkage studies of specific IgE responses toward common inhaled allergens.

Methods: We studied 328 individuals in 58 African American families participating in the CSGA. Specific IgE responses toward *Dermatophagoides farinae*, cat, dog, American cockroach, rye grass, and Bermuda grass, as measured by skin tests, were used for multipoint linkage analysis with polymorphic markers on chromosomes 5q31-q33 and 11q13.

Results: Specific IgE response toward American cockroach showed evidence for linkage to chromosomes 5q31-q33 ($P = .0050$) and 11q13 ($P = .017$). Specific IgE response toward dog showed evidence for linkage with chromosome 5q31-q33 ($P = .0043$). Evidence for linkage with chromosome 11q13 was obtained for specific IgE responses toward *Dermatophagoides farinae* ($P = .012$), cat ($P = .035$), and Bermuda grass ($P = .017$). The presence of a positive ST response for at least 1 of 30 common allergens showed evidence for linkage to chromosomes 5q31-q33 ($P = .017$) and 11q13 ($P = .00058$).

Conclusions: These data support that genes on both chromosomes 5q31-q33 and 11q13 confer susceptibility to upregulated IgE-mediated immune responses in this African American population. The putative genes on chromosomes 5q31-q33 and 11q13, however, showed contrasting effects on atopy, which may result from strong gene-environmental interactions. (J Allergy Clin Immunol 1998;102:449-53.)

Key words: Atopy, skin prick test, chromosome 5q31-q33, chromosome 11q13, multipoint linkage analysis

Atopy, an inherited condition causing an ability to produce significant amounts of specific IgE antibodies to allergens, is associated with bronchial asthma, allergic rhinitis, and atopic dermatitis. The estimated prevalence of atopy, defined as the presence of at least 1 positive specific IgE response, ranged from 16% in Spain to 45% in New Zealand in a study of 16 European countries.¹ Specific IgE responsiveness toward house dust mite is associated with asthma and bronchial hyperresponsiveness.² Specific IgE responses toward allergens derived from cat, dog, cockroach, and pollens also importantly contribute to the development of allergic diseases. In particular, a clear correlation was recently demonstrated among cockroach allergy, the levels of exposure toward cockroaches, and asthma-related health problems in inner-city children.³ The ability to react to a particular allergen is determined by both genetic and environmental features. There is compelling evidence that susceptibility to atopy is multifactorial.⁴

More than 10 regions have been identified as candidate regions influencing total serum IgE levels, atopy, and asthma.^{5,6} Among them, the chromosomal regions 5q31-q33 and 11q13, have been studied most extensively and are relatively well characterized. Originally, 2 groups reported evidence for linkage between markers on chromosome 5q31-q33 and total serum IgE levels.^{7,8} Also, linkage between generalized IgE responsiveness and markers on chromosome 11q13 has been reported.^{9,10} These findings were replicated in some other populations.^{5,6,11} These regions are also linked to or associated with parasitic infection,^{12,13} indicating genes on these regions are likely to regulate IgE-mediated overall immune responses.

From ^athe Division of Clinical Immunology, The Johns Hopkins Asthma & Allergy Center, Baltimore; ^bthe Department of Biostatistics, The Johns Hopkins School of Hygiene, Baltimore; ^cthe Department of Epidemiology, The Johns Hopkins School of Hygiene, Baltimore; ^dQueensland Institute of Medical Research, Queensland; ^eALK laboratories, Hörsholm; ^fthe Department of Microbiology, Howard University College of Medicine, Washington; and ^gthe National Heart, Lung, and Blood Institute (NHLBI), Bethesda.

† Professor David G. Marsh was actively involved in the design and implementation of this study. He passed away on March 29, 1998, after a heroic battle against brain cancer. The authors wish to dedicate this paper to his memory.

Supported by United States Public Health Service grant HL/AI 49612, National Institutes of Health grant AI20059, and a grant from Nippon Boehringer Ingelheim Co, Ltd.

Received for publication Mar 5, 1998; revised May 20, 1998; accepted for publication May 20, 1998.

Reprint requests: Shau-Ku Huang, PhD, Johns Hopkins Asthma and Allergy Center, 5501 Hopkins Bayview Circle, Baltimore, Maryland 21224.

