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Inheritance of Total Serum IgE (Basal Levels) in Man[1]

DEBORAH A. MEYERS,* TERRI H. BEATY,† LINDA R. FREIDHOFF,* AND DAVID G. MARSH*

*Division of Clinical Immunology, Department of Medicine, The Johns Hopkins University School of Medicine at the Good Samaritan Hospital; and †Department of Epidemiology, School of Hygiene, The Johns Hopkins University, Baltimore, MD

SUMMARY

Since allergic individuals with atopic allergy tend to have higher total serum IgE levels than do nonallergic subjects, family studies of total serum IgE levels are necessary in delineating the genetic and environmental factors involved in the expression of allergic disease. However, previous studies do not agree as to the genetic basis of total IgE production. To try to resolve this conflict, a total of 278 individuals from 42 nuclear families ascertained for large family size (at least four children) were studied. The families were not selected for the presence of allergic disease. Segregation analysis showed that the mixed model of recessive inheritance of high levels was most appropriate for these data—with ~36% of the total phenotypic variation in log[IgE] attributable to genetic factors, equally divided between a Mendelian component and a more general polygenic component. Thus, these data suggest some role for Mendelian control of basal IgE levels, but there is significant familial aggregation in IgE levels over and above that due to a Mendelian factor.

INTRODUCTION

The importance of a positive family history of atopic allergy is recognized by the practicing allergist in the evaluation of a patient with IgE-mediated aller-

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Address for correspondence and reprints: Dr. Deborah A. Meyers, Division of Clinical Immunology, Department of Medicine, The Johns Hopkins University School of Medicine at the Good Samaritan Hospital, 5601 Loch Raven Boulevard, Baltimore, MD 21239.

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gies. However, well-designed family studies are needed to elucidate the genetic and environmental factors involved in the expression of allergic disease. Since allergic individuals tend to have higher total serum IgE levels than do nonallergic subjects, there have been several family studies of total serum IgE levels (Marsh et al. 1974; Gerrard et al. 1978; Blumenthal et al. 1981; Meyers et al. 1982; Hasstedt et al. 1983). Unfortunately, these studies do not agree as to the genetic basis of total IgE production. To try to resolve this conflict, we have studied a total of 278 individuals from 42 nuclear families (both parents and all available children). The families were not selected for the presence of allergic disease and were drawn from our ongoing study of employees of Westinghouse Electric Corporation in the Baltimore area (Freidhoff et al. 1981).

The first evidence for a genetic basis for total serum IgE levels in man came from the study of Marsh et al. (1974), in which was found evidence for recessive inheritance of "high" total IgE levels. Gerrard et al. (1978) also found evidence for recessive inheritance of "high" levels with a significant polygenic component. However, Blumenthal et al. (1981) found overall evidence for dominant inheritance of "high" levels but raised the possibility of genetic heterogeneity among pedigrees. In addition, in our study of Amish families (Meyers et al. 1982), the codominant mode of inheritance gave the best fit to the data, whereas in our study of Mormon pedigrees (Hasstedt et al. 1983), a more general polygenic model best fitted the data. Our current study of randomly ascertained families was designed to try to resolve these differences.

METHODS

Families

A total of 278 individuals (both parents and all available children) in 42 nuclear families were studied. Each family was selected for the study through a parent who worked at the Westinghouse Electric Corporation and who had previously completed our original questionnaire sent to a total of 2,097 employees (Freidhoff et al. 1981). All probands had stated that they had four or more children >6 years of age by one spouse and that the whole family would be available for sampling. Therefore, families were not ascertained through the presence of allergic disease but were selected for large family size. Each family was visited during February–mid-May when blood samples were drawn for determination of total IgE levels and typing of HLA and other blood groups and when skin testing by means of the puncture method was performed. In most cases, a second blood sample was drawn at a random time during the year to complete the HLA and other blood-group typings and to obtain a second determination of serum IgE levels.

