American Journal of Medical Genetics 104:23–30 (2001)

Segregation Analyses of Asthma and Respiratory Allergy: The Humboldt Family Study

Yue Chen,[1]* Audrey H. Schnell,[2] Donna C. Rennie,[3,4] Robert C. Elston,[2] Lori A. Lockinger,[3] and James A. Dosman[3]

[1]*Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada*
[2]*Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, Ohio*
[3]*Centre for Agricultural Medicine and Department of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada*
[4]*College of Nursing, University of Saskatchewan, Saskatoon, Saskatchewan, Canada*

We performed segregation analyses of asthma and respiratory allergy based on data from 309 nuclear families comprising 1,053 individuals living in the town of Humboldt, Saskatchewan, in 1993, using the REGD program of the S.A.G.E. program package. For adults, information on asthma and history of respiratory allergy was provided by the subjects themselves, and for children by their parents. When asthma was considered as the trait in segregation analysis, models of no major effect, with or without familial effects, were rejected, but they were not rejected after adjusting for history of respiratory allergy. The major gene hypothesis was not rejected before adjusting for history of respiratory allergy. When respiratory allergy was analyzed as the trait, both major gene and multifactorial models fitted the data well, regardless of whether there was adjustment for asthma or not. Other covariates adjusted for in the segregation analyses were age, sex, number of household smokers, current smoking, number of household members, generation, and house type. The data suggest that a major gene related to respiratory allergy may explain the familial aggregation of asthma.

KEY WORDS: allergy; asthma; families; genetics; major gene; respiratory; segregation

INTRODUCTION

There is abundant evidence indicating that asthma is both environmental and genetic. It is possible that a number of genetic mechanisms are involved in the development of asthma; however, the modes of inheritance are largely unknown [Sandford et al., 1996]. Some segregation analyses have suggested major gene control of asthma [Lawrence et al., 1994; European Community Respiratory Health Survey Group, 1997], whereas the major gene effect is less convincing in other studies [Holberg et al., 1996; Jenkins et al., 1997].

The inflammatory response of airways to aeroallergens is potentially the most important underlying mechanism for the genetic control of asthma [Sandford et al., 1996]. There is evidence of major gene effects on total serum immunoglobulin E (IgE) [Gerrard et al., 1978; Blumenthal et al., 1981; Marsh et al., 1981; Martinez et al., 1994; Meyers, 1994], which is an indicator of allergic reaction and an important characteristic of allergy. If allergy-mediating genetic effects on the development of asthma is a major mechanism for major gene control of asthma, we would expect the observed major gene effects on asthma to be explained by respiratory allergy.

In a previous analysis of 309 nuclear families, Chen et al. [1998] performed a segregation analysis for wheeze, an important clinical characteristic of asthma. Before a history of respiratory allergy was included as a covariate, the data showed that the transmission parameters for a major type were not significantly different from their Mendelian expectations and the hypothesis of a nontransmitted major factor was rejected, suggesting that a major gene influences the expression of wheeze. However, when respiratory allergy was included as a covariate, the Mendelian

Grant sponsor: Saskatchewan Health Services Utilization and Research Commission; Grant sponsor: U.S. Public Health Service, National Institute of General Medical Sciences; Grant number: GM 28356; Grant sponsor: National Center for Research Resources; Grant number: 1 P41 RR03655.

*Correspondence to: Dr. Yue Chen, Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, 451 Smyth Road, Ottawa, Ontario, Canada K1H 8M5. E-mail: chen@zeus.med.uottawa.ca

Received 4 August 2000; Accepted 27 July 2001

DOI 10.1002/ajmg.10026

hypothesis was rejected, suggesting that allergy is the reason for the major gene control of wheeze. In this report, we conduct segregation analyses for both self-reported physician-diagnosed asthma and history of respiratory allergy. The analyses further support the "allergic inflammation" theory that genetic predisposition to allergic reaction causes asthma [Sandford et al., 1996].

MATERIALS AND METHODS

Study Subjects and Data Collection

We conducted a family study in the town of Humboldt, Saskatchewan, in 1993, and ascertained young families through parents who reported having at least one child between ages 6 and 17 years living in the town [Chen et al., 1998, 1999b]. Canvassers contacted all households within the town and left a questionnaire for all adults aged 18–74 years [Chen et al., 1995]. The questionnaire was completed in the home by adult subjects and returned during a prearranged clinic visit. The questionnaire ascertained whether or not the respondent was the parent of a child aged 6–17 years and, if so, requested information on the names and ages of the children. The children's portion of the study was carried out in each of four schools in the town (one high school and three primary schools) on the basis of lists of enrolled students aged 6–17 years attending each school. Subjects less than 18 years of age who were not attending school were identified by means of a total town canvass that was conducted for the adult portion of a cross-sectional study [Chen et al., 1995]. There were a total of 1,019 eligible children and adolescents aged 6–17 years, and 892 (87.5%) of them participated in the cross-sectional study. Of 2,327 potential adult subjects 18–74 years of age, 1,998 participated, resulting in a response rate of 85.9% [Chen et al., 1995]. Almost all town residents (99.6%) were of Caucasian background.