1/1/91996

TABLE I. Summary of the ST responses to 6 common inhaled allergens in 328 African American subjects

	No. of subjects with positive ST responses		No. of subjects without positive ST responses	
	201 asthmatic subjects	127 nonasthmatic subjects	201 asthmatic subjects	127 nonasthmatic subjects
Der f (M/F)	23/21	15/14	73/84	46/52
Cat (M/F)	34/29	19/17	62/76	42/49
Dog (M/F)	25/21	12/11	71/84	49/55
American cockroach (M/F)	24/27	13/9	72/78	48/57
Rye grass (M/F)	32/28	15/15	64/77	46/51
Bermuda grass (M/F)	34/28	15/11	61/77	45/54

No allergens showed significant differences in the prevalence of positive ST responses according to sex.

Abbreviations used

CSGA: Collaborative Study on the Genetics of Asthma

Der p: *Dermatophagoides pteronyssinus*

Der f: *Dermatophagoides farinae*

EST: Expressed sequence tag

IBD: Identity by descent

NPL: Nonparametric measures of linkage

ST: Skin test

Recently, we conducted a genome-wide search for genes influencing *Dermatophagoides pteronyssinus* (Der p)-specific IgE responsiveness, which also provided some evidence in favor of linkage with chromosomes 5q31-q33 and 11q13 in African American families ascertained through an asthmatic sib pair.¹⁴

To clarify the relative contribution of genes on chromosomes 5q31-q33 and 11q13 to atopy in this African American population, we extended our analysis to IgE responsiveness to a panel of common allergens consisting of *Dermatophagoides farinae* (Der f), *Felis domesticus* (cat), *Canis familiaris* (dog), *Periplaneta americana* (American cockroach), *Lolium perenne* (rye grass), and *Cynodon dactylon* (Bermuda grass).

METHODS

Subjects and phenotype

We studied 328 (157 men and 171 women) individuals in 58 African American families (13 extended families and 45 nuclear families) participating in the Collaborative Study on the Genetics of Asthma (CSGA). The detailed characteristics of the families and the study design and protocol for the CSGA have been described elsewhere.^{11,14,15} Briefly, these families were ascertained through a pair of asthmatic sibs, and both probands and family were interviewed, underwent pulmonary function and skin prick testing, and provided blood for both genetic analysis and measurement of total and specific IgE levels. Asthma was diagnosed by the following criteria: (1) presence of at least 2 symptoms (cough, wheezing, or dyspnea); (2) either a fall in baseline FEV₁ by 20% or greater at 25 mg/mL or greater methacholine or a 15% or greater increase in baseline FEV₁ after bronchodilator use; (3) nonsmoking subject; (4) current age of 6 years or greater; and (5) absence of conflicting pulmonary disease.^{5,15}

Skin testing was conducted by using the standard individual prick technique as previously described.^{15,16} A total of 30 standardized allergens commonly found in urban areas were examined, including *Dermatophagoides pteronyssinus* (Der p), *Dermatophagoides*

farinae (Der f), *Felis domesticus* (cat), *Canis familiaris* (dog), *Periplaneta americana* (American cockroach), *Blattella germanica* (German cockroach), *Lolium perenne* (rye grass), *Ambrosia artemisiifolia* (short ragweed), *Cynodon dactylon* (Bermuda grass), *Artemisia vulgaris* (common mugwort), *Quercus alba* (caucasian oak), *Betula verrucosa* (silver birch), *Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Rattus norvegicus* (rat), and *Mus musculus* (mouse). A test response for a specific allergen was considered positive if the diameter of the wheal was at least 3 mm larger than that of the negative control (saline) wheal.

Genotype

DNA was extracted from venous blood by standard techniques. The PCR was performed as described previously.⁷ The genotypes were used to check for paternity, and markers were used to confirm compatibility with Mendelian inheritance. Six polymorphic markers on chromosome 5q31-q33 (*D5S642*, *IL4*, *D5S666*, *IL9*, *D5S436*, and *D5S2090*), and six markers on chromosome 11q13 (*D11S1313*, *FCER1B*, *PYGM*, *D11S987*, *FGF3*, and *D11S1369*) were studied.

Statistical analysis

Specific IgE responsiveness toward Der f, cat, dog, American cockroach, rye grass, and Bermuda grass, as measured by skin tests (STs), was used for linkage analysis because responders toward these allergens are highly prevalent in this African American population. Table I shows the number of responders toward these allergens. We also analyzed atopy, which was defined as the presence of at least 1 positive ST toward any of the allergens ($n = 30$) examined.

