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Evidence for Mendelian Inheritance of Serum IgE Levels in Hispanic and Non-Hispanic White Families

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Summary

Considerable evidence is available suggesting a significant genetic component in the pathogenesis of asthma, but the mechanism of inheritance is not well understood. The main objective of this study was to assess if total serum IgE level, a known intermediate phenotype for asthma, is under the control of a major autosomal gene. We studied nuclear families participating in the Tucson Children's Respiratory Study in Tucson and originally selected because they belonged to a health maintenance organization. One hundred twenty-five Hispanic and 673 non-Hispanic White nuclear families were eligible; 50 Hispanic families (with 191 subjects) and 241 non-Hispanic White families (with 886 subjects) were included. Prevalence of asthma, hay fever, and parental smoking was similar among eligible families who were included and those who were not. Segregation analyses using regressive models for continuous traits showed that the best fit to the data was given by a model of Mendelian codominant inheritance of a major autosomal gene associated with higher serum IgE level. Log-likelihood for this model was not significantly different from that of the best-fitting ("unrestricted") model ($P=.3$) and was significantly better than log-likelihood for a dominant model ($P<.0001$) and a recessive model ($P<.0001$). An environmental model showed significant departure ($P<.0001$) from the unrestricted model. Tests for genetic heterogeneity showed no significant difference between the two ethnic groups. The data strongly suggest that total serum IgE levels are controlled by a major autosomal codominant gene.

Introduction

There is considerable evidence suggesting that asthma has a strong hereditary component (Sibbald and Turner-Warwick 1979). However, the mode of inheritance of the disease has not been elucidated. Moreover, the complex nature of the asthmatic syndrome, the strong influence of environmental factors in its pathogenesis, and the existence of more than one phenotype that goes under the name of "asthma" (Morgan and Martinez 1992) make genetic studies of asthma particularly challenging. In this context, the recent report by Cookson and Hopkin (1988) of a major gene for atopy and asthma, with linkage to chromosome 11q, has been the focus of considerable interest and controversy (Marsh and Meyers 1992). Unfortunately, several independent researchers have been unable to reproduce the results of Cookson and Hopkin (Lympany et al. 1992; Marsh and Meyers 1992).

We recently showed that the prevalence of physician-diagnosed asthma after the age of 6 years was closely related to total serum IgE level in a population sample (Burrows et al. 1989). This relation was found in all age groups and was independent of the results of allergy skin-prick tests. In a subsequent report, Sears et al. (1991) confirmed these findings in a large group of children in New Zealand and observed that no asthma was reported in children with the lowest IgE levels (i.e., <32 IU/ml). These studies suggested that an IgE-mediated response may be responsible for most cases of asthma in the community. Moreover, the close correlation between the risk of having asthma and the total IgE level supports the assumption that elucidating the inheritance mechanism for total serum IgE levels as an intermediate phenotype may be an important step in understanding the genetic basis of asthma.

Although twin studies have clearly shown that total IgE production is under strong genetic control (Hanson et al. 1991), family segregation studies have yielded conflicting results as to the possible mechanism of inheritance. Previous studies have provided evidence for recessive inheritance of high levels with a very frequent "low" gene (Marsh et al. 1974; Gerrard 1978), as well as with a very rare "low" gene (Meyers et al. 1987); for codominant inheritance (Meyers et al. 1982); and for polygenic control (Hasstedt et al. 1983). The factors that could account for these conflicting reports have been extensively reviewed (Borecki et al. 1985; Meyers 1990), and both ascertainment bias and the timing of IgE measurement may be involved.

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In this study, we sought to elucidate the mechanism of inheritance of total serum IgE level in a large population sample unselected as to atopic status. For this purpose, we applied segregation analysis to total IgE levels ascertained in Hispanic and non-Hispanic White families living in Tucson.

Subjects and Methods

The families involved in this report were part of the Tucson Children's Respiratory Study, a long-term longitudinal study designed as a prospective investigation of the risk factors for asthma and other acute and chronic lower-respiratory illnesses in infancy and childhood. Detailed accounts of the study design have been published previously (Taussig et al. 1989). Over 1,200 healthy infants were enrolled at birth between May 1980 and October 1984. Healthy newborns were considered to be those who did not require oxygen for >6 h after birth, had no major congenital anomalies, and had no severe heart or systemic disease. Since all mothers had to use the services of a health maintenance organization to be eligible for enrollment, and since insurance was almost invariably provided by an employer, the great majority of the population may be considered middle class.