We excluded step-offspring and adopted offspring, and identified 214 young families with both parents who participated in the study, and 95 families in which only one parent participated. All the data on 1,053 individuals from these 309 families were used in this analysis.

A self-administered questionnaire for adults covered information on sociodemographic factors, smoking, alcohol consumption, exercise, home environment, history of allergy, and individual and family history of respiratory symptoms and diseases. A questionnaire for the adolescents aged 12–17 years consisted of two parts. The first part of the questionnaire was designed for completion by the parent(s). In this part, the parents provided information on the child's sociodemographic characteristics, history of allergy, respiratory symptoms and diseases, and home environment. The adolescents completed a second portion of the questionnaire by themselves at school on lifestyle topics, including active smoking and drinking habits. For children 6–11 years of age, their parents completed a questionnaire that ascertained information concerning the child's lifestyle, similar to the adult and adolescent questionnaires, except that information on active smoking was not collected.

Physician-diagnosed asthma was defined as a positive response to the question asking if a doctor had ever said the subject had asthma. A history of allergy was ascertained by asking the following question: "Have you (Has this child) ever had an allergic reaction to things that: 1. Are eaten or ingested (e.g., food or medicine)? 2. Are inhaled (e.g., pollen, dust, animal fur, or smoke)? 3. Come in contact with the skin (e.g., detergents, wool, or metal)? 4. Other? Specify: ___." Respiratory allergy was defined as an affirmative response to the second choice.

A current smoker was defined as a person who reported smoking every day or almost every day currently and had smoked at least 20 packs during the lifetime. Household exposure to environmental tobacco smoke (ETS) was estimated based on the number of household smokers other than the subject himself/herself. Type of house was either single-family house or other.

Statistical Analysis

We performed segregation analyses for asthma and respiratory allergy separately. In order to determine which covariates should be included in the segregation analyses, we conducted logistic regression analyses ignoring the familial nature of the data with a backward elimination process, using the PROC LOGISTIC program in the SAS system [SAS, 1996], with either asthma or respiratory allergy as the dependent variable. The following covariates were considered for inclusion: sex, age, smoking, number of household smokers, type of house, number of household members, and generation (parent or offspring). In addition, all possible two-way interactions with sex were included, as were age^2 and age^3. Thus a full model with all these main effects and interactions was initially fitted, and the least significant effect was eliminated from the model. This process was repeated until only covariates significant at the 0.10 level remained. Those covariates significant for either asthma or respiratory allergy as the dependent variable were then included in all segregation analyses.

Segregation analysis was performed using the REGD program, which is part of the Statistical Analysis for Genetic Epidemiology (S.A.G.E.) computer package [S.A.G.E., 1998]. REGD performs maximum likelihood segregation analysis of a dichotomous trait using a modified class A regressive logistic model [Bonney, 1986] that allows for residual sib correlation [Karunaratne et al., 1998]. The models allow for up to three types of individuals (AA, AB, and BB), where type refers to the presence of two factors (A and/or B) that can be transmitted from generation to generation. Type is defined in terms of transmission: two people are of the same type only if their offspring by a mate of given type have the same phenotypic distribution. The probability that factor A is transmitted from parent to offspring is a transmission probability that depends on the parent's type: the probability that a person of a given type

transmits factor A to offspring. The word "type" is used generally, whatever the mode of transmission, Mendelian inheritance being a specific mode of transmission in which the types are genotypes and the transmission probabilities for the three genotypes (AA, AB, and BB) are 1, 0.5, and 0, respectively. Mendelian inheritance, if it occurs, is assumed to be through a single autosomal locus with two alleles (A and B), where A is the allele associated with the disease. If the Hardy-Weinberg equilibrium is assumed, then the relative frequencies of the three genotypes in the population are q^2, $2q(1-q)$, and $(1-q)^2$ for AA, AB, and BB, respectively, where q is the frequency of allele A.