There were a total of 11 family members from whom it was not possible to obtain a blood sample during the time of the year when IgE levels are believed to be at their lowest (basal) levels (February–mid-May for the Baltimore area). Four of these were the two parents and the only two available children in one family who were all sampled in mid-November. The remaining seven subjects were children from six different families. Four of these seven were skin-test

negative to seasonal allergens, and the remaining three (who were sampled in June and August) were skin-test positive to rye grass and/or ragweed.

It should be noted that, as has been reported previously (Meyers et al. 1986), all family members were skin tested with the following crude antigens: short ragweed, rye grass, mixed tree and mixed weed pollens, cat and dog danders, *Alternaria*, mixed molds, house dust, and house dust mite plus histamine and diluent controls. None of the family members were receiving immunotherapy for allergies. Also, none of the subjects were on steroids, a substance that can affect IgE levels.

Total IgE Determinations

Total serum IgE levels were measured by means of a modification of the direct RIST radioimmunoassay (Schellenberg and Adkinson 1975), in duplicate, in at least two separate assays. An assay was repeated if the coefficient of variation was $> \pm 10\%$ either within or between assays. IgE values were computed in nanograms per milliliter (1 IU = 2.42 ng/ml), by means of a standard serum of known content that had been standardized against the World Health Organization reference.

Statistical Analyses

The data were stored and analyzed on The Johns Hopkins University's VAX 730. Log transformation of the total IgE data was performed to reduce skewness. Furthermore, for biological reasons (the logarithmic increase in cell number resulting from cell division), logarithmic transformation is appropriate. The distribution of log[IgE] in the total sample was not significantly different from a normal distribution. Regression analyses were performed to determine differences in total IgE levels due to age. If appropriate, data were then age and sex adjusted before family analyses were performed (Meyers et al. 1986).

As a measure of the potential degree of genetic control, the observed phenotypic variation in log[IgE] was partitioned into components attributable to (1) additive genetic differences among family members, (2) shared environments among sibs, and (3) shared environment between spouses. Maximum-likelihood estimates of these components were obtained by means of Fisher's scoring algorithm under the assumption of multivariate normality (Lange et al. 1976), although the robust approach described by Beaty et al. (1985) was also used. Because all of the 42 families were nuclear families, it was difficult to discriminate between arbitrary nongenetic and true genetic sources of covariance among relatives, since shared environments will mimic shared genes and vice versa. However, if a genetic model explained a larger proportion of the total variation in log[IgE] or gave a greater improvement in the likelihood of the model, we felt justified in testing more specific genetic models by means of segregation analysis.

Segregation analysis was performed using the method of maximum likelihood and the pedigree analysis package (PAP; Hasstedt and Cartwright 1981) on a VAX 730. Mendelian, polygenic, and sporadic models were fitted to the data. The mixed model (major gene plus polygenic inheritance) was also fitted to the

data, by means of the approximation for pedigree analysis developed by Hasstedt (1982). The parameters for the models are (1) p—the gene frequency for the "low" allele; (2) μ_1, μ_2, and μ_3—the means for the three distributions for the three genotypes with a common variance, σ^2; (3) σ—the common SD for the three genotypic distributions; and (4) H_p—the portion of residual variation about genotypic means attributable to polygenic factors (σ^2_g). The conventional heritability (H) can be calculated from this value as $H_p [\sigma^2_g/(\sigma^2 + \sigma^2_{mg})]$, where σ^2_{mg} is the variance due to the major gene (Hasstedt 1982).

RESULTS

Data from 42 nuclear families (both parents and all available children) comprising a total of 278 individuals were analyzed. The mean ± SD number of children per family was 4.62 ± 1.19 (mean ± SD age of parents = 48.76 ± 5.49 years; mean ± SD age of children = 19.65 ± 6.50 years). The results of the studies on HLA typing, blood group markers, and red cell enzymes in these families will be reported elsewhere. However, it should be noted that data on one child were deleted from all analyses because of nonpaternity, as detected by the HLA typing.