Parents were asked at birth to define their "ethnic group or ancestry." For the purpose of this study, families were considered to be "non-Hispanic Whites" if both parents declared that they were "White"; they were considered to be "Hispanic" if both parents responded that they were "Mexican American." Very few families of other ethnic groups were enrolled, reflecting their low numeric representation in our community, and they were thus not included in this report. A small number of families had parents of different ancestries (Hispanic and non-Hispanic White). These families were not considered in the analyses; one of the objectives of this study was to assess genetic heterogeneity across ethnic backgrounds, and there was not enough statistical power to include these families in a separate group.

Serum samples for this study were obtained when the enrolled child was ~6 years old. By this time, 493 of 673 non-Hispanic White families and 97 of 128 Hispanic families originally enrolled were still participating in the study and were living in Tucson. There were 241 non-Hispanic White families with 886 subjects and a mean of 1.7 siblings, and there were 50 Hispanic families with 191 subjects and a mean of 1.8 siblings, for which both biological parents and at least one child were available. All these families gave consent for phlebotomy and are included in this report. At the time of the study, families were not tested for nonpaternity. All efforts were made to obtain samples in all children >5 years of age; each parent and only members of the nuclear family (excluding half siblings) were included in the analyses.

Total Serum IgE Analysis

Blood samples for total serum IgE analysis were obtained throughout the year, without preference for a particular season. Serum IgE levels were assayed by paper radioimmunosorbent test (PRIST) using commercially available kits (Pharmacia Diagnostics). The calibration curve run with each batch included the following IgE concentrations: 0.1, 0.25, 0.5, 1, 2, 5, 10, 20, 30, and 40 IU/ml. A plot of log concentration versus logit fraction counts-per-minute (cpm) bound (after subtracting fraction cpm bound for diluent) was linear. All samples were assayed in duplicate and were routinely diluted 10-fold or further if necessary. The threshold for the assay was regarded as 0.1 IU/ml, because the calibration standard at this concentration always had fraction cpm values above the blank.

Statistical Methods

All analyses were performed on the log transformation of the serum IgE levels. Since these levels change significantly with age and sex (Burrows et al. 1989), lod (Z) scores were obtained for log IgE separately for each sex and ethnic group in 10-year intervals. This method was chosen because the association between IgE and age is complex and no simple function fitted the data in the age span studied (6–65 years). There was no significant difference, in Z-score values, between ethnic groups, sexes, or age groups.

Since the assumption of normality conditional on type is critical for the methods described below (Elston 1980), the IgE Z scores were simultaneously normalized using the standardized Box-Cox transform (Box and Cox 1964). The SAGE package was used for this purpose (SAGE 1992). This algorithm computes parameters λ_1 and λ_2, with the implied restriction that $\lambda_2 > -T$, where T is the smallest Z-score log IgE value. Each trait value t is replaced by

$$\frac{(t+\lambda_2)^{\lambda_1} - 1}{\lambda_1 t_{G1}^{(\lambda_1 - 1)}} \text{ if } \lambda_1 \neq 0,\ t_{G1} \ln(t+\lambda_2) \text{ if } \lambda_1 = 0\,. \quad (1)$$

where t_{G1} is the geometric mean defined as

$$t_{G1} = \left[\prod_{i=1}^{N} (t_i+\lambda_2)\right]^{1/N}, \quad (2)$$

where t_1 is the trait (Z-score log 10 IgE) value of individual i, and N the number of individuals in the data set. Results were expressed as Z scores; for this purpose, Z scores were recalculated from the means of the Box-Cox transforms obtained for the different models.

Segregation analyses were performed using the regressive models for continuous traits, developed by Bonney (1984), which have been incorporated into the SAGE computer software package (SAGE 1992). In these models, the distribution of a quantitative trait is specified by conditioning each individual's value on that of her or his pro-

genitors, without specifying a particular scheme of causal relationships. The model assumes that the trait is a linear function of the major genotype, the phenotypes and genotypes of the antecedents, and other covariates. Mendelian inheritance is presumed to be through a single autosomal locus with two alleles, called here "A" and "B," (in our case, with the putative A allele being associated with high levels of IgE). Thus, the segregation of a possible major locus is assessed by letting the mean μ of the trait depend on an underlying qualitative factor u = AA, AB, or BB. This u factor has been called "type" or "ousiotype" (Cannings et al. 1978) and is assumed to be transmissible between generations. Two individuals have the same type if and only if the expected phenotypic distribution of their offspring by a given mate are identical, and this is true for every possible type of mate (SAGE 1992). Types may thus be transmitted in both a Mendelian and non-Mendelian (environmental, cultural, etc.) manner. Genotypes are the special cases of types that transmit to the offspring in Mendelian fashion. When the offspring types are distributed independently of the parents' types (e.g., an "environmental" model), the existence of only one type of person (as defined above) can be inferred. In this situation, it is nevertheless convenient to refer to several types of persons, each with its own phenotypic distribution, determined, for example, by different environmental conditions. The model, however, allows for only one type, the corresponding phenotypic distribution being a mixture distribution.

