

GENETIC SUSCEPTIBILITY TO ASTHMA — BRONCHIAL HYPERRESPONSIVENESS COINHERITED WITH A MAJOR GENE FOR ATOPY

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Abstract Background. Bronchial hyperresponsiveness, a risk factor for asthma, consists of a heightened bronchoconstrictor response to a variety of stimuli. The condition has a heritable component and is closely related to serum IgE levels and airway inflammation. The basis for these relations is unknown, as is the mechanism of genetic susceptibility to bronchial hyperresponsiveness. We attempted to define the interrelation between atopy and bronchial hyperresponsiveness and to investigate the chromosomal location of this component of asthma.

Methods. We studied 303 children and grandchildren of 84 probands with asthma selected from a homogeneous population in the Netherlands. Ventilatory function, bronchial responsiveness to histamine, and serum total IgE were measured. The association between the last two variables was evaluated. Using analyses involving pairs of siblings, we tested for linkage between bronchial hyperresponsiveness and genetic markers on chromosome 5q31-q33, previously shown to be linked to a genetic locus regulating serum total IgE levels.

BRONCHIAL hyperresponsiveness is a fundamental characteristic of asthma thought to have a heritable component.¹ Longitudinal studies in children show that bronchial hyperresponsiveness precedes asthma and is a risk factor for the development of asthma.^{2,3} Studies in both humans and animals have demonstrated a genetic predisposition to bronchial hyperresponsiveness,²⁻¹⁰ such as greater concordance for this trait among monozygotic twins than among dizygotic twins.^{9,10} Bronchial hyperresponsiveness to carbachol appears to be inherited as an autosomal dominant trait,⁴ but the bimodal distribution of bronchial responsiveness to methacholine is not controlled by a single gene.⁵ Although these studies confirm a strong heritable predisposition to bronchial hyperresponsiveness, the genetic regulation and chromosomal location of this trait remain unknown.

Bronchial hyperresponsiveness is accompanied by bronchial inflammation and an allergic diathesis in patients with asthma.¹¹⁻¹⁹ Even in children with no history or symptoms of atopy or asthma, bronchial hyperresponsiveness is strongly associated with elevated serum IgE levels.¹⁷ We and others have recently identified a

Results. Serum total IgE levels were strongly correlated ($r=0.65$, $P<0.01$) in pairs of siblings concordant for bronchial hyperresponsiveness (defined as a ≥ 20 per cent decrease in the forced expiratory volume in one second produced by histamine [threshold dose, ≤ 16 mg per milliliter]), suggesting that these traits are coinherited. However, bronchial hyperresponsiveness was not correlated with serum IgE levels ($r=0.04$, $P>0.10$). Analyses of pairs of siblings showed linkage of bronchial hyperresponsiveness with several genetic markers on chromosome 5q, including D5S436 ($P<0.001$ for a histamine threshold value of ≤ 16 mg per milliliter).

Conclusions. This study demonstrates that a trait for an elevated level of serum total IgE is coinherited with a trait for bronchial hyperresponsiveness and that a gene governing bronchial hyperresponsiveness is located near a major locus that regulates serum IgE levels on chromosome 5q. These findings are consistent with the existence of one or more genes on chromosome 5q31-q33 causing susceptibility to asthma. (N Engl J Med 1995; 333:894-900.)

major locus regulating serum IgE levels on chromosomes 5q31-q33.^{20,21} This chromosomal region is rich in candidate genes, many of which regulate IgE production either directly or indirectly and affect the activation and proliferation of cells involved in inflammatory processes associated with bronchial hyperresponsiveness, allergy, and asthma.^{11-19,22-28} Thus, chromosome 5q31-q33 may also represent a candidate region for the genetic regulation of bronchial hyperresponsiveness.

Although population studies clearly show a very strong association between atopy and bronchial hyperresponsiveness,¹⁷⁻¹⁹ they cannot identify patterns of inheritance or the number of genes involved, the magnitude of their effects, or in most cases, their location.²⁹ However, linkage analysis can facilitate the dissection of the genetics of complex diseases such as asthma.²⁹ To explain the close interrelation between bronchial hyperresponsiveness and atopy, we used family studies to investigate whether these traits are coinherited. Because a major gene regulating serum IgE has previously been mapped to chromosome 5q31-q33,^{20,21} we also tested whether genetic susceptibility to bronchial hyperresponsiveness, provoked by histamine, was coinherited with markers from this region.