The distribution of log[IgE] levels was not significantly different from a normal distribution (fig. 1). Males had a significantly higher mean log[IgE] than did females (by *t*-test, $P < .05$; table 1). There was no significant difference between the sexes for log[IgE] levels in the smaller number of skin test–positive subjects (table 1). As expected (Marsh et al. 1981; Freidhoff 1987), there was a higher proportion of skin test–positive males than skin test–positive females (42% vs. 27%, respectively). The mean ± SD ages for males (28.3 ± 14.8 years) and females (28.6 ± 15.0 years) were very similar. No significant relationships were found between total log[IgE] levels and age, except in skin test–positive females ($r = -.44$; $P \leq .01$; $N = 34$). Dividing the total sample by sex for the age groups <20 and >20 did not reveal any further significant age-associated differences in log[IgE] levels.

For the purposes of the genetic analyses, the following decisions were made in regard to age and sex adjustment of log[IgE] levels on the basis of our results (Freidhoff et al. 1983) and other results in the literature (Barbee et al. 1981; Freidhoff 1987): Female log[IgE] values were adjusted to male values using a factor of 1.1. For adult males and adult females (age ≥20 years), log[IgE] values were adjusted to those at age 20 years (using a slope of −0.01/year). Since previous studies have not demonstrated an age effect in children beyond the age of 7 years (Gerrard et al. 1974; Barbee et al. 1981; Freidhoff 1987), no age adjustments were made for children and young adults of either sex (age range of 7–20 years). Significant differences in total IgE levels between smokers and nonsmokers have been reported (Warren et al. 1982), although we have not been able to confirm these findings (Freidhoff et al. 1986). Smoking was not considered to be a factor in any of the analyses, since there were few smokers in the present study and there were no significant differences in mean log[IgE] levels between smokers and nonsmokers in either males or females (Meyers et al. 1986).

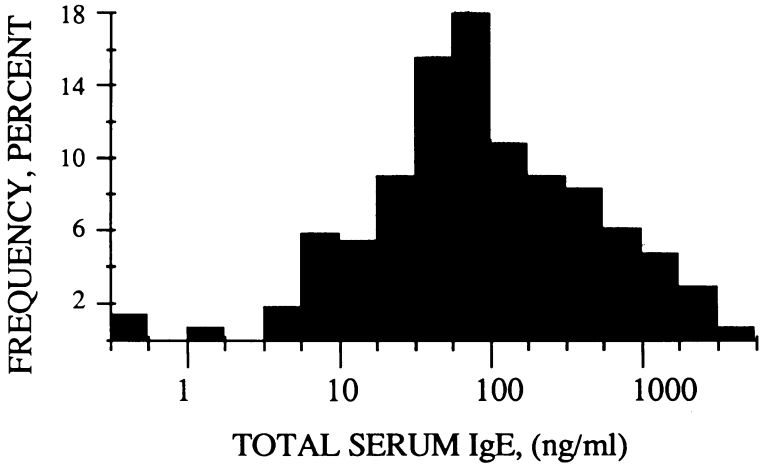

FIG. 1.—Distribution of log[IgE] in the family members

Variance-Component Analysis

Table 2 shows the results of partitioning the observed variance in log[IgE] into components attributable to additive genetic factors, unobserved environmental factors shared among sibs, and unobserved environmental factors shared between parents. As seen in the table, when considered alone, additive genetic factors accounted for 30.7% of the variation in log[IgE] levels. The hypothesis that this genetic component is zero was rejected on the basis of both the conventional likelihood-ratio test ($\chi^2 = 18.36$ with 1 df, $P < .001$) and the robust score test proposed by Beaty et al. (1985) (4.41, $P < .001$). When the sib component was considered along with the additive genetic component, there was little further improvement in the log likelihood, and therefore the hypothesis that $\sigma^2_{sib} = 0.0$ cannot be rejected. It should be noted that the SEs given in the table for each estimator are robust to the assumption of multivariate normality within these families. Interestingly, there was a significant correlation between spouses in these families, which was reflected in the σ^2_{PP}

TABLE 1

MEAN VALUES FOR TOTAL IgE LEVELS

Sample (*N*)	Basal Log[IgE]	Geometric Mean IgE (ng/ml)
Males (150)	2.02 ± 0.74[a]	104.7
Skin-test positive (63)	2.53 ± 0.61	338.8
Females (128)	1.84 ± 0.72[a]	69.2
Skin-test positive (34)	2.29 ± 0.77	195.0
Total (278)	1.94 ± 0.74	87.1
Skin-test positive (97)	2.44 ± 0.67	275.4

[a] A significant difference ($P < .05$) in log[IgE] levels was seen between males and females.