We performed multipoint linkage analysis with the GENE-HUNTER (version 1.0) program, which infers the identity by descent (IBD) sharing among all affected relatives in multiplex families at each location. The nonparametric measures of linkage (NPL score) were used for this analysis because the mode of inheritance is not well understood for these phenotypes in this study.¹⁷ Order and distance (in centimorgans) between genetic markers in 5q31-q33 and 11q13 were determined on the basis of published data derived from maps of Génethon¹⁸ and Cooperative Human Linkage Center (CHLC)¹⁹ on Genome Data Base (<http://www.gdb.org>).

Maternal inheritance of atopy on chromosome 11q13 was examined. We counted the amount of IBD sharing for markers *D11S987* and *FCER1B* between affected sib pairs concordant for atopy, assuming that the expected proportion of affected sib-pair sharing of IBD from either parent was 0.5. Chi-square estimation from 2×2 tables was used to test the significance of difference between sharing of maternal/paternal marker alleles from 0.5. To calculate the number of IBD sharing between affected sibs, we constructed haplotypes by minimizing the number of recombinations between adjacent markers in each family, and affected sib pairs were included in the analysis only if the 2 alleles from the specified parent could be individually recognized.

TABLE II. Multipoint linkage between positive ST responses to 6 common inhaled allergens and chromosome 5q31-q33

	<i>D5S666</i>		<i>IL4</i>		<i>D5S642</i>		<i>IL9</i>		<i>D5S436</i>		<i>D5S2090</i>	
	NPL	P value	NPL	P value	NPL	P value	NPL	P value	NPL	P value	NPL	P value
Der f	0.26	.24	0.15	.33	0.3	.21	0.32	.2	0.25	.25	0.54	.083
Cat	0.07	.43	−0.01	.54	−0.12	.58	−0.16	.61	−0.08	.55	0.29	.28
Dog	1.09	.0062	1.15	.0043	1.13	.0047	0.98	.012	0.72	.047	0.81	.029
American cockroach	0.32	.21	0.31	.22	0.56	.09	0.85	.029	1.23	.0050	0.97	.016
Rye grass	0.69	.079	0.68	.081	0.64	.094	0.34	.23	0.23	.3	0.24	.29
Bermuda grass	0.32	.26	0.17	.36	0.36	.23	0.41	.21	0.55	.14	0.37	.23
Atopy*	1.13	.09	0.92	.13	0.84	.15	1.18	.082	1.95	.017	1.59	.037

The map distances for *D5S666-IL4-D5S642-IL9-D5S436-D5S2090* are 1.0, 1.0, 4.0, 10.0, and 2.0 cM, respectively.

A positive ST response was defined as a wheal diameter ≥ 3 mm of that produced by the negative control.

*Atopy was defined as the presence of a positive ST response to at least 1 allergen.

TABLE III. Multipoint linkage analysis among positive ST responses to 6 common inhaled allergens and chromosome 11q13

	<i>D11S1313</i>		<i>FCER1B</i>		<i>PYGM</i>		<i>D11S987</i>		<i>FGF3</i>		<i>D11S1369</i>	
	NPL	P value	NPL	P value	NPL	P value	NPL	P value	NPL	P value	NPL	P value
Der f	0.29	.22	0.57	.07	0.55	.07	0.9	.012	0.31	.2	0.47	.11
Cat	0.77	.073	0.79	.067	0.68	.097	0.97	.035	0.62	.12	0.79	.068
Dog	0.36	.19	0.5	.12	0.07	.42	0.15	.35	−0.077	.56	0.29	.24
American cockroach	0.73	.049	0.8	.036	0.23	.28	0.38	.18	0.48	.12	0.96	.017
Rye grass	0.33	.23	0.61	.1	0.3	.25	0.29	.26	0.63	.45	0.43	.8
Bermuda grass	1.05	.027	1.13	.019	0.53	.15	1.16	.017	0.65	.11	1.08	.024
Atopy*	3.048	.0016	3.29	.0010	2.99	.0017	3.61	.00058	0.81	.15	1.19	.079

The map distances for *D11S1313-FCER1B-PYGM-D11S987-FGF3-D11S1369* are 1.1, 4.5, 3.1, 3.7, and 1.9 cM, respectively.

