

Evidence for Major Genetic Control of Wheeze in Relation to History of Respiratory Allergy: Humboldt Family Study

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We report the results of segregation analyses for wheeze before and after a history of respiratory allergy was taken into consideration. The analyses were based on data from 309 nuclear families with 1,053 individuals living in the town of Humboldt, Saskatchewan in 1993, and were performed by using the REGD program of the SAGE package. For adults, information on wheeze and history of respiratory allergy was provided by themselves, and for children, by their parents. Segregation analyses were first conducted before adjustment for history of respiratory allergy. Other covariates were adjusted including sex, current smoking, household exposure to tobacco smoke, and type of house. A single locus model with residual familial effects fit the data well, but none of the Mendelian models (recessive, dominant, and codominant) could be distinguished. The no-parent-offspring-transmission hypothesis was rejected. However, when the variable of respiratory allergy was included in the models as a covariate, both Mendelian and environmental hypotheses were rejected. The Mendelian model had a relatively lower value of Akaike's Information Criterion than did the environmental model (1095.56 versus 1111.24). The data suggest that a single locus gene explains a portion of wheeze that is related to respiratory allergy, and that common environmental factors and/or polygenes also account for a certain familial aggregation of wheeze. *Am. J. Med. Genet.* 75:485–491, 1998.

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INTRODUCTION

Wheezing is a manifestation of asthma, and is used to identify asthma status [Sears et al., 1982; Speight et al., 1983; Lebowitz et al., 1984; Crockett et al., 1986; Andrae et al., 1988; Kirschner et al., 1990; Forastiere et al., 1992]. Not all individuals who wheeze have asthma; however, the genetic mechanisms of wheeze are of interest in understanding the genetic mechanisms of asthma.

There is evidence for a genetic contribution to the occurrence of asthma; however, the mode of inheritance is unclear [Sandford et al., 1996]. As a complex disorder, it is possible that a number of mechanisms are involved in the development of asthma. The inflammatory response of airways to aeroallergens is considered to be the most frequent underlying mechanism [Sandford et al., 1996]. As an intermediate phenotype, total serum immunoglobulin E (IgE) has been extensively studied. There is evidence of major gene effects on IgE, although the genetic mechanism of IgE production remains controversial [Meyers, 1994; Sandford et al., 1996]. Both atopy and bronchial hyperresponsiveness (BHR) are predictors of asthma and are related. However, individuals with BHR may not be atopic or have symptoms of asthma, suggesting that BHR is a separately inherited phenotypic trait [Sandford et al., 1996]. Because of the lack of a unique clinical manifestation of asthma, allergic status and BHR, as major components of asthma, are studied most frequently. However, the molecular relationships between these components and asthma require further study [Postma et al., 1995].

The approach of studying clinical phenotypes of asthma is also useful. A recent segregation analysis of physician-diagnosed asthma indicated that a recessive component could influence the development of asthma [Holberg et al., 1996]. However, the evidence was not strong. Both Mendelian and environmental models were rejected, although the Mendelian model fit the data better than the environmental model [Martinez and Holberg, 1995; Holberg et al., 1996].

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In this report, we present the results of segregation analyses of wheeze based on data from a random sample of nuclear families. We found that our findings of a major gene effect on wheeze varied when history of respiratory allergy was taken into consideration.

MATERIALS AND METHODS

Study Subjects and Data Collection

The study was conducted in the town of Humboldt, Saskatchewan in 1993, the methods of which have been detailed previously [Chen et al., 1996a, 1997a,b]. In brief, nuclear families were ascertained through parents who reported having at least one child between the ages of 6 and 17 years living in this area. 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 determined whether or not the respondent was the parent of children aged 6–17 years, and if so, requested information on the names and ages of the children. The portion of the study that involved children was carried out in each of four schools in the town (one high school and three primary schools). Lists of enrolled students aged 6–17 years were available for each school. Subjects less than 18 years old who were not attending school were identified by means of a total town canvass that was conducted for the adult portion of the cross-sectional study [Chen et al., 1995]. Almost all town residents (99.6%) were of Caucasian background.

After excluding step-offspring and adopted offspring, we identified 214 nuclear 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. Eight subjects, who were excluded in a previous analysis because of no pulmonary function test results [Chen et al., 1997a], were included in the present analysis.