TABLE 2

RESULTS FROM VARIANCE-COMPONENT ANALYSES OF log[IgE] IN 42 NUCLEAR FAMILIES

MODEL	NO. OF COMPONENTS	RELATIVE LOG LIKELIHOOD	MAXIMUM-LIKELIHOOD ESTIMATES OF COMPONENTS OF VARIANCE[a]			
			σ^2_A	σ^2_{sib}	σ^2_{PP}	σ^2_R
Residual	1	0.0				61.92 ± 8.18
Additive genetic	2	9.13	18.70 ± 7.43			42.12 ± 8.22
Sibship environment	2	5.97		13.53 ± 4.02		48.69 ± 8.07
Parent environment	2	4.01			25.25 ± 6.35	41.07 ± 8.39
Genetic and sibship	3	9.34	17.59 ± 8.51	3.03 ± 4.05		40.63 ± 8.36
Genetic and parents	3	13.13	24.32 ± 7.45		24.77 ± 10.51	12.60 ± 11.58
Parents and sibship	3	9.38		12.75 ± 3.81	24.45 ± 11.01	24.80 ± 9.38

[a] A = Additive; sib = sibs; PP = parent-parent; and R = random environment.

component in table 2. This component was significant even in the presence of the additive genetic component ($\chi^2 = 8.00$ with 1 df, $P < .001$; robust score test, 3.01, $P < .001$). The biological significance of this correlation between parents that is seen in these randomly associated families is difficult to determine. A nongenetic model with both factors shared between spouses and a sibship component gave little improvement in the log likelihood compared with the single-component genetic model.

Segregation Analysis

Since the variance-component analyses suggested a significant role for genetic factors in IgE production, segregation analysis was performed. Specific genetic models were examined to test for Mendelian inheritance of total IgE levels versus a more general polygenic model of inheritance. The parameter estimates for each model fitted to the data are shown in table 3. Differences in the estimated phenotypic variance (σ^2) of the sporadic model in table 3 and σ^2_R in the residual model in table 2 simply reflect the different scaling factors used in the two analyses. For the recessive and dominant major gene models, the estimates of the parameters were essentially mirror images of one another; therefore, only the estimates for the major gene model for dominant inheritance of high levels are given here.

Tests of hypotheses about the relative importance of Mendelian genes versus polygenic factors can be obtained by comparing the relative ln likelihoods shown in table 3. For example, to test the significance of the polygenic component, an approximate χ^2-statistic of 13.32 with 1 df is computed by taking twice the difference in the relative ln likelihood of the mixed model (recessive inheritance of high levels) and the Mendelian model. Thus, the hypotheses of no polygenic component is rejected for these families. Similarly, the hypotheses of no Mendelian component is also rejected ($\chi^2 = 2(13.51–9.17) = 8.68$ with 2 df, $P = .01$).

The likelihood of the codominant mixed model shown in table 3 maximized at a lower bound for μ_1, thereby invalidating similar tests of Mendelian versus polygenic inheritance. However, we would point out that, compared with the mixed model, the addition of a third genotypic mean did not produce a great improvement in the log likelihood (13.51 vs. 14.94, respectively). A dominant mixed model was also examined, but it too maximized at a boundary, thereby making valid comparisons impossible.

Under the mixed model of recessive inheritance of high levels, which was the best-fitting model for these data, 36.7% of the variation in log[IgE] could be attributed to genetic factors. Approximately half of this amount (18% of the total phenotypic variation) is due to differences in the genotypes at a major locus, and half is attributable to more general polygenic variation among individuals.