The penetrance function for an affected individual is taken to be $\exp(\beta_u + \text{covariates} + \text{familial effects})/[1 + \exp(\beta_u + \text{covariates} + \text{familial effects})]$, and for an unaffected individual $1/[1 + \exp(\beta_u + \text{covariates} + \text{familial effects})]$, where β_u is the baseline parameter for a person with (geno)type u. The familial effects include spouse and parental effects, quantified by regressive coefficients in order to allow for additional parental correlation not accounted for by major genotype [Bonney, 1986]. REGD also allows for the inclusion of a sib covariate that measures the proportion of other sibs in a sibship who are affected. Letting r be the number of affected sibs and s the total number of sibs in the sibship, the sib covariate is $r/(s-1)$ if the sib is unaffected, $(r-1)/(s-1)$ if the sib is affected, and 0 if there is only one sib in the sibship. In other words, the covariate for a particular sib is the proportion of the other sibs in the sibship who are affected.

Models corresponding to a no major effect, a dominant mode, and a recessive mode of inheritance were fitted to the data. More complex models were also tested by allowing for multifactorial effects of mothers, fathers, and sibs. When estimating the multifactorial effects, restrictions were placed on the model such that the effect of an unaffected parent could not be greater than 0, and the effect of an affected parent could not be less than 0. A purely multifactorial model with no major gene effect, allowing for multifactorial effects of mothers, fathers, and sibs, was also fitted to the data. Multifactorial effects were also added to the best-fitting Mendelian (dominant or recessive) model. The likelihoods of two models were tested, one against the other, when one could be considered as a special case of the other. Under certain conditions, the difference in $\log_e$ likelihoods is asymptotically distributed as a chi-square statistic (χ^2_{df}) when the more restricted model holds, with degrees of freedom (df) equal to the difference in the number of independent parameters being estimated between the two models. We use this distribution as an approximation in the upper tail for all cases [Atwood et al., 1995], although sometimes the asymptotic distribution is a mixture of chi-square distributions [Self and Liang, 1987]. The no major effect and major gene models (dominant and recessive) were compared to a general model where the transmission probabilities are estimated, but with the restriction of homogeneity of the trait distribution across generations [Demenais and Elston, 1981]. The major gene model with a multifactorial component was compared to the model with only a major gene effect and to the model with only a multifactorial component (no major gene component).

Several sets of initial estimates were used for each model fitted in order to find the global maximum, rather than a local maximum, of the likelihood. The analyses were done using asthma (or respiratory allergy) as the trait 1) incorporating only covariates other than respiratory allergy (or asthma), and 2) adding respiratory allergy (or asthma) as a covariate.

RESULTS

Table I shows the distribution of subjects with asthma and respiratory allergy by family size and family member phenotypes. Fifty-six (18.1%) of the 309 nuclear families had one asthmatic case, and 12 (3.9%) had two or more asthmatic cases. The corresponding numbers for history of respiratory allergy were 94 (30.4%) and 85 (27.5%), respectively.

There were a total of 1,410 parent-child, sib-sib, and spouse pairs in this analysis. Table II shows the distribution of subjects with asthma and a history of respiratory allergy among these pairs. There were a total of 18 (1.3%) parent-child and sib-sib pairs where both had asthma and no spouse pairs where both had asthma. In 147 (10.4%) of all pairs, both subjects had a history of respiratory allergy.

In all the segregation analyses, we included the following covariates: age, age^2, sex, number of household smokers, smoking, number of household members, generation (parental or offspring), the interaction of the number of household smokers with sex, and the interaction of generation with sex. Table III presents the results of the segregation analysis of asthma

TABLE I. Number (%) of Subjects With Asthma and Respiratory Allergy by Family Size

Family size	Number of families	Number of family members with asthma				Number of family members with respiratory allergy				
		0	1	2	3	0	1	2	3	4
2	49	42 (85.7)	6 (12.2)	1 (2.0)		24 (49.0)	19 (38.8)	6 (12.2)		
3	134	112 (83.6)	19 (14.2)	3 (2.2)		58 (43.3)	36 (26.9)	32 (23.9)	8 (6.0)	
4	83	64 (77.1)	18 (21.7)	1 (1.2)		36 (43.4)	25 (30.1)	12 (14.5)	7 (8.4)	3 (3.6)
5	38	21 (55.3)	12 (31.6)	1 (2.6)	4 (10.5)	11 (28.9)	12 (31.6)	9 (23.7)	5 (13.2)	1 (2.6)
6	4	2 (50.0)	1 (25.0)	1 (25.0)		1 (25.0)	2 (50.0)	1 (25.0)		
7	1			1 (100.0)					1 (100.0)	
Total	309	241 (78.0)	56 (18.1)	8 (2.6)	4 (1.3)	130 (42.1)	94 (30.4)	60 (19.4)	21 (6.8)	4 (1.3)

TABLE II. Number (%) of Subjects With Asthma and Respiratory Allergy Among Parent–Child, Sib–Sib and Spouse Pairs*