A self-administered questionnaire for adults asked about information on sociodemographic factors, smoking, alcohol consumption, exercise, home environment, history of allergy, individual and family history of respiratory symptoms and diseases. A questionnaire for 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, parent(s) provided information on the child's sociodemographic characteristics, history of allergy, respiratory symptoms and diseases, and home environment. A second portion of the questionnaire for adolescents was completed by the adolescents themselves at school on lifestyle topics including active smoking and drinking habits. For children aged 6–11 years, a questionnaire that ascertained information concerning the child's lifestyle, similar to adult and adolescent questionnaires, was completed by their parents. We did not collect information on active smoking for children less than 12 years of age.

Wheeze was defined as a positive response to the question: "Does your (/this child's) chest ever sound

wheezy or whistling?" 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. Estimation of household exposure to environmental tobacco smoke (ETS) was based on the number of household smokers other than the subject him/herself.

Statistical Analysis

Class A regressive logistic model [Bonney, 1986] was performed for segregation analyses, using the REGD program of the Statistical Analysis for Genetic Epidemiology package [SAGE, 1994]. The parameters of the model were estimated by the method of maximum likelihood, which included type frequencies (ψ_{AA} , ψ_{AB} , ψ_{BB}), transmission probabilities (τ_{AA} , τ_{AB} , τ_{BB}), baseline parameters (β_{AA} , β_{AB} , β_{BB}), and residual familial effects including effects of spouse (δ_s), mother (δ_m), and father (δ_f). "Type" [Go et al., 1978] or "ousiotype" [Cannings et al., 1978] was suggested to describe an underlying discrete factor related to a phenotype, which may or may not follow Mendelian transmission. Covariates (ξ s) adjusted in the model included sex (male, female), current smoking (no, yes), number of household smokers (0, 1, 2+), type of house (unattached one-family house, other) and history of respiratory allergy (no, yes). There was no discernible trend in the prevalence of wheeze by age.

A major gene effect was assumed to result from segregation at a single locus having two alleles, A and B. Allele A was associated with the affected state. We assumed random mating and Hardy-Weinberg equilibrium for population frequencies of the types. The baseline parameters were not sex-dependent.

We estimated the parameters of transmission probabilities of parents transmitting the A allele to offsprings. Under Mendelian transmission, $\tau(AA) = 1$, $\tau(AB) = 1/2$, and $\tau(BB) = 0$. The nontransmitted environmental effect was obtained with the three transmission probabilities being equal to q_A [$\tau(AA) = \tau(AB) = \tau(BB) = q_A$] [SAGE, 1994].

A likelihood-ratio test (LRT) was used to select the most parsimonious model, which is minus twice the difference in the log_e likelihood (lnL) between models before and after reducing parameters. The LRT is distributed asymptotically as a chi-square with degrees of freedom (df) equal to the difference in the number of parameters between two models. However, if the value of a parameter under the null hypothesis is at the boundary of the parameter space, the LRT statistic does not follow a simple chi-square distribution [Khoury et al., 1993]. When one parameter is at boundary value, the LRT follows a mixture of a chi-square distribution with 1 df and a degenerate chi-square dis-

TABLE I. Number (%) of Subjects With Wheeze by Family Size

Family size	Number of families	Number (%) of subjects with wheeze						
		0	1	2	3	4	5	6
2	49	25 (51.0)	16 (32.7)	8 (16.3)				
3	134	63 (47.0)	37 (27.6)	24 (17.9)	10 (7.5)			
4	83	26 (31.3)	27 (32.5)	23 (27.7)	6 (7.2)	1 (1.2)		
5	38	11 (28.9)	11 (28.9)	8 (21.1)	3 (7.9)	5 (13.2)		
6	4		2 (50.0)		1 (25.0)		1 (25.0)	
7	1							1 (100.0)
Total	309	125 (40.5)	93 (30.1)	63 (20.4)	20 (6.5)	6 (1.9)	1 (0.3)	1 (0.3)

tribution with 0 df. When two parameters are at boundary values, the LRT follows a mixture of one-fourth a chi-square with 2 df, one-half a chi-square with 1 df, and one-fourth a chi-square with 0 df [Self and Liang, 1987]. In addition, the LRT is based on a comparison of strictly hierarchical models. For several alternative nonhierarchical models, the better-fitting model was considered with a lower value of the Akaike's information criterion [$AIC = -2 \ln L + 2$ (number of parameters estimated)] [Akaike, 1974].