DISCUSSION

This study of the inheritance of total IgE levels was performed for two reasons. First, total log[IgE] levels represent an objective measurement that is

TABLE 3

RESULTS OF SEGREGATION ANALYSES IN 42 NUCLEAR FAMILIES

Model	p	μ_1	μ_2	μ_3	σ^2	H_p	Relative ln Likelihood[a]
Sporadic		1.91 ± .05	= μ_1	= μ_1	0.619 ± .003	...	0.0
Polygenic	...	1.90 ± .06	= μ_1	= μ_1	0.608 ± .002	0.31 ± .09	9.17
Dominant	0.79 ± .09	1.61 ± .11	2.39 ± .15	= μ_2	0.474 ± .003	...	6.85
Codominant	0.81 ± .08	2.15 ± .09	1.59 ± .16	0.26 ± .55	0.458 ± .003	...	8.99
Mixed (high recessive)	0.97 ± .02	1.99 ± .06	0.50 ± .68	= μ_2	0.482 ± .002	0.23 ± .09	13.51
Codominant mixed[b]	0.017 ± .012	0.004 ± .309	0.005 ± .394	1.96 ± .58	0.512 ± .002	0.254 ± .091	14.94

[a] Difference in the ln likelihoods between the model given and the sporadic model.
[b] Boundary problems.

correlated with the presence of clinical allergic disease. Although not all subjects with high total IgE levels are clinically allergic, understanding the genetic and environmental factors involved in the expression of this trait would serve as a foundation for genetic studies of allergy. Second, previous family studies on the inheritance of total serum IgE levels have given conflicting results (Marsh et al. 1974; Gerrard et al. 1978; Blumenthal et al. 1981; Meyers et al. 1982; Hasstedt et al. 1983). The current study was designed to resolve these conflicts by studying randomly ascertained nuclear families selected for large family size (four or more children) (Meyers and Marsh 1981). Also, since allergic subjects have significant increases in their total IgE levels following exposure to a relevant antigen, family members were not sampled during the pollen seasons, to ensure that total IgE levels were most likely to be at their basal levels. Although important differences still exist, we feel that our results do help to resolve the conflict. Additional evidence for recessive inheritance of "high" levels with a significant polygenic component (as first postulated by Marsh et al. [1974] and Gerrard et al. [1978]) was obtained. However, a small gene frequency (.03) for the "low" allele was seen, suggesting that this gene may be present only in a small number of families.

There were two interesting results of the variance-component analysis (table 2). The first was that additive genetic factors accounted for 30.7% of the variation in log[IgE] levels, a finding that allowed us to reject the null hypothesis that this genetic component is zero. The second and unexpected finding was the significant correlation in log[IgE] levels between the parents. It is difficult to determine which factors may have caused this correlation. In trying to ascertain a random sample of individuals or families, the problem always occurs that subjects with the trait in question may be more willing to participate in the study. If the family were more likely to participate because both parents were allergic, this may explain the significant correlation in total IgE levels. However, this possibility is improbable, since the parents did not show a significant correlation in degree of skin-test positivity and the families did not have a larger proportion of skin test–positive subjects than that seen in the general population (Meyers et al. 1986). Questionnaire data on exposure to relevant allergens were collected, but it is very difficult to quantify exposure on the basis of such data. Preliminary analysis of this data showed no correlations with total IgE levels. If the parent-parent correlation is due to the sharing of a similar environment (i.e., similar exposure to allergens), it will be very difficult to show this on the basis of the crude level of exposure that can be calculated from questionnaire data.

Since, as expected, the variance-component analysis showed a significant genetic component in IgE level (implying genetic determination of IgE production), segregation analysis was performed. Although evidence for recessive inheritance of "high" levels with a significant polygenic component was found, important differences between our results and those from previous studies still exist.

The study by Marsh et al. (1974) provided the first evidence that basal serum IgE levels in man are inherited. A complex segregation analysis was not done;

but, by postulating a cut-point between "low" and "high" IgE phenotypes, these authors classified families into different mating types and found that a recessive model of inheritance of "high" levels fit the data. Indeed, the next study on total IgE levels (Gerrard et al. 1978) seemed to confirm the results of the original study. Gerrard et al. (1978) analyzed total IgE levels by means of both path analysis and segregation analysis in 173 small nuclear families. In the segregation analysis, the mixed model with recessive inheritance of "high" levels with a significant polygenic component gave the best fit to the data. A high gene frequency of .50 was obtained, which is similar to that of the previous study (Marsh et al. 1974) but very different from the "high"-allele frequency of .97 seen in the present study.