	Number of pairs	Number of pair members with asthma			Number of pair members with respiratory allergy		
		0	1	2	0	1	2
Parent–child	901	779 (86.5)	113 (12.5)	9 (1.0)	513 (56.9)	292 (32.4)	96 (10.7)
Sib–sib	295	236 (80.0)	50 (16.9)	9 (3.1)	170 (57.6)	96 (32.5)	29 (9.8)
Spouse	214	195 (91.1)	19 (8.9)	0 (0)	115 (53.7)	77 (36.0)	22 (10.3)
Total	1410	1210 (85.8)	182 (12.9)	18 (1.3)	798 (56.6)	465 (33.0)	147 (10.4)

*Distinct pairs; each family member may belong to more than one pair.

without adjustment for a history of respiratory allergy. In the general model, the transmission probabilities were estimated. Since models were easily overparameterized, we made one baseline parameter (β_{AB}) equal to β_{AA} or β_{BB}, corresponding to a dominant or recessive model, respectively. When compared with the general model, a no major effect model with no familial components was rejected ($\chi^2 = 13.84$, df = 4, $P < 0.01$), as was a dominant model ($\chi^2 = 6.66$, df = 2, $P < 0.05$). However, a recessive major gene model was not rejected ($\chi^2 = 0$, df = 2, $P = 1.00$). The inclusion of multifactorial familial effects did not significantly improve the recessive model. A model with no major effect but only multifactorial familial effects fitted significantly worse than the recessive model with multifactorial familial effects.

Table IV shows the results of segregation analysis for asthma after adjustment for history of respiratory allergy, as well as the other covariates. The no major effect without a multifactorial component model fitted the data, as well as the general model ($\chi^2 = 2.50$, df = 4, $P > 0.05$).

Table V shows the results of segregation analysis of history of respiratory allergy without asthma included as a covariate. A no major effect model with no multifactorial component was rejected ($\chi^2 = 32.06$, df = 4, $P < 0.01$). Neither the recessive nor the dominant model was rejected, with the dominant model having a slightly larger $\log_e$ likelihood. The addition of a familial multifactorial component did not significantly improve the dominant model ($\chi^2 = 7.76$, df = 3). The addition of a major gene component did not

TABLE III. Parameter Estimates (and Standard Errors) From Segregation Analysis of Asthma Without Inclusion of Respiratory Allergy as a Covariate

Parameter	General[a]	NME[b,c]	Dominant[c]	Recessive[c]	Recessive with multifactorial[d]	Multifactorial[e]
q	0.23	—	0.03	0.23 (0.02)	0.22	—
β_{AA}	15.10	−4.63	−2.71	15.10 (15.37)	72.83	−4.79
β_{AB}	−148.60	—	−2.71	−147.82 (107.11)	−6.25	—
β_{BB}	−148.60	—	−5.84	−147.82 (107.11)	−6.25	—
Parent unaffected	—	—	—	—	0[f]	0[f]
Parent affected	—	—	—	—	0.34	0.99
Sibling	—	—	—	—	−3.24	0.68
Age	0.54	0.06	0.39	0.54 (0.34)	0.87	0.67
Sex	94.24	0.38	0.67	93.22 (302.59)	−0.07	0.39
No. of household smokers	0.85	0.53	0.70	0.85 (0.35)	0.96	0.53
Smoking	1.33	0.57	0.56	1.33 (0.99)	1.39	0.59
No. of household members	1.63	0.51	1.51	1.63 (0.63)	1.67	0.47
Generation	139.56	1.04	1.51	138.78 (107.11)	−4.46	0.96
No. of household smokers x sex	−0.89	−0.86	−1.05	−0.89 (0.62)	−0.78	−0.91
Age^2	−0.02	−0.00	−0.00	−0.02 (0.01)	−0.04	−0.00
Generation x sex	−93.99	−0.11	−0.15	−92.96 (302.59)	0[g]	−0.09
Ln (likelihood)	−273.06	−279.98	−276.39	−273.06	−271.87	−276.12
χ^2	—	13.84	6.66	0.00	2.38	8.50
Degrees of freedom	—	4	2	2	3	2
P value		< 0.01	< 0.05	NS[h]	NS	< 0.05

[a]Estimation of τ_{AA}, τ_{AB}, τ_{BB} with restriction of homogeneity across generations.
[b]No major effect model.
[c]Compared to the general model.
[d]Compared to the recessive model.
[e]Compared to the recessive with multifactorial model.
[f]Parameter became fixed at or near a bound during estimation.
[g]Parameter fixed at 0, with no change in likelihood, in order to obtain standard deviations.
[h]Not significant ($P > 0.05$).