RESULTS

Table I presents the distribution of subjects with wheeze by family size. Of 309 nuclear families, there were 184 (59.5%) multiplex affected families.

Table II shows the distribution of subjects with wheeze among parent-child, sib-sib and spouse pairs. In total, there were 1,410 pairs in this analysis, and among them, 184 pairs (13.0%) were both affected.

Table III shows the prevalence of wheeze associated with sex, history of respiratory allergy, current smoking status, number of household smokers, and type of house. The prevalence of wheeze was higher in males than in females. Current smoking and household ETS exposure were positively associated with the prevalence of wheeze. The subjects who were living in unattached one-family houses had a lower risk of wheezing than did other subjects.

We first performed a segregation analysis for wheeze, adjusting for sex, smoking, household expo-

sure to ETS, and type of house, but not history of respiratory allergy. Table IV presents eight different models with the maximum likelihood estimates of the parameters for wheeze. In the general model (model 1), we estimated 14 parameters and their standard deviations, of which the parameters for the covariates are not presented (available upon request). The estimates of gene frequency, transmission probabilities, baseline parameters, and residual familial effects were all arbitrary. The environmental hypothesis was rejected when a comparison was made between the environmental model (model 2), in which all transmission probabilities were fixed to be equal to gene frequency, and the general transmission model. However, the Mendelian model (model 3) fit the data as well as the general model. Therefore, the Mendelian hypothesis could not be rejected. Compared to the unrestricted or codominant model (model 3), the A dominant and A recessive models (models 4 and 5) fit the data equally well. When the single locus or the familial effect was

TABLE III. Prevalence of Wheeze by Covariates Among Participants

	Number of subjects	Cases	%	Relative risk	95% confidence interval
Gender					
Male	501	166	33.1	1.00	
Female	552	148	26.8	0.81	0.67–0.97
Respiratory allergy					
No	760	156	20.5	1.00	
Yes	293	158	53.9	2.63	2.20–3.13
Current smoking					
No	928	243	26.2	1.00	
Yes	125	71	56.8	2.17	1.80–2.62
Number of household smokers (ETS)					
0	806	230	28.5	1.00	
1	179	54	30.2	1.06	0.82–1.36
2+	68	30	44.1	1.55	1.16–2.06
Type of house					
Unattached one-family house	936	263	28.1	1.00	
Other	117	51	43.6	1.55	1.23–1.95

TABLE II. Number (%) of Subjects Among Parent-Child, Sib-Sib and Spouse Pairs

	Number of pairs	Number (%) of subjects with wheeze		
		0	1	2
Parent-child	901	478 (53.1)	314 (34.9)	109 (12.1)
Sib-sib	295	146 (49.5)	100 (33.9)	49 (16.6)
Spouse	214	113 (52.8)	75 (35.0)	26 (12.1)
Total	1,410	737 (52.3)	489 (34.7)	184 (13.0)

TABLE IV. Parameter Estimates (\pm Standard Deviations) From Segregation Analysis of Wheeze After Adjustment of Covariates[†] Except History of Respiratory Allergy