The incorporation of types introduces two sets of parameters that can be estimated from the different models. The type frequencies are the population frequencies of the types. They are designated as ψu, for u = AA, AB, or BB, and their addition is always equal to 1. If the frequencies are in Hardy-Weinberg equilibrium proportions, they can be defined in terms of q_A, the frequency of allele A, as follows:

$$\psi_{AA} = q_A^2; \quad \psi_{AB} = 2q_A(1-q_A); \quad \psi_{BB} = (1-q_A)^2 . \quad (3)$$

The transmission parameters are the probability that a parent of type u transmits an allele A to the offspring, for u = AA, AB, or BB. For Mendelian transmission, these correspond to $\tau_{AA} = 1$, $\tau_{AB} = .5$, and $\tau_{BB} = 0$.

There are several classes of regressive models for continuous traits, depending on the assumed correlations between siblings. In this study we used class D models, which assume that correlations between siblings are equal (e.g., do not depend on the sibling's rank) but are not due to common parentage alone (Bonney 1986). Class D models applied to continuous data have been shown to yield results equivalent to those of mixed models (Demenais and Bonney 1989; Morton et al. 1991).

Modes of Transmission

In our segregation analyses we fitted one unrestricted model and eight hypothetical models to the data set. For each Mendelian and non-Mendelian model, the values of the different parameters estimated were computed by the method of maximum likelihood.

The *unrestricted model* adjusts all parameters to the empirical data for each family, without restrictions. This provides the best fit to the data and thus the "baseline" with which to compare the main hypotheses.

The first hypothesis is that *no major type* can be deduced. This means that there is only one type distribution.

The second hypothesis (*codominant*) is Mendelian inheritance of a single allele for high levels of IgE, A, but with no dominance restriction. This means that only AA individuals will have high levels of total serum IgE. For BB individuals, levels are expected to be low; and AB individuals have levels that are intermediate between AA and BB individuals. This is the more general hypothesis of Mendelian inheritance, and it includes the third and fourth hypotheses as special cases.

The third hypothesis is Mendelian inheritance of a single *dominant* allele A for high levels of IgE. This implies that AA individuals and AB individuals both have similar, high levels of IgE, while only BB individuals have lower levels of total serum IgE.

The fourth hypothesis states that a single *recessive* allele A for high levels of IgE is inherited in a Mendelian fashion. In this case, only AA individuals have high levels of IgE, whereas AB and BB individuals are expected to have similar, lower levels of IgE.

The fifth hypothesis states that serum IgE levels are attributable to random *environmental* factors that are transmitted independent of types. Thus, all three transmission probabilities are constrained to equal q_A.

Three other models were included, which test for residual familial correlations beyond major-gene segregation (ρ_S [spouse correlation], ρ_{PO} [parent offspring correlation], and ρ_{SS} [correlation between any two siblings]). These test for the presence of a polygenic component, the effect of common shared environment, or other genetically mediated factors in addition to the major gene. In the seventh model, the family correlations were added to the unrestricted model and were tested against it. In the eighth and ninth model a similar procedure was performed, but the residual family correlations were added to the Mendelian model that best fitted the data and to the environmental model, respectively.

For each model, twice the negative of the log-likelihood was computed. To assess departure from a given hypothesis, the difference, in this parameter, between the appropriate models was used. This difference has a χ^2 distribution and can be used to compare models with df determined by the difference in the number of parameters. Evidence for the presence of a major locus was considered to be present if the following three criteria were met (Go et al. 1978; Demenais et al. 1993): (*a*) the overall distribution of the data fitted a mixture of normal distributions