METHODS

Ascertainment of Study Families

Since the early 1960s Beatrixoord, near Groningen, the Netherlands, has served as a rehabilitation facility and a regional referral center for patients with asthma and airways disease. Between 1962 and 1970, 1284 patients with obstructive airways disease were evaluated while their symptoms were clinically stable. Eighty-four families

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were selected by identifying in each case a proband with symptomatic asthma who was 45 years of age or younger and who had bronchial hyperresponsiveness to histamine at the time of the first study.³⁰

Clinical Assessment

The original evaluation of the probands included the performance of skin tests with common allergens, pulmonary-function testing, and testing of bronchial responsiveness with histamine.³¹ The probands were restudied approximately 25 years later, along with all their available children, grandchildren (six years of age and older), and spouses. Testing of relatives included a standard respiratory questionnaire (modified version of the British Medical Council questionnaire with additional questions on symptoms and therapy of allergy and asthma), pulmonary-function testing, measurement of bronchial responsiveness to inhaled histamine, skin tests, and measurement of serum total IgE.^{30,31}

The level of serum total IgE (expressed as international units per milliliter) was used as an index of atopy and measured by solid-phase immunoassay (Pharmacia Diagnostics, Uppsala, Sweden). The mean of duplicate samples was used. The test was repeated if the difference between duplicate samples exceeded 5 percent. Segregation analyses of \log_{10} serum total IgE levels suggested recessive inheritance of high IgE levels in this population.²¹ The mean IgE levels associated with the low IgE and high IgE phenotypes were 38 and 437 IU per milliliter, respectively.²¹ In the frequency distribution, a level of 100 IU per milliliter best distinguished the high- from the low-phenotype group; we therefore defined persons with elevated serum total IgE levels as those with levels above 100 IU per milliliter.

Bronchial responsiveness was tested in family members according to the method of de Vries et al.³² because this method was used to assess the probands between 1962 and 1970. To test bronchial responsiveness, the subjects first inhaled a diluent for 30 seconds of normal breathing and then inhaled doses of histamine that were doubled every 5 minutes (from 0.5 mg per milliliter to 32 mg per milliliter). The test was stopped when the forced expiratory volume in one second (FEV_1) fell by 20 percent or more, or the highest concentration of histamine (32 mg per milliliter) was reached. For subjects with less than a 20 percent decrement in FEV_1 at the highest concentration of histamine, a threshold value of 64 mg of histamine per milliliter was arbitrarily assigned. The lowest concentration of histamine that induced a decline in the FEV_1 of at least 20 percent was termed the threshold value. Subjects were classified as positive or negative for bronchial hyperresponsiveness on the basis of their histamine threshold value (with positive status defined by a value of either ≤ 16 or ≤ 32 mg per milliliter). Bronchial hyperresponsiveness was also expressed as the provocation concentration of histamine causing a 20 percent decrease in the FEV_1 (PC_{20}) and was estimated by extrapolation from the dose-response curve.

Molecular Methods

DNA was extracted from peripheral leukocytes from members of the 84 families, as described previously (no DNA was available from 8 additional families that have been studied previously).^{21,31} Genomic DNA was diluted to a concentration of 200 μ g per milliliter for amplification. Simple-sequence-repeat loci³³ were selected from the Genome Data Base (Welch Library, Johns Hopkins University, Baltimore) and included those used to demonstrate linkage to a major locus regulating serum total IgE.²¹ The products were amplified by the polymerase chain reaction³⁴ and sized according to previously described methods.²¹ The samples were handled as described by Weber and May³³ with minor modifications. One or two simple-sequence-repeat loci were loaded on each gel. Genotypes were determined from two independent readings of each autoradiograph by persons who were unaware of the families' clinical characteristics.

Linkage Analyses

Linkage analysis is an analytic method to test for cosegregation at meiosis of a chromosomal region determining a trait or disorder. In the absence of a genetic model for the inheritance of bronchial hyperresponsiveness, and assuming that multiple genes on different chro-

mosomes regulate this trait, we used a nonparametric approach to test for linkage. Linkage analyses were performed with methods involving affected pairs of siblings (Sibpal, Sage, Louisiana State University, New Orleans),³⁵ an established approach for the investigation of the genetic basis of complex traits, such as bronchial hyperresponsiveness, atopy, and asthma. Affected pairs of siblings are usually tested first, since a proportion of unaffected pairs of siblings may be gene carriers who do not express the trait. In contrast to lod-score methods, in this method the model for inheritance (dominant, recessive, and so on) does not need to be specified. Thus, the clinical characteristics of the parents are not used in testing for linkage; the pertinent observation is how often two affected offspring share copies of the same parental marker allele.³⁶ If the same copy of a marker allele is observed in different offspring, the alleles are said to be inherited in a manner that is termed "identical by descent." Linkage is suggested when affected pairs of siblings are identical by descent for a marker allele significantly more often than expected by chance (50 percent). The transmission of a specific marker allele with a disease gene in different offspring suggests that the marker locus is linked with the disease or located close enough to it on the same chromosome that they cosegregate during meiosis. The disease trait can then be mapped because the chromosomal location of the marker is known.