	General, with FE ^a (1)	Environmental, with FE (2)	Mendelian, with FE			Mendelian, without FE (6)	FE only (7)	Sporadic (8)
			Arbitrary (3)	Dominant (4)	Recessive (5)			
q_A^b	0.48 \pm 0.06	0.47 \pm 0.10	0.22 \pm 0.10	0.18 \pm 0.07	0.58 \pm 0.08	0.25 \pm 0.08	[1.0] ^k	[1.0] ^k
τ (AA) ^c	0.83 \pm 0.11	= q_A	[1.0] ^k	[1.0] ^k	[1.0] ^k	[1.0] ^k		
τ (AB)	0.64 \pm 0.08	= q_A	[0.5] ^k	[0.5] ^k	[0.5] ^k	[0.5] ^k		
τ (BB)	(0.00) ^l	= q_A	[0.0] ^k	[0.0] ^k	[0.0] ^k	[0.0] ^k		
β (AA) ^d	4.85 \pm 1.76	-0.19 \pm 2.93	3.62 \pm 3.07	2.09 \pm 0.68	2.34 \pm 0.90	2.06 \pm 1.23	-0.19 \pm 0.22	-0.32 \pm 0.21
β (AB)	-1.01 \pm 0.98	-0.19 \pm 1.58	1.67 \pm 0.98	2.09 \pm 0.68	-2.03 \pm 0.87	1.44 \pm 0.82		
β (BB)	-3.74 \pm 2.50	-0.19 \pm 2.50	-2.12 \pm 1.48	-1.60 \pm 0.73	-2.03 \pm 0.87	-2.06 \pm 1.18		
δ_s^e	1.44 \pm 0.87	0.41 \pm 0.16	0.62 \pm 0.33	0.68 \pm 0.32	0.70 \pm 0.42	[0] ^l	0.41 \pm 0.16	[0] ^l
δ_m^f	0.60 \pm 0.54	0.47 \pm 0.11	0.05 \pm 0.31	0.19 \pm 0.21	0.18 \pm 0.024	[0] ^l	0.47 \pm 0.11	[0] ^l
δ_f^g	-1.11 \pm 1.15	0.06 \pm 0.12	-0.53 \pm 0.31	-0.46 \pm 0.29	-0.53 \pm 0.34	[0] ^l	0.06 \pm 0.12	[0] ^l
-2lnL ^h	1,170.40	1,196.11	1,174.92	1,175.26	1,176.40	1,187.02	1,196.11	1,221.61
Models compared		2 vs. 1	3 vs. 1	4 vs. 3	5 vs. 3	6 vs. 3	7 vs. 3	8 vs. 3
LRT ⁱ		25.71*	4.52 (NS) ^j	0.34 (NS)	1.48 (NS)	12.10*	21.29*	46.69*
df		3-4	3-4	1	1	3	3	6

[†]Coefficients of covariates including sex, smoking, environmental tobacco smoke and type of house are not presented in the table, and are -0.55 (\pm 0.26), 2.35 (\pm 0.55), 0.07 (\pm 0.23) and -1.14 (\pm 0.44), respectively, for model 5 that has the lowest AIC value.

^aFE, family effects.

^b q_A , gene frequency.

^c τ (AA), τ (AB), and τ (BB), transmission probabilities.

^d β (AA), β (AB), and β (BB), baseline parameters for types AA, AB and BB.

^e δ_s , effects of spouse.

^f δ_m , effects of mother.

^g δ_f , effects of father.

^hlnL, log likelihood.

ⁱLRT, likelihood-ratio test.

^jNS, not significant.

^kParameters are fixed and not estimated in the models.

^lThe parameter is maximized at its boundary value.

* $P < 0.01$.

fixed to zero (models 6 and 7), each model had significantly worse fits than the model including both components, suggesting that both a single locus and polygenic or environmental factors are responsible for the familial aggregation of wheeze. All covariates, except household ETS exposure, remained significant in the Mendelian models.

Table V shows the results of segregation analysis for wheeze after adjustment for history of respiratory allergy as well as other covariates. Comparisons of the environmental (model 2) and Mendelian (model 3) models with the general transmission model (model 1) indicated that both hypotheses of no-parent-offspring and Mendelian transmissions were rejected. The AIC

TABLE V. Parameter Estimates (\pm Standard Deviations) From Segregation Analysis of Wheeze After Adjustment of Covariates[†] Including History of Respiratory Allergy[‡]

	General, with FE (1)	Environmental, with FE (2)	Mendelian, with FE (3)	General, without FE (4)	FE only (5)	Sporadic (6)
q_A	0.54 \pm 0.04	0.66 \pm 0.15	0.46 \pm 0.05	0.40 \pm 0.07	[1.0] ^a	[1.0] ^a
τ (AA)	0.58 \pm 0.11	= q_A	[1.0] ^a	0.65 \pm 0.19		
τ (AB)	(1.00) ^b	= q_A	[0.5] ^a	0.78 \pm 0.08		
τ (BB)	(0.00) ^b	= q_A	[0.0] ^a	(0.00) ^b		
β (AA)	1.32 \pm 0.63	-3.13 \pm 1.21	2.98 \pm 1.27	2.81 \pm 1.39	-0.74 \pm 0.24	-0.32 \pm 0.21
β (AB)	-3.00 \pm 1.35	0.34 \pm 3.41	-2.10 \pm 1.49	-1.25 \pm 1.10		
β (BB)	-7.26 \pm 2.83	0.34 \pm 12.75	-7.35 \pm 2.85	-6.00 \pm 2.31		
δ_s	0.63 \pm 0.33	0.58 \pm 0.25	0.67 \pm 0.42	[0] ^a	0.45 \pm 0.17	[0] ^a
δ_m	1.10 \pm 0.36	0.68 \pm 0.30	-0.23 \pm 0.45	[0] ^a	0.45 \pm 0.12	[0] ^a
δ_f	-0.73 \pm 0.28	0.06 \pm 0.18	-0.98 \pm 0.53	[0] ^a	0.08 \pm 0.13	[0] ^a
ζ_{allergy}	3.44 \pm 1.04	2.38 \pm 0.93	3.91 \pm 1.11	3.50 \pm 1.19	1.60 \pm 0.16	1.60 \pm 0.16
-2lnL	1,058.86	1,087.11	1,071.56	1,174.04	1,188.39	1,110.28
Models compared		2 vs. 1	3 vs. 1	4 vs. 1	5 vs. 1	6 vs. 1
LRT		28.25*	12.70*	15.18*	29.53*	51.14*
df		— ^c	— ^c	3-4	— ^c	— ^c