Table 1

Characteristics of Eligible Families Who Did or Did Not Participate in the Study

	Non-Hispanic White			Hispanics		
	Participants (241)[a]	Nonparticipants (432)[a]	*P*	Participants (50)[a]	Nonparticipants (75)[a]	*P*
At least one asthmatic parent (%)	23.2	25.0	.68	14.0	10.7	.78
At least one parent with hay fever (%)	65.1	58.8	.12	50.0	44.0	.63
Maternal smoking (%)	15.4	20.9	.10	6.0	8.0	.94
Paternal smoking (%)	31.8	27.9	.34	26.0	30.1	.76
Maternal education (% ≤12 years)	8.3	16.2	.005	28.6	52.0	.02
Mother's marital status at child's birth (% married)	98.8	96.0	.2	100.0	91.9	.2
No. of household members (mean ± SD)	4.0 ± 1.1	3.9 ± 1.1	.4	4.4 ± 1.3	4.4 ± 1.3	1.0

[a] In some cases, percentages were calculated from slightly smaller numbers of families, because of missing values for some families.

significantly better than a single normal distribution; (*b*) there was no significant departure from the Mendelian hypothesis (i.e., $\tau_{AA} = 1$; $\tau_{AB} = .5$; and $\tau_{BB} = 0$); and (*c*) there was a significant departure from the environmental hypothesis (i.e., $\tau_{AA} = \tau_{AB} = \tau_{BB} = q_A$).

To allow for comparisons between nonhierarchical models, Akaike's information criterion (AIC) (Akaike 1974) was also used to assess which model best fitted the data. This criterion is calculated by adding twice the number of parameters estimated to twice the negative of the log-likelihood of each model.

Etiologic heterogeneity between ethnic groups was assessed by fitting the most parsimonious model to the combined data set and to each ethnic group separately. A χ^2 test for heterogeneity was computed as (Khoury et al. 1993)

$$\chi^2 = 2[\ln L(\text{model} \mid \text{all data}) - \sum_{i=1}^{2} \ln L(\text{model} \mid \text{ethnic subset}_i)]. \quad (4)$$

Results

Table 1 shows a comparison of different characteristics, ascertained by questionnaire at enrollment, in families included and not included in the study. There was no difference, for either ethnic group, in parental history of asthma or hay fever, between families who were included in the study and those who were not. However, non-Hispanic White parents were much more likely to report a diagnosis of asthma than were Hispanic parents, regardless of participation status. Neither prevalence of smoking by parents nor family size differs significantly by participation status, whereas maternal education was significantly higher in families included in the study compared with those excluded from the study.

Table 2 shows the familial correlation coefficients for total IgE levels for the population under study. There was no significant spouse-spouse correlation in total IgE levels, whereas mother-offspring and father-offspring correlations were similar and reached statistical significance. There was a significant correlation in total IgE levels between siblings. Both ethnic groups showed similar trends in intrafamily correlations, although sib-sib correlation (.20±.13) did not quite reach statistical significance for Hispanic families.

There was no significant relation between total serum IgE and month during which the sample was obtained. Also, plots of the relation between sampling months and serum IgE levels did not reveal any discernible trends.

Table 3 shows the results of fitting class D regressive models to the data for the whole sample (Hispanic and non-Hispanic Whites). This segregation analysis allowed the rejection of the first hypothesis: no major type (model 1 vs. model 2 [$P<.0001$]). However, the hypothesis of Mendelian codominant inheritance of allele A could not be rejected (model 3 vs. model 2 [$P=.3$]). The hypotheses of Mendelian recessive inheritance and Mendelian dominant inheritance of allele A were rejected (model 4 vs. model 3 [$P<.0001$] and model 5 vs. 3 [$P<.0001$], respectively). The environmental hypothesis was also rejected (model 6 vs. model 2 [$P<.0001$]). The AIC confirmed that

Table 2

Correlation Coefficients ± SD for Log Total IgE, between Family Members (291 Families, 1,077 Subjects)

	ρ	*P*
Spouse-spouse	.05 ± .06	.40
Mother-offspring	.19 ± .03	<.0001
Father-offspring	.18 ± .03	<.0001
Sib-sib	.31 ± .06	<.0001

Table 3

Results of Segregation Analysis for Serum Total IgE Levels (291 Hispanic and Non-Hispanic White Families)