TABLE IV. Parameter Estimates (and Standard Errors) From Segregation Analysis of Asthma With Inclusion of Respiratory Allergy as a Covariate

Parameter	General[a]	NME[b,c]	Recessive[c]	Dominant[c]	Dominant with multifactorial[d]	Multifactorial[e]
q	0.15	—	0.64	0.15 (0.18)	0.51	—
β_{AA}	−4.51	−4.99	−4.76	−4.51 (1.93)	−5.12	−5.09
β_{AB}	−4.51	—	−7.39	−4.51 (1.93)	−5.12	—
β_{BB}	−7.03	—	−7.39	−7.03 (0.32)	−27.01	—
Parent unaffected	—	—	—	—	0[f]	0[f]
Parent affected	—	—	—	—	0.86	0.86
Sibling	—	—	—	—	−0.03	0.33
Respiratory allergy	3.23	2.77	3.16	3.23 (0.53)	2.92	2.74
Age	−0.01	−0.02	−0.01	−0.01 (0.08)	−0.01	−0.01
Sex	0.14	0.17	0.14	0.14 (0.53)	0.18	0.17
No. of household smokers	0.78	0.62	0.81	0.78 (0.35)	0.75	0.63
Smoking	0.76	0.66	0.78	0.76 (0.50)	0.70	0.67
No. of household members	0.67	0.63	0.66	0.67 (0.33)	0.67	0.61
Generation	0.85	0.42	0.78	0.85 (1.16)	0.48	0.34
No. of household smokers x sex	−1.15	−0.96	−1.16	−1.15 (0.53)	−1.13	−0.98
Age^2	−0.00	−0.00	−0.00	−0.00 (0.00)	−0.00	−0.00
Generation x sex	0.42	0.35	0.43	0.42 (0.65)	0.43	0.38
Ln (likelihood)	−220.28	−221.53	−220.46	−220.28	−219.56	−219.65
χ^2		2.50	0.36	0.00	1.44	0.18
Degree of freedom		4	2	2	3	2
P value		NS[g]	NS	NS	NS	NS

[a]Estimation of τ_{AA}, τ_{AB}, τ_{BB} with restriction of homogeneity across generations.
[b]No major effect model.
[c]Compared to the general model.
[d]Compared to the dominant model.
[e]Compared to the dominant with multifactorial model.
[f]Parameter became fixed at or near a bound during estimation.
[g]Not significant ($P > 0.05$).

significantly improve the purely multifactorial model ($\chi^2 = 0.00$, df = 2). Therefore, in this analysis it was not possible to determine whether the familial component was due to a single major gene or to a multifactorial component.

Segregation analysis of respiratory allergy showed similar results when asthma was included as a covariate (Table VI); the no major effect model was rejected ($\chi^2 = 28.64$, df = 4, $P < 0.01$). Neither the recessive nor the dominant model was rejected, with the dominant model having a value of slightly larger $\log_e$ likelihood. The inclusion of familial effects did not significantly improve the dominant model, nor did the inclusion of a dominant component significantly improve the multifactorial model.

DISCUSSION

In this segregation analysis of asthma, the major gene hypothesis was not rejected before adjusting for history of respiratory allergy, whereas the no major gene effect models, with or without familial effects, were rejected. However, the no major gene effect models were not rejected after adjusting for history of respiratory allergy. These results were similar to previous findings of wheeze based on data from the Humboldt Family Study, where the familial effects were related to history of respiratory allergy [Chen et al., 1998]. Although wheeze is an important clinical phenotype of asthma, these two conditions are not equivalent, and only some wheezing children have or develop asthma [Sherman et al., 1990; Martinez et al., 1995]. Therefore, this analysis provides more straightforward information on major gene control of asthma and its relationship to respiratory allergy.

Initial segregation analyses (data not shown) of the data showed a very significant departure from homogeneity across generations, indicating that none of the models could adequately explain the data. However, this discrepancy was completely removed when generation and the interaction of generation with sex were included as covariates in the analysis. It can be seen in Tables V and VI that the interaction of generation with sex was significant in the analysis of respiratory allergy. In Tables III and IV, it is seen that the coefficient of the sib covariate was negative in the recessive-with-multifactorial model. However, none of the conclusions changed if this coefficient was constrained to be positive. The occurrence of asthma has been increasing over the last few decades [World Health Organization, 1995], which can hardly be explained by genetic factors. The removal of the heterogeneity when generation and the interaction of generation with sex were included as covariates suggests a change in environmental factors (e.g., air

TABLE V. Parameter Estimates (and Standard Errors) From Segregation Analysis of Respiratory Allergy Without Inclusion of Asthma as a Covariate