A positive ST response was defined as a wheal diameter ≥ 3 mm of that produced by the negative control.

*Atopy was defined as the presence of a positive ST response to at least 1 allergen.

TABLE IV. Test for maternal inheritance of atopy on chromosome 11q13 in African American families

<i>D11S987*</i>			<i>FCER1B†</i>		
IBD sharing	Paternal allele	Maternal allele	IBD sharing	Paternal allele	Maternal allele
+	49	63	+	52	65
−	56	38	−	50	33

We assumed that the expected proportion of affected sib pairs sharing of IBD from father or mother was the same (0.5). IBD was estimated by haplotypes that were constructed by minimizing the number of recombinations between adjacent markers in each family. The 2 alleles from the specified parent were recognized for 105 affected sib pairs (paternal allele) and 101 affected sib pairs (maternal allele) in *D11S987* and for 102 affected sib pairs (paternal allele) and 98 affected sib pairs (maternal allele) in *FCER1B*.

* $\chi^2 = 5.1$, $P = .024$.

† $\chi^2 = 4.8$, $P = .028$.

RESULTS

Two hundred seventy-six (87.2%) individuals were defined as atopic in the African American population in this study. There were 201 individuals assigned as having asthma. Among these asthmatic individuals, 174 (86.6%) individuals showed positive ST responses toward at least 1 allergen, 61 (30.3%) individuals toward Der p and/or Der f allergens, 63 (31.3%) individuals toward cat allergen, 46 (22.9%) individuals toward dog allergen, and 51 (25.4%) individuals toward American cockroach allergen (Table I).

We found evidence for linkage of atopy with 3 markers on chromosome 5q31-q33 and 4 markers on chromosome 11q13 (Tables II and III). Also on chromosome 5q31-q33, we found evidence for linkage with positive ST responses toward dog allergen at all 6 markers and positive ST responses toward American cockroach allergen at 3 markers. Chromosome 11q13 showed weak evidence for linkage with Der f and cat allergens at *D11S987*, with American cockroach allergen at 3 markers, and with Bermuda grass allergen at 4 markers (Tables II and III).

Forty-nine affected sib pairs (46.7%) shared paternal alleles and 63 affected sib pairs (62.4%) shared maternal alleles at marker *D11S987*. Fifty-two affected sib pairs (51%) shared paternal alleles and 65 affected sib pairs (66.3%) shared maternal alleles at *FCER1B*. Sharing of maternal alleles IBD was significantly different from the expected 0.5 for both *D11S987* ($\chi^2 = 5.1$, $P = .024$) and *FCER1B* ($\chi^2 = 4.8$, $P = .028$) (Table IV).

DISCUSSION

On the basis of our prior findings that specific IgE responsiveness toward Der p is linked to markers on chromosomes 5q31-q33 and 11q13,¹⁴ we extended our analysis to examine relative roles of these regions on atopy. We provided further evidence for linkage of specific IgE responses toward several common inhaled allergens, such as cat, dog, cockroach, and pollens, with genes on chromosomes 5q31-q33 and 11q13 in this African American population. Our current findings support previous contentions that genes on these regions confer susceptibility to overall IgE regulation in some populations.⁷⁻¹⁰

Chromosome 5q31-q33 showed the strongest evidence for linkage with IgE responses toward dog allergen (*IL4*) and American cockroach allergen (*D5S436*), but weaker evidence for linkage with atopy. In contrast, *D11S987* on chromosome 11q13 showed the strongest evidence for linkage with atopy but only weak evidence for linkage with specific IgE responsiveness toward Der f, cat, and Bermuda grass. A nearby marker (5.6 cM), *D11S1369*, showed modest evidence for linkage toward American cockroach.