	Test of Major-Gene Effect						Test of Residual Family Correlations		
	No Major Type	Unrestricted	Mendelian Codominant	Mendelian Dominant of High Allele	Mendelian Recessive of High Allele	Environmental, $\tau = q_A$	Unrestricted, with Family Correlations	Mendelian Codominant, with Family Correlations	Environmental, with Family Correlations
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9
Gene frequency q_A	...	.27	.34	.28	.71	.39	.28	.33	.47
Mean IgE Z scores:									
μ_{AA}	.02	1.54	1.27	.65	.60	.25	1.46	1.16	.30
μ_{AB}	.02	.46	.39	.65	−.60	.50	.41	.41	.29
μ_{BB}	.02	−.74	−.69	−.57	−.60	−.73	−.80	−.63	−.71
Transmission probabilities:[a]									
τ_{AA}	...	[1.00]	(1.00)	(1.00)	(1.00)	.39	[1.00]	(1.00)	.47
τ_{AB}	...	.44	(.50)	(.50)	(.50)	.39	.40	(.50)	.47
τ_{BB}	...	.05	(.00)	(.00)	(.00)	.39	.13	(.00)	.47
Family correlations:									
ρ_{PO}	...	...	...	...	...	...	.19	.11	.33
ρ_{SS}	...	...	...	...	...	...	.38	.19	.39
ρ_S	...	...	...	...	...	...	.12	.10	.07
−2 ln likelihood	3,034.2	2,946.2	2,949.9	2,969.8	2,974.4	3,031.7	2,937.2	2,944.9	2,949.1
AIC	3,042.2	2,968.2	2,963.9	2,981.8	2,986.4	3,045.7	2,965.2	2,964.9	2,969.1
Models compared	1 vs. 2	...	3 vs. 2	4 vs. 3	5 vs. 3	6 vs. 2	7 vs. 2	8 vs. 3	9 vs. 7
χ^2	88.0****	...	3.7*	19.9****	24.5****	85.5****	9.0**	5.0*	11.9***
df	6–7	...	3–4	1	1	3–4	3	3	3–4

[a] Values in square brackets are fixed by the maximum-likelihood algorithm; and values in parentheses are fixed by the model.

* $P = .3$.

** $P < .05$.

*** $P < .025$.

**** $P < .0001$.

the codominant-inheritance model fitted better than all other major-gene models; AIC was smaller for this model than for all the other models tested, including the unrestricted model. The estimated gene frequency (±SD) for allele A was .34 ± .06, with mean IgE Z scores of 1.54, 0.46, and −0.74 for AA, AB, and BB individuals, respectively. These mean IgE Z scores correspond to the following geometric means for total IgE (in IU/ml): for boys <10 years (mean ± SD age 6.7±1.2)—776.3, 102.3, and 10.5 for AA, AB, and BB individuals, respectively; for girls <10 years (mean ± SD age 6.8±1.4)—524.8, 87.1, and 11.5 for AA, AB, and BB individuals, respectively.

Table 3 also shows the tests for the hypotheses of residual family correlations. Adding these correlations to the unrestricted model was associated with a change in log-likelihood that reached statistical significance (model 7 vs. model 2 [$P<.05$]). However, the hypothesis that no residual family correlations exist beyond the major-gene inheritance pattern that best fitted the data (e.g., Mendelian codominant) could not be definitely rejected (model 8 vs. model 3). The AIC under the codominant-inheritance hypothesis with family correlations was very similar to that under the codominant-inheritance hypothesis without family correlations, suggesting that both models fitted the data equally well. An environmental model with family correlations had a higher AIC than did the Mendelian codominant model with family correlations. This environmental model fitted the data significantly worse ($P<.05$) than did the most general model with family correlations.

Tables 4 and 5 show the same type of segregation analysis for the data of non-Hispanic White and Hispanic families, respectively. Results for both ethnic groups were consistently similar to those obtained for the sample as a whole: the overall distribution of the data fitted a mixture of normal distributions significantly better than did a single normal distribution, and thus the hypothesis of no major type was rejected; the hypothesis of Mendelian codominant inheritance of allele A could not be rejected for either ethnic group, whereas the hypotheses of Mendelian dominant inheritance and Mendelian recessive inheritance of allele A were both rejected; the environmental hypothesis was also rejected. The gene frequency for allele A among Hispanic families (.21±.10) was lower than that for allele A among non-Hispanic White families (.37±.06).

Tests for residual family correlations among Hispanic and non-Hispanic White families also yielded results very similar to those reported for the sample as a whole (tables 4 and 5, last two rows). Addition of covariates for both active smoking by parents and environmental tobacco-smoke exposure by family members (as assessed by the presence of a smoker in the household) had no significant effect on any of the reported results. A test for genetic heterogeneity across ethnic groups showed no significant difference in pattern of genetic inheritance: χ^2 for heterogeneity was 2.7 with 11 df ($P=.9$).