Parameter	General[a]	NME[b,c]	Recessive[c]	Dominant[c]	Dominant with multifactorial[d]	Multifactorial[e]
q	0.14	—	0.40	0.14 (0.84)	0[f]	—
β_{AA}	−1.55	−2.36	38.46	−1.55 (2.05)	−0.83	−2.64
β_{AB}	−1.55	—	−3.40	−1.55 (2.05)	−0.83	—
β_{BB}	−4.68	—	−3.40	−4.68 (1.97)	−2.64	—
Parent unaffected	—	—	—	—	−0.12	−0.12
Parent affected	—	—	—	—	0.66	0.66
Sibling	—	—	—	—	1.06	1.06
Age	0.17	0.10	0.15	0.17 (0.07)	0.11	0.11
Sex	0.60	0.41	0.63	0.60 (0.35)	0.41	0.41
No. of household smokers	0.12	0.03	0.17	0.12 (0.28)	−0.01	0.06
Smoking	−0.11	−0.05	0.02	−0.11 (0.35)	−0.52	−0.05
No. of Household members	−0.19	−0.16	−0.37	−0.19 (0.25)	−0.19	−0.19
Generation	1.46	0.80	0.79	1.46 (0.97)	0.51	0.51
No. of household smokers x sex	−0.09	−0.04	−0.10	−0.09 (0.37)	−0.03	−0.03
Age^2	−0.00	−0.00	−0.00	−0.00 (0.00)	−0.00	−0.00
Generation of x sex	−1.12	−0.74	−1.52	−1.12 (0.48)	−0.74	−0.74
Ln (likelihood)	−596.85	−612.88	−599.07	−596.85	−592.97	−592.97
χ^2		32.06	4.44	0.00	7.76	0.00
Degree of freedom		4	2	2	3	2
P value		< 0.01	NS[g]	NS	NS	NS

[a]Estimation of τ_{AA}, τ_{AB}, τ_{BB} with restriction of homogeneity across generations.
[b]No major effect model.
[c]Compared to the general model.
[d]Compared to the dominant model.
[e]Compared to the dominant with multifactorial model.
[f]Parameter became fixed at or near a bound during estimation.
[g]Not significant ($P > 0.05$).

pollution) over generations may be responsible for the increase in asthma occurrence. It is not known if gene-environmental interaction has an impact on the development of asthma.

Major gene effects on asthma have been observed in previous studies. Lawrence et al. [1994] studied 131 families in the United Kingdom and calculated an asthma score based on questionnaire information and measurements of bronchial hyperresponsiveness to histamine inhalation. The study showed a heritability of 0.28 and suggested evidence of major gene control for asthma. In a pooled analysis of 13,963 families and 75,392 individuals, the European Community Respiratory Health Survey Group [1997] demonstrated a major gene effect that is responsible for the regulation of physician-diagnosed asthma. They indicated that the putative major gene could be a gene also involved in allergy but did not provide further evidence. Less strong support for the major gene control of asthma was provided by two other studies. In a study of 7,394 families (41,506 individuals) in Australia, Jenkins et al. [1997] found that both a non-Mendelian oligogenic model and a Mendelian codominant model fitted the data well and concluded that asthma was not fully described by a single-gene model. In a segregation analysis of physician-diagnosed asthma based on the data from 906 nuclear families, Holberg et al. [1996] found that a recessive component influenced the expression of physician-diagnosed asthma, which could not be accounted for by serum IgE levels. Since the potential major gene effect on physician-diagnosed asthma was independent of serum IgE in the Tucson study, it was suggested that a separate major gene might be related to the liability of asthma [Rich, 1995]. However, there was lack of convincing evidence of a major gene effect on physician-diagnosed asthma in that study, and single two-allele-locus models were rejected [Holberg et al., 1996].

Our segregation analyses provide evidence that the putative major gene involved in the pathogenesis of asthma is related to respiratory allergy. We were not able to determine whether the familial component for respiratory allergy was due to a single locus gene or to a multifactorial component, since both models were not rejected. However, previous studies have documented major genetic effects on some phenotypes of allergy, IgE in particular [Meyers, 1994; Sandford et al., 1996; Los et al., 1999]. There may be a number of mechanisms involved in the development of asthma; however, the allergic inflammation theory that genetic predisposition to allergic reaction causes asthma [Sandford et al., 1996] is the most popular. When we adjusted for the effect of respiratory allergy in this analysis, we removed the genetic effect that is related to respiratory allergy. Thus, the results coincide with the allergic inflammation theory.