We also analyzed bronchial hyperresponsiveness as a quantitative trait using a regressive approach to identify the relation between siblings for the actual PC_{20} values and the proportion of marker alleles identical by descent.³⁵ As with least-squares regression analysis, this method uses the regression of the squared difference in the actual PC_{20} value on the estimated proportion of alleles identical by descent from all pairs of siblings from all families to test for linkage.

Statistical Analysis

All clinical and genotype data were managed with Paradox on an IBM personal computer (IBM, Research Triangle Park, N.C.). Pearson correlation coefficients and chi-square tests were performed with SAS software (SAS Institute, Cary, N.C.). All P values are two-tailed except those for analyses of affected pairs of siblings, in which a one-tailed test was used because we were testing only for an increased sharing of alleles.

If the serum total IgE level is assumed to be strongly correlated with susceptibility to bronchial hyperresponsiveness,¹¹⁻¹⁹ and each is largely determined by genetic background,^{2-10,20,21} then these traits should be inherited independently at meiosis if the genes responsible are located on different chromosomes. To test the hypothesis that genes determining serum IgE level and susceptibility to bronchial hyperresponsiveness are co-inherited (cosegregate at meiosis), we examined whether there was a correlation in serum total IgE values between pairs of siblings who were concordant for bronchial hyperresponsiveness or for the absence of bronchial hyperresponsiveness and whether there was a correlation in $\log_{10} PC_{20} FEV_1$ values between pairs of siblings who were concordant for elevated serum total IgE values (\log_{10} value, >2). If these traits are not genetically linked (segregate independently at meiosis), then siblings concordant for one trait would not be expected to be concordant for the second trait.

RESULTS

Relation between the Inheritance of Bronchial Hyperresponsiveness and Serum Total IgE Levels

Table 1 lists the clinical and physiologic data on the first-degree (children) and second-degree (grandchildren) offspring included in our analyses, the 84 probands and their spouses, and the spouses of 29 of the probands' children. There were no half-siblings. Only 19.5 percent of the spouses, including those of the probands' offspring, met the criteria for bronchial hyperresponsiveness ($PC_{20} \leq 32$ mg of inhaled histamine per milliliter), whereas 33.6 percent of the first-degree off-

Table 1. Clinical and Physiologic Characteristics of the Proband, Their First- and Second-Degree Offspring, and Their Spouses.

CHARACTERISTIC	PROBANDS* (N = 84)	SPOUSES† (N = 113)	OFFSPRING	
			1ST DEGREE (N = 247)	2ND DEGREE (N = 56)
Male sex (%)	56.0	50.4	48.6	50.0
Age (yr)				
Mean	51.1	48.2	25.4	13.7
Range	37–71	30–72	8–48	7–25
Percentage with bronchial hyperresponsiveness (PC ₂₀ , ≤32 mg/ml)	89.3	19.5	33.6	35.7
Percentage of predicted FEV ₁	67.8	98.2	95.0	96.6
FEV ₁ /FVC (%‡)	58.5	77.8	81.7	82.7

*Data were based on the reevaluation of these subjects.

†This category includes 29 spouses of the probands' children (first-degree offspring).

‡FVC denotes forced vital capacity.

spring and 35.7 percent of the second-degree offspring were classified as having bronchial hyperresponsiveness. Only six kindreds had at least one affected pair of siblings whose spouses were also hyperresponsive to histamine.

Serum total IgE levels were correlated in 35 pairs of siblings (the offspring of the probands) who were concordant for bronchial hyperresponsiveness (histamine threshold value, ≤32 mg per milliliter) ($r = 0.40$,

$P < 0.05$) (Fig. 1A), suggesting that these traits are coherited. When a more conservative definition of bronchial hyperresponsiveness was used (histamine threshold value, ≤16 mg per milliliter), serum total IgE values were correlated in 15 pairs of siblings who met this criterion ($r = 0.65$, $P < 0.01$) (Fig. 1B). Eleven of these 15 pairs of siblings (73 percent) had elevated IgE levels (>100 IU per milliliter, or a \log_{10} value >2). Among these 15 pairs of siblings, only 7 subjects did not report symptoms of asthma. The PC₂₀ values for pairs of siblings with elevated IgE levels are shown in Figure 2. Bronchial hyperresponsiveness was not correlated with IgE levels ($r = 0.04$, $P > 0.10$).