Discussion

In this report, further evidence is provided that supports the hypothesis first proposed by Marsh et al. (1974) and later corroborated by Gerrard et al. (1978)—i.e., that a major autosomal gene controls total serum IgE levels. This finding is particularly important in view of the recent reports of a linear relation between risk of developing asthma and total serum IgE levels in a large population sample (Burrows et al. 1989). If, as suggested in the latter study, virtually all cases of asthma are associated with some type of IgE-related reaction, a better understanding of the genetic mechanisms that control total IgE production may significantly contribute to defining the genetic basis of asthma. It has been shown that segregation analysis based on the methods used in this study does not lead to the false assertion of a major locus caused by the presence of polygenic heritability or by environmentally caused skewness or platykurtosis (Go et al. 1978; Demenais et al. 1993). These models are also apparently resistant to spurious associations (McGuffin and Huckle 1990), particularly when the three criteria described in Subjects and Methods are met. However, cultural inheritance and other environmental causes of familial correlation may mimic Mendelian transmission, and therefore no amount of statistical analysis can prove the existence of a major locus (Elston 1980). In this context, it is important to consider that remarkably similar patterns of inheritance and gene frequencies were found for non-Hispanic Whites and Hispanics, and there was no statistically significant genetic heterogeneity by ancestry. The concordance of the results of analyses performed in two ethnic groups that can be legitimately presumed to differ significantly in their environmental background strongly suggests that the associations observed in this study are not attributable to spurious nongenetic factors.

Although the results of this study confirm the presence of a major autosomal locus controlling for total serum IgE levels, the most likely mode of inheritance observed (e.g., autosomal codominant) differs from that described in the studies of Marsh et al. (1974) and Gerrard et al. (1978) (e.g., autosomal recessive inheritance of "high" levels). Moreover, other studies with a smaller number of nuclear families (Meyers et al. 1982, 1987, 1991) or in which a few large pedigrees were assessed (Blumenthal et al. 1981; Hasstedt et al. 1983) yielded contradictory results. Several possible explanations for these discrepancies have been recently explored (Meyers 1990). Genetic heterogeneity (i.e., the association of the same phenotype with the inheritance of different genetic determinants) has been postulated on the basis of a study of three large pedigrees selected because several members in each pedigree were allergic to ragweed (Blumenthal et al. 1981). It has been argued, however, that a selection process based on atopic subjects may give rise to ascertainment bias (Meyers 1990). It is also pos-

Table 4

Results of Segregation Analysis for Serum Total IgE Levels (241 Non-Hispanic White Families)

	Test of Major-Gene Effect						Test of Residual Family Correlations		
	No Major Type	Unrestricted	Mendelian Codominant	Mendelian Dominant of High Allele	Mendelian Recessive of High Allele	Environmental, $\tau = q_A$	Unrestricted, with Family Correlations	Mendelian Codominant, with Family Correlations	Environmental, with Family Correlations
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9
Gene frequency q_A	...	.27	.37	.29	.71	.37	.28	.35	.46
Mean IgE Z scores:									
μ_{AA}	.02	1.49	1.19	.63	.62	.34	1.37	1.15	.31
μ_{AB}	.02	.46	.34	.63	−.60	.53	.41	.38	.30
μ_{BB}	.02	−.74	−.76	−.60	−.60	−.71	−.81	−.71	−.71
Transmission probabilities:[a]									
τ_{AA}	...	[1.00]	(1.00)	(1.00)	(1.00)	.37	[1.00]	(1.00)	.46
τ_{AB}	...	.48	(.50)	(.50)	(.50)	.37	.43	(.50)	.46
τ_{BB}	...	[.00]	(.00)	(.00)	(.00)	.37	.09	(.00)	.46
Family correlations:									
ρ_{PO}	...	...	...	...	...	...	.16	.08	.34
ρ_{SS}	...	...	...	...	...	...	.41	.23	.42
ρ_S	...	...	...	...	...	...	.18	.15	.11
−2 ln likelihood	2,500.7	2,426.3	2,428.4	2,445.7	2,449.2	2,498.2	2,418.0	2,422.9	2,428.1
AIC	2,508.7	2,448.3	2,442.4	2,457.7	2,461.2	2,512.2	2,446.0	2,442.9	2,448.1
Models compared	1 vs. 2	...	3 vs. 2	4 vs. 3	5 vs. 3	6 vs. 2	7 vs. 2	8 vs. 3	9 vs. 7
χ^2	74.4****	...	2.1*	19.4****	20.8****	71.9****	8.3***	5.5*****	10.1**
df	6–7	...	2–4	1	1	2–4	2–3	3	3–4

[a] Values in square brackets are fixed by the maximum-likelihood algorithm; and values in parentheses are fixed by the model.