The allergic status in this study was based on self-reporting and was subject to reporting bias. Objective tests may be helpful, but allergy is also a complex disorder and lacks highly specific measurements. The

TABLE VI. Parameter Estimates (and Standard Errors) From Segregation Analysis of Respiratory Allergy With Inclusion of Asthma as a Covariate

Parameter	General[a]	NME[b,c]	Recessive[c]	Dominant[c]	Dominant with multifactorial[d]	Multifactorial[e]
q	0.05	—	0.38	0.05 (0.12)	0.01	—
β_{AA}	45.30	−2.30	1.74	23.02 (−0.28)	32.41	−2.63
β_{AB}	45.30	—	−3.35	23.02 (−0.28)	32.41	—
β_{BB}	−2.75	—	−3.35	−2.75 (1.32)	−2.73	—
Parent unaffected	—	—	—	—	−0.13	−0.23
Parent affected	—	—	—	—	0.59	0.61
Sibling	—	—	—	—	0.91	1.01
Asthma	3.27	2.79	3.73	3.27 (0.33)	2.92	2.83
Age	0.12	0.10	0.15	0.12 (0.06)	0.12	0.12
Sex	0.36	0.37	0.52	0.36 (0.25)	0.37	0.36
No. of household smokers	−0.17	−0.15	−0.33	−0.17 (0.21)	−0.15	−0.16
Smoking	−0.15	−0.17	−0.22	−0.15 (0.32)	−0.16	−0.16
No. of household members	−0.34	−0.30	−0.39	−0.34 (0.21)	−0.36	−0.32
Generation	0.46	0.64	0.52	0.46 (0.76)	0.46	0.54
No. of household smokers x sex	0.34	0.23	0.50	0.33 (0.18)	0.26	0.27
Age^2	−0.00	−0.00	−0.00	−0.00 (0.00)	−0.00	−0.00
Generation x sex	−1.17	−0.83	−1.50	−1.17 (0.43)	−0.91	−0.85
Ln (likelihood)	−539.30	−553.62	−541.56	−539.30	−536.03	−536.17
χ^2		28.64	4.52	0.00	6.54	0.28
Degree of freedom		4	2	2	3	2
P value		< 0.01	NS[f]	NS	NS	NS

[a]Estimation of τ_{AA}, τ_{AB}, τ_{BB} with restriction of homogeneity across generations.
[b]No major effect model.
[c]Compared to the general model.
[d]Compared to the dominant model.
[e]Compared to the dominant with multifactorial model.
[f]Not significant ($P > 0.05$).

expression of allergy is dependent on exposure. IgE levels may not reflect the history of allergy. Not all allergic individuals have elevated IgE levels. Total IgE levels vary in allergic subjects after exposure to relevant allergens [Martinez et al., 1994]. These differences may explain, at least in part, the discrepancy between our results adjusted for respiratory allergy and those adjusted for IgE reported by Holberg et al. [1996].

There are some concerns and limitations for this study. First, the information on both asthma and allergy was either self- or parent-reported, which could be subject to reporting biases. However, the definition of asthma in this study was similar to the definition used in the original American Thoracic Society Standardization Project questionnaire, which has been used in various epidemiological studies and has been validated. In addition, there is evidence that various definitions of asthma have little influence on estimates of incidence (Larsson, 1995). Even if children of asthmatics were more likely to be labeled as asthmatic or parents with asthma were more likely to report their children being asthmatic to a certain degree, such a reporting bias would not explain what we have observed, namely that any major gene effect is more likely related to respiratory allergy. In addition, the prevalence of asthma and allergy are comparable to those from other Canadian studies [Chen et al., 1999a; Habbick et al., 1999]. Second, self-reported asthma did not distinguish between extrinsic and intrinsic asthma, which may share different mechanisms. If we could have shown differences in major genetic effects on extrinsic and intrinsic asthma in relation to respiratory allergy, the results might be more interesting. Third, the sample size is relatively small, which limits the ability to test various genetic models.

In conclusion, a major gene that is related to respiratory allergy may be involved in the pathogenesis of asthma. The inflammatory response of airways to aeroallergens is believed to be the most frequent underlying mechanism of asthma, and our findings support this theory.

ACKNOWLEDGMENTS

We thank D. Still (mayor), W. Herman (town administrator), W. German, N. Trach, J. Hergott (co-chairs of the local organizing committee), M. Gillis-Cipywnyk, and all of the volunteers who provided canvassing and other field work in the study. Yue Chen is a Canadian Institutes of Health Research Investigator Award recipient.

REFERENCES

Atwood LD, Wilson AF, Bailey-Wilson JE, Carruth JN, Elston RC. 1995. On the distribution of the likelihood ratio test statistic for a mixture of two normal distributions. Com Stats 25:733–740.

Blumenthal MN, Namboodiri K, Mendall N, Bleich P, Elston RC, Yunis E. 1981. Genetic transmission of IgE levels. Am J Med Genet 10:219–228.