Linkage Analyses

Table 2 shows the results of linkage analyses in the pairs of siblings with bronchial hyperresponsiveness (histamine threshold value, ≤32 mg per milliliter). These loci are listed in the order in which they currently appear on genetic maps (in which the beginning of the list indicates the most centromeric location)³⁷ of chromosome 5q31-q33 covering a region of approximately 18 cM (Fig. 3). There was statistically significant evidence of linkage with D5S436 and several markers located nearby. The markers were considered informative when maternal and paternal alleles could be distinguished in the offspring. Markers D5S658 and D5S436, spanning a distance of approximately 3 mil-

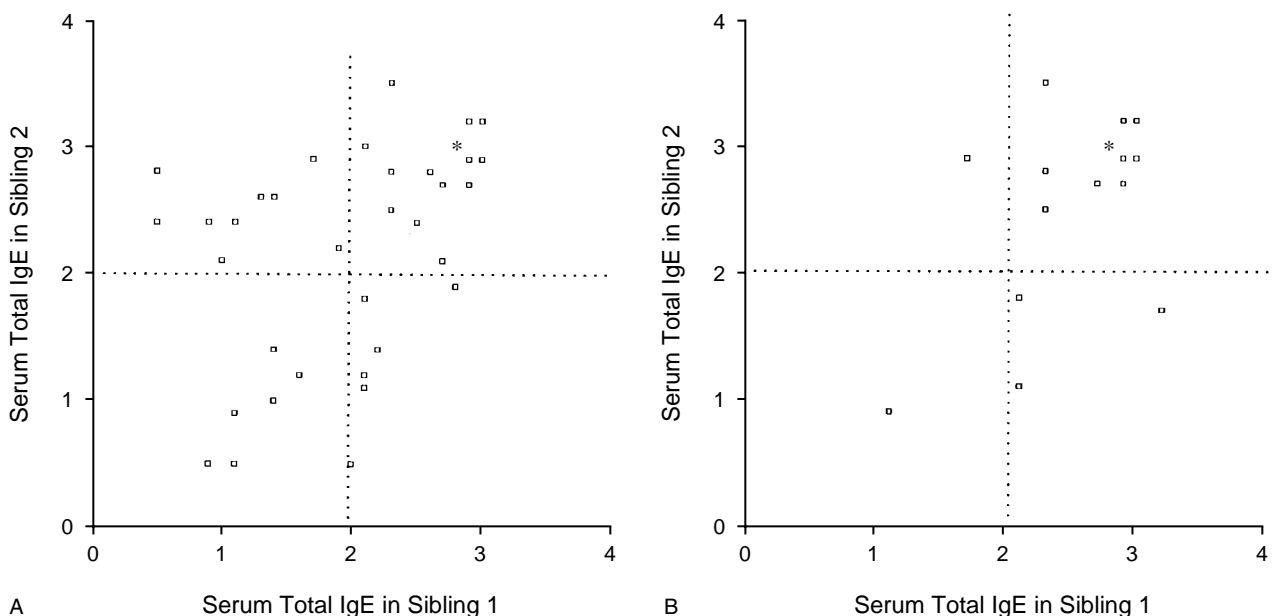


Figure 1. Relation of Serum Total IgE Values in Pairs of Siblings Concordant for Bronchial Hyperresponsiveness to Histamine Producing a ≥20 Percent Decrease in FEV₁.

The siblings are the offspring of the probands (children and grandchildren). In Panel A, analysis of serum total IgE levels (\log_{10} values) in 35 pairs of siblings with bronchial hyperresponsiveness (histamine threshold value, ≤32 mg per milliliter) shows a significant correlation ($r = 0.40$, $P < 0.05$), suggesting that these traits may cosegregate at meiosis. In Panel B, analysis of serum total IgE levels in 15 pairs of siblings with bronchial hyperresponsiveness (histamine threshold value, ≤16 mg per milliliter) shows a significant correlation ($r = 0.65$, $P < 0.01$) despite the use of a more conservative definition of bronchial hyperresponsiveness. When these pairs of siblings were subdivided on the basis of IgE values, the majority had elevated levels (\log_{10} value, >2). All of these pairs of siblings share one or more parental alleles for D5S436 or D5S658. The asterisks indicate two sets of overlying values.