The third family study of total serum IgE levels was the first study of large pedigrees rather than of nuclear families. Blumenthal et al. (1981) analyzed data from three large pedigrees; but the same model did not give the best fit for each pedigree, thus suggesting possible genetic heterogeneity. Using a mixed model, these authors found no evidence for a significant polygenic component. Their estimate of heritability (49.5%) was similar to that of Gerrard et al. (1978). Ascertainment bias was a problem in the Blumenthal et al. (1981) study because the pedigrees were selected because of multiple members with ragweed allergy. In fact, in some of these families a dominant major gene for ragweed allergy may be segregating (Blumenthal et al. 1974).

The study of Pennsylvania Amish pedigrees is the only study of total IgE levels in an inbred population (Meyers et al. 1982). In analyzing the fit of major gene models, the codominant model gave the best fit to the data, although other Mendelian models could not be ruled out (Meyers et al. 1982). Mixed models were not fitted to the data. The last study to be considered is the investigation of IgE levels in five Mormon pedigrees (Hasstedt et al. 1983). Since the Mormon population is not inbred, the results should be more applicable to the general Caucasian population than is the Amish study. Samples were collected throughout the year, although the members of each nuclear family were usually sampled at the same time. Although heritability of total IgE levels was estimated as being ~60%, no evidence for a major gene was found. A mixed model with a major gene and a polygenic component did not fit the data significantly better than did the model with polygenic inheritance alone. Linkage studies were performed, and no evidence of any marker being linked to the postulated IgE locus was found (Meyers et al. 1983).

On the basis of these results, one could speculate that the basal level of total serum IgE is largely under polygenic control but that there is a major gene present in some families. In addition, there may be major genes influencing response to specific allergens (Willcox and Marsh 1978; Borecki et al. 1985). Given this hypothesis, the time of the year when samples were collected in the various studies may help to explain their differing results. Since the subjects in the study of Gerrard et al. (1978) were sampled when IgE levels in allergic family members would be elevated (i.e., during summer months), this could at least partially explain the definite presence of a major gene inferred from their results. In the study of Hasstedt et al. (1983), in which no evidence for a major

gene was found, the family members were sampled throughout the year. This may have made it difficult to detect, in the presence of a strong polygenic factor, the presence of a major gene for total IgE levels. The study of Blumenthal et al. (1981), in which evidence for major gene control was found with possible genetic heterogeneity, would also support this hypothesis, since these families may have a major gene segregating for ragweed allergy.

In summary, these data on randomly ascertained families suggest that there is some role for Mendelian control of basal IgE levels but that there is significant familial aggregation in IgE levels over and above that due to a Mendelian factor. Variance-component analysis revealed a significant between-spouse correlation that cannot be due to genetic factors. Segregation analysis showed that the mixed model of recessive inheritance of high levels was most appropriate for these data, with ~36% of the total phenotypic variation in log[IgE] attributable to genetic factors, equally divided between a Mendelian component and a more general polygenic component. Although our data would appear to support earlier evidence (Marsh et al. 1974; Gerrard et al. 1978) for recessive inheritance of "high" IgE levels, it should be noted that the "low"- and "high"-phenotype distributions seen in the present study are quite different from those in previous studies. Specifically, a mean log[IgE] of 0.50 was obtained for the "low" phenotype with a gene frequency of only .03 for the "low" allele.

The results of the present study would seem to conform more closely to the mouse data of Watanabe et al. (1976). In studies involving SJL (low-IgE) and BALB/c (high-IgE) mice and their F_1 hybrids and $F_1 \times$ SJL backcrosses, they found that high IgE responsiveness is inherited as a recessive trait. The SJL mouse, which normally produces little or no IgE antibody response to any antigen, would seem to correspond more closely to the people in the present study who are designated as having the "low" IgE phenotype than they do to those so designated in the study of Marsh et al. (1974). Finally, it is clear that other genetic and environmental factors play an important role in the regulation of basal serum IgE levels.

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