The genetic regulation for specific IgE responsiveness appeared heterogeneous, suggesting environmental variables may be important in controlling expression of these genes on chromosomes 5q31-q33 and 11q13. Linkage of chromosome 11q13 was observed in Japanese families only with marked symptomatic atopy.^{20,21} The African American families in this study are also characterized by high prevalence of atopy (more than 80% of individuals have at least one positive ST response) partly because these families were originally recruited through asthmatic probands.^{5,15} Accordingly, high exposure levels of relevant allergens may be an important factor to trigger expression of genetic effects on chromosome 11q13. Conversely, appropriate environmental features, such as exposure levels, molecular structures of allergens, and routes and duration of exposure, may be crucial for the putative gene or genes on chromosome 5q31-q33 to exert their effects in genetically predisposed individuals because linkage on chromosome 5q31-q33 is more specific to each allergen than linkage on chromosome 11q13. The importance of these environmental conditions has been elucidated for the genetic effects of *HLA-D*.^{4,22} The possible interaction between genes on chromosome 5q31-q33 or 11q13 and environmental conditions could partly explain why the genetic effects are often difficult to replicate in different populations.

Maternal inheritance of the gene or genes on chromosome 11q13 has been demonstrated in some populations.^{6,23} We found that the proportion of IBD sharing of

maternal alleles in affected sib pairs for atopy at marker *D11S987* and *FCER1B* was significantly greater than the expected 0.5 (Table IV), suggesting maternal inheritance of atopy genes on chromosome 11q13 in the African American population in the study.

FCER1B has been implicated as a most promising candidate gene for atopy on chromosome 11q13.^{6,10} However, the results of multipoint linkage analysis in this study showed the highest NPL score of 3.61 at marker *D11S987*, which is about 8 cM downstream from *FCER1B*. There is a highly uneven distribution of expressed sequence tag (EST) on chromosome 11. Chromosome 11q13 is the most EST-dense region, with 288 ESTs mapping in a 10 cM region in the vicinity of *D11S1313*.²⁴ A major genetic contribution on chromosome 11q13 could come from a presently unknown gene or genes rather than *FCER1B* in this population.

A polymorphic marker within the *IL4* gene showed the strongest evidence for linkage with total serum IgE levels in the study by Marsh⁷ et al of the Pennsylvania Old Order Amish families. Meyers et al,⁸ in their study of linkage to high total IgE levels among 92 Dutch families, obtained the highest lod score (3.61) with marker *D5S436*, which is about 15 cM downstream from *IL4*. In our study, IgE responsiveness toward dog allergen yielded significant evidence for linkage to *IL4* and flanking markers *D5S666* and *D5S642*, a region of only 2 cM, but responsiveness toward American cockroach allergen was linked to *D5S436*. The region 5q31-q33 does have several good candidate genes for atopy, including genes encoding IL-3, IL-4, IL-5, IL-12, IL-13, GM-CSF, interferon regulatory factor-1, β_2 -adrenergic receptor, and glucocorticoid receptor. Therefore it is likely that our observations identify 2 distinct loci on chromosome 5q31-q33. At present, it is difficult to extrapolate only 1 or 2 genes as promising candidates on these regions. To confirm candidate regions, further efforts are needed to find polymorphisms at each of the candidate genes for linkage disequilibrium mapping.

In conclusion, our results support that genes on chromosomes 5q31-q33 and 11q13 influence IgE-mediated immune responses in some manner. Our study also showed contrasted genetic effects between chromosomes 5q31-q33 and 11q13, indicating the importance of environmental conditions to trigger genetic effects on these regions. It is conceivable that genes on chromosomes 5q31-q33 and 11q13, which are responsible for high IgE responsiveness toward these common allergens, play crucial roles for the development of asthma and other allergic diseases in this population.

We thank the families and investigators in the CSGA for their cooperation in this study. We also thank Xielun Xue, Xin Liu, Margarita Kreynina, Maria Stockton, Dana Mulkern, and Kimberly Donnelly for technical assistance.

REFERENCES

1. Burney P, Malmberg E, Chinn S, Jarvis D, Luczynska C, Lai E. The distribution of total and specific serum IgE in the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1997;99:314-22.