[†]Covariates included sex, respiratory allergy, smoking, environmental tobacco smoke and type of house. Only the coefficient of respiratory allergy is presented in the table.

[‡]For definition of abbreviations, see Table IV.

^aParameters are fixed and not estimated in the models.

^bThe parameter is maximized at its boundary value.

^cTwo parameters in model 1 are maximized at boundary values, and the LRT follows a mixture of one-fourth a chi-square with 2 df, one-half a chi-square with 1 df, and one-fourth a chi-square with 0 df [Self and Liang, 1987].

* $P < 0.01$.

value was smaller for the Mendelian model (1095.56) as compared to the environmental model (1111.24). The other reduced models (models 4–6) that did not include familial effects (model 4), a major type (model 5) or both (model 6) were each rejected when compared with the general model.

DISCUSSION

In this analysis, we used traditional segregation models which allow for a single two-allele locus and residual nonspecific familial effects. Before adjustment for history of respiratory allergy, the transmission parameters for the 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. Residual familial effects were still significant, indicating that the major type could not explain all the familial effects on wheeze.

However, after adjustment for history of respiratory allergy, both the Mendelian and environmental hypotheses were rejected. This suggests that respiratory allergy may play an important role in the regulation of familial wheeze, and by inference, familial asthma as well. A suggested major pathogenetic mechanism of asthma is that the symptoms of asthma are caused by allergic inflammation in the airways of affected individuals [Sandford et al., 1996]. Structural and functional changes may remain and result in persistent respiratory symptoms including wheeze. The putative major gene may be related to respiratory allergy. Since allergy influences wheeze, the major gene may also have an indirect effect on wheeze. When regressing out the effect of respiratory allergy, we might also remove some of the variation due to the underlying genetic factors, which reflects the lack of Mendelian mode of inheritance after adjustment for history of respiratory allergy. Thus, this study potentially provides evidence to support the “allergic inflammation” theory that genetic predisposition to allergic reaction causes symptoms of asthma [Sandford et al., 1996].

A recent segregation analysis of physician-diagnosed asthma based on data from 906 nuclear families in Tucson, Arizona, suggested that a recessive component may influence the expression of physician-diagnosed asthma, which cannot be accounted for by serum IgE levels [Holberg et al., 1996]. Various studies have suggested a major gene control of serum IgE, an important phenotype of allergy, although all different modes of inheritance of the increased IgE levels were observed, including autosomal recessive [Gerrard et al., 1978; Marsh et al., 1981; Meyers et al., 1987, 1994], dominant [Blumenthal et al., 1981], and codominant [Martinez et al., 1994]. Since the observed major gene effect on “physician-diagnosed” asthma was independent of serum IgE in the Tucson study, it has been suggested that there is a separate major gene related to the liability of asthma [Rich, 1995]. However, the evidence of major gene effects on asthma is not totally convincing in the study by Holberg et al. [1996], since all the Mendelian models were rejected, although the recessive model fit the data better than the environmental

model. In our present segregation analysis of wheeze, after adjustment for history of respiratory allergy, the major type did not simply follow either a Mendelian or environmental fashion. More complex mechanisms may be involved with the mixture distributions.