Bonney GE. 1986. Regressive models for familial disease and other binary traits. Biometrics 42:611–625.

Chen Y, Rennie DC, Reeder BA. 1995. Age-related association between body mass index and blood pressure: the Humboldt Study. Int J Obes 19:825–831.

Chen Y, Rennie DC, Lockinger LA, Dosman JA. 1998. Evidence for major genetic control of wheeze in relation to history of respiratory allergy. Am J Med Genet 75:485–491.

Chen Y, Dales R, Krewski D, Breithaupt K. 1999a. Increased effects of smoking and obesity on asthma among female Canadians: the National Population Health Survey 1994–95. Am J Epidemiol 150: 255–262.

Chen Y, Dosman JA, Rennie DC, Lockinger LA. 1999b. Major genetic mechanism of airway-parenchymal dysanapsis of the lung: the Humboldt Family Study. Genet Epidemiol 16:95–110.

Demenais FM, Elston RC. 1981. A general transmission probability model for pedigree data. Hum Hered 31:93–99.

European Community Respiratory Health Survey Group. 1997. Genes for asthma? An analysis of the European Community Respiratory Health Survey. Am J Respir Crit Care Med 156:1773–1780.

Gerrard JW, Rao DC, Morton NE. 1978. A genetic study of immunoglobulin E. Am J Hum Genet 30:46–58.

Habbick BF, Pizzichini MM, Taylor B, Rennie D, Senthilselvan A, Sears MR. 1999. Prevalence of asthma, rhinitis and eczema among children in 2 Canadian cities: the International Study of Asthma and Allergies in Childhood. CMAJ 160:1824–1828.

Holberg CJ, Elston RC, Halonen M, Wright AL, Taussig LM, Morgan WJ, Martinez FD. 1996. Segregation analysis of physician-diagnosed asthma in Hispanic and non-Hispanic white families. Am J Respir Crit Med 154:144–150.

Jenkins MA, Hopper JL, Giles GG. 1997. Regressive logistic modeling of familial aggregation for asthma in 7,394 population-based nuclear families. Genet Epidemiol 14:317–332.

Karunaratne PM, Elston RC, Loman N, Olsson H, Ranstam J. 1998. Analysis of Swedish male breast cancer family data: a simple way to incorporate a common sibling effect. Genet Epidemiol 15:201–212.

Larsson L. 1995. Incidence of asthma in Swedish teenagers: relation to sex and smoking habits. Thorax 50:260–264.

Lawrence S, Beasly R, Doull I, Begishvili B, Lampe F, Holgate ST, Morton NE. 1994. Genetic analysis of atopy and asthma as quantitative traits and ordered polychotomies. Ann Hum Genet 58:359–368.

Los H, Koppelman GH, Postma DS. 1999. The importance of genetic influences in asthma. Eur Respir J 14:1210–1227.

Marsh DG, Myers DA, Bias WB. 1981. The epidemiology and genetics of atopic allergy. N Engl J Med 305:1551–1559.

Martinez FD, Holberg CJ, Halonen M, Morgan WJ, Weight AL, Taussig LM. 1994. Evidence for Mendelian inheritance of serum IgE levels in Hispanic and non-Hispanic white families. Am J Hum Genet 55:555–565.

Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, the Group Health Medical Associates. 1995. Asthma and wheezing in the first six years of life. N Engl J Med 332:133–138.

Meyers DA. 1994. Approaches to genetic studies of asthma. Am J Respir Crit Care Med 150:S91–S93.

Rich SS. 1995. Results of genetic studies in man. Clin Exp Allergy 25(Suppl.):95–96.

S.A.G.E. 1998. Statistical Analysis for Genetic Epidemiology, release 3.1. Computer program package available from the Department of Epidemiology and Biostatistics. Case Western Reserve University School of Medicine, Cleveland, Ohio.

Sandford A, Weir T, Pare P. 1996. The genetics of asthma. Am J Respir Crit Care Med 153:1749–1765.

SAS Institute, Inc. 1996. SAS/STAT® user's guide, release 6.12. Cary, NC: SAS Institute, Inc.

Self SG, Liang KY. 1987. Asymptotic properties of maximum likelihood estimators and likelihood ratio test under non-standard conditions. J Am Stat Assoc 82:605–610.

Sherman CB, Tosteson TD, Tager IB, Speizer FE, Weiss ST. 1990. Early childhood, predictors of asthma. Am J Epidemiol 132:83–95.

World Health Organization. 1995. Global initiative for asthma: global strategy for asthma management and prevention NHLBI/WHO workshop report. U.S. National Institutes of Health.