* $P = .5$.

** $P < .05$.

*** $P < .025$.

**** $P < .001$.

***** $P > .10$.

Table 5

Results of Segregation Analysis for Serum Total IgE Levels (50 Hispanic Families)

	Test of Major-Gene Effect						Test of Residual Family Correlations		
	No Major Type	Unrestricted	Mendelian Codominant	Mendelian Dominant of High Allele	Mendelian Recessive of High Allele	Environmental, $\tau = q_A$	Unrestricted, with Family Correlations	Mendelian Codominant, with Family Correlations	Environmental, with Family Correlations
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9
Gene frequency q_A	...	.30	.21	.39	.78	.81	.07	.11	.33
Mean IgE Z scores:									
μ_{AA}	.02	1.60	1.79	.45	.45	−.01	.03	1.96	.52
μ_{AB}	.02	.38	.66	.45	−.70	.06	.99	.94	.52
μ_{BB}	.02	−.48	−.40	−.79	−.70	−2.32	−.16	−.30	−.60
Transmission probabilities:[a]									
τ_{AA}	...	[1.00]	(1.00)	(1.00)	(1.00)	.81	[1.00]	(1.00)	.33
τ_{AB}	...	.33	(.50)	(.50)	(.50)	.81	.20	(.50)	.33
τ_{BB}	...	.22	(.00)	(.00)	(.00)	.81	.50	(.00)	.33
Family correlations:									
ρ_{PO}	...	...	...	...	...	...	.15	.16	.37
ρ_{SS}	...	...	...	...	...	...	.01	.03	.30
ρ_S	...	...	...	...	...	...	−.09	−.04	−.19
−2 ln likelihood	533.3	514.0	518.9	524.5	524.7	527.4	516.8	516.5	517.4
AIC	541.3	536.0	532.9	536.5	536.7	541.4	544.8	536.5	537.4
Models compared	1 vs. 2	...	3 vs. 2	4 vs. 3	5 vs. 3	6 vs. 2	7 vs. 2	8 vs. 3	9 vs. 7
χ^2	19.4***	...	4.9*	5.6**	5.8**	13.4***	2.8*	2.5*	.6*
df	6–7	...	3–4	1	1	3–4	3	3	3–4

[a] Values in square brackets are fixed by the maximum-likelihood algorithm; and values in parentheses are fixed by the model.

* $P = .25$.

** $P < .025$.

*** $P < .01$.

sible that the results obtained on a few pedigrees may not be applicable to the general population.

The possibility has also been raised that the time of the year at which the blood sample for IgE studies is obtained may affect the results of segregation analyses (Borecki et al. 1985). It is known that total IgE levels can significantly vary in allergic subjects after exposure to relevant allergens. It thus has been proposed that different studies may be assessing "basal levels" or "nonbasal levels" of total serum IgE and that this may explain the discrepancies observed. For the Canadian study by Gerrard et al. (1978), for example, samples were obtained during the summer months (Borecki et al. 1985), and it is reasonable to surmise that exposure to aeroallergens (or lack thereof) during that time of the year may have influenced these results.

In this study, blood samples for IgE measurements were obtained throughout the year. Our group has previously shown that, in Tucson, seasonal groupings of pollen types exist that essentially span the entire year, because of the city's mild climate and situation in the arid Southwest of the United States (Holberg et al. 1987). A strategy to obtain blood samples at other than allergen seasons would thus have been logistically very arduous. Interestingly, only the study of 23 Amish nuclear families by Meyers et al. (1982) used a sampling strategy similar to ours. In agreement with the findings reported herein, the best fit to the Amish data was given by a codominant mode of inheritance, but the .70 frequency for the "high" allele was higher than the frequency for the "high" allele in our study. The Amish are a highly inbred population and geometric reported mean IgE levels in both males and females were significantly higher than those of other family studies (Meyers et al. 1982). It is thus possible that the "high" allele may be particularly frequent among the Amish.