It is a matter of speculation as to why the major gene effects, which are dependent on allergic status, were observed on wheeze in the present study, but not on physician-diagnosed asthma in the Tucson study [Holberg et al., 1996]. Asthma is a complex condition for which no universal definition has as yet been established [Rich, 1995]. Asthma has a number of phenotypic expressions including increased IgE levels and BHR, skin test responses, and symptoms (wheeze, cough, and breathlessness). Some of these are more specific than others. New phenotypes of asthma continue to be identified [Boguniewicz and Hayward, 1996]. The phenotypic expressions vary between individuals with asthma. There has likely been a trend in the medical community to equate wheeze with asthma, and to treat cases of wheeze as though they are asthma [Speight et al., 1983]. However, a recent study suggested that only a small portion of infant wheezing episodes are related to a predisposition of asthma [Martinez et al., 1995]. Wheeze with infections in early life is less likely to develop into atopy and asthma, and in our present study children under the age of 6 years were not included. Wheeze in later childhood is strongly related to atopy and BHR [Cogswell, 1992].

The putative major gene for wheeze described in the present study, which is dependent on respiratory allergy, may or may not have significant effects on physician-diagnosed asthma. It is possible that a higher apparent frequency of wheeze as compared to physician-diagnosed asthma among the general population makes the underlying gene for wheeze more detectable by the methods we use. In addition, physician-diagnosed asthma appears to be a complex phenotype, while wheeze appears to be relatively simple. It is possible that less complex mechanisms are involved in the regulation of wheeze than are involved in the regulation of physician-diagnosed asthma. If wheeze is considered as “mild” asthma, and reported physician-diagnosed asthma as “severe” asthma, less complex mechanisms may be involved in “mild” asthma than in “severe” asthma. The segregation analyses of both physician-diagnosed asthma and respiratory allergy were unsuccessful because the parameters for the transmission probabilities were frequently maximized at their boundary values and some of models did not converge. It could be interesting to determine if the Mendelian component affects reported asthma and respiratory allergy.

It is debatable whether wheeze, except that experienced in early childhood, is equivalent to “mild” asthma. If it is, we speculate that a single locus gene is responsible for the expression of “mild” asthma that is mediated by respiratory allergy, and that “mild” asthma may need a second gene or multiple loci in order to become “severe” asthma, or needs further environmental factors to result in the development of “mild” asthma into “severe” asthma. If it is a reasonable hypothesis, then further studies should be con-

ducted to determine the genetic mechanism(s) for different stages of asthma and its development.

In this study, we used class A regressive model for segregation analyses. Compared to class D regressive model, class A makes the further assumption that the sibs are correlated only because of common parentage, which may or may not be the case. An analysis of continuous traits showed that the class A model is robust with respect to the estimation of the parent-offspring correlation, in the presence of sib correlations, exceeding that explained by common parentage [Demenais and Bonney, 1989]. The restriction was related to false inference of a major gene in two out of ten replicates [Demenais and Bonney, 1989]. However, the class D regressive model has not been well developed for discrete traits [Elston, 1993]. In this analysis, there is no apparent reason to think that false inference of a major gene happened before adjustment for respiratory allergy, and disappeared thereafter.

In population-based studies, questionnaires are frequently used to identify wheeze and allergy status and are largely dependent on awareness by respondents of those conditions. Responses, therefore, can be subjective. In particular, parents' subjective definition of the presence of wheeze in themselves and their children might induce an artificial aggregation of wheeze, which is the focus of the analysis. However, there was little difference in the reporting of wheeze between father-child pairs (11%) and mother-child pairs (13%). Furthermore, previous work demonstrated agreement between parent response and children response to the question of child wheeze [Riedler et al., 1994].

Some may claim that not using an objective test to identify allergic status is a limitation of the study. However, like asthma, allergy is also a complex disorder and lacks highly specific measurements. The expression of allergy is dependent on exposure. Not all allergic individuals have positive skin test responses and elevated IgE levels. Total IgE levels vary in allergic subjects after exposure to relevant allergens and with the time of the year at which the blood sample for IgE studies is obtained [Martinez et al., 1994]. It is speculated that the variations in skin test technique and in extract potency could explain most of the variability in the reported prevalence of atopy [Frew, 1992]. It would be helpful to make a comparison based on the data from both objective measurements and self-reporting information.

In summary, this analysis suggests that wheeze is likely controlled, in part, by a major gene. Environmental factors or polygenes or both may influence familial wheeze as well. Allergy plays an important role in the major gene effect on wheeze.

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