2. Sears MR, Herbison GP, Holdaway MD, Hewitt CJ, Flannery EM, Silva PA. The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma. *Clin Exp Allergy* 1989;19:419-24.
3. Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med* 1997;336:1356-63.
4. Marsh DG, Meyers DA, Bias WB. The epidemiology and genetics of atopic allergy. *N Engl J Med* 1981;305:1551-9.
5. Collaborative Study on the Genetics of Asthma. A genome-wide search for asthma susceptibility loci in ethnically diverse population. *Nat Genet* 1997;15:389-92.
6. Daniels SE, Bhattacharya S, James A, Leaves NI, Young A, Hill MR, et al. A genome wide search for quantitative trait loci underlying asthma. *Nat Genet* 1996;383:247-50.
7. Marsh DG, Neely JD, Breazeale DR, Ghosh B, Freidhoff LR, Ehrlich-Kautzky E, et al. Linkage analysis of IL4 and other chromosome 5q31.1 markers and total serum immunoglobulin E concentrations. *Science* 1994;264:1152-6.
8. Meyers DA, Postma DS, Panhuysen CIM, Xu J, Amelung PJ, Levitt RC, et al. Evidence for a locus regulating total serum IgE levels mapping to chromosome 5. *Genomics* 1994;23:464-70.
9. Cookson WOCM, Sharp PA, Faux JA, Hopkin JM. Linkage between immunoglobulin E response underlying asthma and rhinitis and chromosome 11q. *Lancet* 1989;1:1292-5.
10. Sandford AJ, Shirakawa T, Moffat MF, Daniels SE, Ra C, Faux JA, et al. Localisation of atopy and the β subunit of high affinity IgE receptor (Fc ϵ RI) on chromosome 11q. *Lancet* 1993;341:332-4.
11. Doull IJ, Lawrence S, Watson M, Begishvili T, Beasley RW, Lampe F, et al. Allelic association of gene markers on chromosomes 5q and 11q with atopy and bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 1996;153:1280-4.
12. Marquet S, Abel L, Hillaire D, Dessein H, Kalil J, Feingold J, et al. Genetic localization of a locus controlling the intensity of infection by *Schistosoma mansoni* on chromosome 5q31-q33. *Nat Genet* 1996;14:181-4.
13. Palmer LJ, Pare PD, Faux JA, Moffatt MF, Daniels SE, LeSouef PN, et al. Fc ϵ R1-b polymorphism and total serum IgE levels in endemically parasitized Australian Aborigines. *Am J Hum Genet* 1997;61:182-8.
14. Hizawa N, Freidhoff LR, Chiu Y-F, Ehrlich E, Luehr CA, Anderson JL, et al. Genetic regulation of *Dermatophagoides pteronyssinus*-specific IgE responsiveness: a multipoint linkage analysis in families recruited through 2 asthmatic sibs. *J Allergy Clin Immunol* 1998;102:435-441.
15. Blumenthal MN, Banks-Schlegel S, Bleecker ER, Marsh DG, Ober C. Collaborative studies on the genetics of asthma—National Heart, Lung and Blood Institute. *Clin Exp Allergy* 1995;25:29-32.
16. Freidhoff LR, Marsh DG, Meyers DA, Hussain R. The structure of an allergy index based on IgE-mediated skin sensitivity to common environmental allergens. *J Allergy Clin Immunol* 1983;72:274-87.
17. Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES. Parametric and non-parametric linkage analysis: a unified multipoint approach. *Am J Hum Genet* 1996;58:1347-63.
18. Gyapay G, Morissette J, Vignal A, Dib C, Fizames C, Millasseau P, et al. The 1993-94 G  n  thon human genetic linkage map. *Nat Genet* 1994;7:246-339.
19. Murray JC, Buetow KH, Weber JL, Ludwigsen S, Scherpbier-Heddema, Manion F, et al. A comprehensive human linkage map with centimorgan density. Cooperative Human Linkage Center (CHLC). *Science* 1994;265:2049-54.
20. Hizawa N, Yamaguchi E, Ohe M, Itoh A, Furuya K, Ohnuma N, et al. Lack of linkage between atopy and locus 11q13. *Clin Exp Allergy* 1992;22:1065-9.
21. Shirakawa T, Hashimoto T, Furuyama J, Moriyama K. Linkage between severe atopy and chromosome 11q13 in Japanese families. *Clin Genet* 1994;46:125-30.
22. Blumenthal MN, Amos BD. Genetic and immunologic basis of atopic responses. *Chest* 1987;91:176S-84S.
23. Cookson WOCM, Young RP, Sandford AJ, Moffatt MF, Shirakawa T, Sharp PA, et al. Maternal inheritance of atopic IgE responsiveness on chromosome 11q. *Lancet* 1992;340:381-4.
24. Inglehearn CF. Intelligent linkage analysis using gene density estimates. *Nat Genet* 1997;16:15.