To try to solve the problems associated with the random noise added, to IgE determinations, by the time of the year at which the blood samples were obtained, Meyers et al. (1987) studied 42 large (at least four siblings) nuclear families at the time when the total IgE levels should have been at their basal levels. An unexpected, high spouse-spouse correlation was observed, suggesting some form of selection bias. Results of the segregation analyses supported the existence of a major gene determining IgE levels, with recessive inheritance of "high" levels, but the frequency of the "low" allele was extremely low (.03). The authors suggested that this may be a third, rare "ultralow" allele in the same locus as the more common "high" and "low" alleles. In agreement with this argument, it has been suggested (Borecki et al. 1985) that the more common alleles present in the putative regulatory locus may only be expressed in response to some form of immunologic challenge (see below).

Meyers et al. (1991) tried to correct for allergic status by introducing allergy skin test as a covariate in their models. However, bivariate analyses by Borecki et al. (1985) have shown that the single major locus regulating IgE levels influences the distribution of liability to develop allergies. In this context, it is methodologically difficult to predict the consequences of adjusting a "dependent" variable (total serum IgE) for another variable (allergy skin tests) that is purported to be biologically determined (at least in part) by the dependent variable.

The bivariate analysis by Borecki et al. (1985) may also help clarify the mode of inheritance of total IgE levels. These authors used the Canadian data set described earlier and first studied by Gerrard et al. (1978), in which a recessive inheritance of "high" levels with a polygenic component was the genetic model that best fitted the data. Interestingly, when these authors studied the impact of the common major gene on the risk of becoming affected by certain groups of allergic conditions (e.g, asthma, eczema, and hay fever, among others), they observed that the codominant model provided the best fit to the data. When all available information concerning various clinical allergic syndromes was included, they found that dominant inheritance best explained their data. Borecki et al. (1985, p. 337) concluded that, although heterozygous individuals "have a normal value of IgE, they are qualitatively different from RR [homozygous for "low" levels in the Marsh et al. 1974 nomenclature] individuals, exhibiting a higher level of hypersensitivity to at least some allergens."

A possible explanation for the discrepancies between our results and those of Borecki et al. (1985) has been provided by Freidhoff et al. (1987). These authors observed that the absolute changes in total serum IgE levels during the grass-pollination season was weakly and negatively correlated with the basal value in a group of ryegrass-sensitive subjects. Although the results may have been influenced by regression toward the mean, they suggest that, as a proportion of their basal values, subjects with lower basal levels show higher responses to allergen challenge than do subjects with higher basal levels. It is thus possible that heterozygous Rr individuals may be more prone to respond with increases in serum IgE levels when exposed to relevant allergens than are either rr individuals (who would have persistently high levels of IgE) or RR individuals (who would have the lowest risk of becoming allergic and, thus, of responding with increases in serum IgE levels to allergen challenges). The proportion of Rr subjects exposed to relevant allergens shortly before bleeds in the different population samples would determine if a codominant model (as in our study and in the study by Meyer et al. [1982] among the Amish) or a recessive high-level model (as in the studies by Marsh et al. [1974] and Gerrard et al. [1978]) best fitted the data. On the other hand, the prevalence of an allergic condition is by definition a retrospective ascertainment of symptoms during long periods of time, and its association with the putative major gene should be less liable to the seasonal influences described above.

Results of this study do not allow us to assign the func-

tion of the major gene apparently identified to a known step in the complex control mechanism for IgE production (Leung 1993). We doubt that this putative gene corresponds to the structural gene for IgE, because this immunoglobulin does not have known alleles that would be variably assessed in the IgE assay. Different subclasses of T-helper lymphocytes are known to produce cytokines that either enhance (TH2) or hinder (TH1) the production of IgE by B cells (Romagnani 1992). Interleukin-4 (IL-4) produced by TH2 cells delivers the first signal needed to induce Ig class switching to the ε locus in the B cell. A second signal can be delivered by any of a number of B-cell activators and suppressors, which, in combination with IL-4, induce or block the expression of ε mRNA transcripts and the synthesis of IgE (Leung 1993). The genes encoding these signaling substances may be good starting points for linkage studies involving the major gene suggested in this and other similar studies of the genetics of total serum IgE.

In summary, segregation analysis of total IgE in a large population sample provides strong support for the hypothesis first proposed by Marsh et al. (1974)—i.e., that these levels are controlled by a major autosomal locus. Ascertainment bias, selection bias, and the time of the year during which blood samples were obtained may explain the reported discrepancies in gene frequency and inheritance mechanism of total serum IgE levels. Genetic linkage analyses are needed to confirm the existence of the putative major-gene locus described in this study.

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