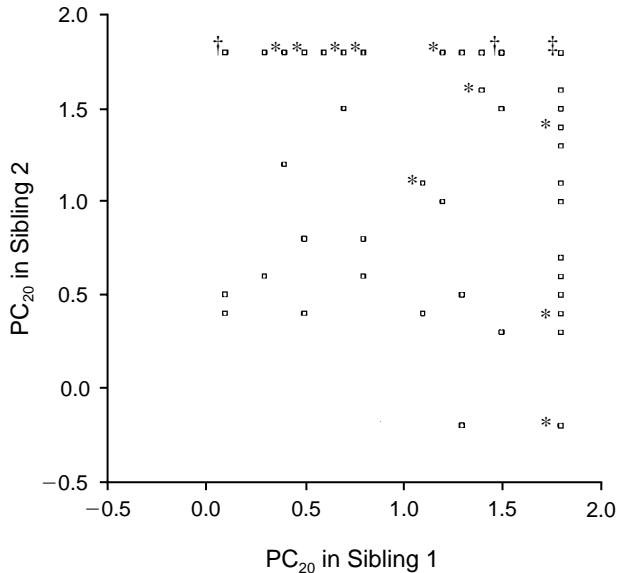


Figure 2. Relation of PC_{20} Values in 72 Pairs of Siblings Concordant for Elevated Serum Total IgE Levels (\log_{10} Value, >2). The study subjects were the children and grandchildren of the probands. In subjects who had no significant response to the inhalation of 32 mg of histamine per milliliter (the highest concentration tested), a PC_{20} value of 64 mg per milliliter was arbitrarily assigned. Bronchial hyperresponsiveness was not correlated with IgE levels ($r=0.04$, $P>0.10$). The asterisks indicate two sets of overlying values, the daggers three sets, and the double dagger four sets.

lion base pairs on chromosome 5q, were informative in 35 pairs of siblings with bronchial hyperresponsiveness. D5S658 and D5S436 showed evidence of linkage with bronchial hyperresponsiveness ($P=0.03$ and $P=0.009$, respectively). The gene candidates fibroblast growth factor acidic and colony-stimulating factor receptor 1 also showed evidence of linkage with bronchial hyperresponsiveness ($P=0.015$ and $P=0.05$, respectively), despite being less informative markers than D5S658 or D5S436. When we used a more conservative histamine threshold of ≤ 16 mg per milliliter we identified linkage between bronchial hyperresponsiveness and D5S436 in 14 pairs of siblings (empirical $P=0.001$; mean proportion of alleles that were identical by descent, 0.77; excess of parental alleles shared, 27 percent).

Table 3 shows the results of linkage analysis of bronchial responsiveness as a qualitative trait (histamine threshold value, ≤ 32 mg per milliliter) with D5S436. When both siblings were negative for bronchial hyperresponsiveness (173 pairs of siblings), there was an increased sharing of marker alleles, whereas if one member of a pair of siblings was positive for bronchial hyperresponsiveness and the other was negative (114 pairs of siblings), the pair tended not to share parental alleles ($P<0.001$). As discussed above, there was an excess sharing of alleles for D5S436 ($P=0.009$) in the 35 pairs of siblings who were concordant for bronchial hyperresponsiveness. The linear regression showed that these data were significant ($P=0.000002$) (Table 3).

Statistical evidence of linkage was not found ($P>0.01$) for D5S470, D5S500, D5S393, or fibroblast growth factor acidic when we conducted a similar analysis using the data from all pairs of siblings. Finally, there was strong statistical evidence of linkage of D5S436 with bronchial hyperresponsiveness when bronchial hyperresponsiveness was analyzed as a quantitative trait ($P<0.001$) (see the Methods section). There was still significant evidence of linkage between bronchial hyperresponsiveness and D5S436 when \log_{10} serum total IgE levels were included as a covariate ($P<0.002$).

DISCUSSION

Dissecting the Complex Components of Asthma

The clinical characterization of asthma is difficult, and this complicates the mapping of genes for the disorder. However, critical components of asthma, such as bronchial-hyperresponsiveness and allergic status, can be defined more objectively. In our studies of families, we adopted a strategy that focused on identifying the genes predisposing subjects to these known abnormalities and the risk factors associated with asthma.^{21,31,38} This strategy optimized the likelihood of success in dissecting the complex genetic factors determining susceptibility to asthma. Although this mapping approach has limitations,²⁹ the recent identification of major loci important in essential hypertension,³⁹ breast cancer,⁴⁰ and diabetes⁴¹ confirms that these methods are useful for investigating the pathogenesis of common complex genetic disorders. Moreover, the study of asthma was recently advanced by the identification of a major genetic locus regulating serum IgE levels on chromosome 5q31-q33.^{20,21}

Evidence Supporting the Colocalization of Bronchial Hyperresponsiveness and a Major Gene Regulating Serum Total IgE

In several different populations, serum IgE levels, bronchial hyperresponsiveness, and asthma are strong-

Table 2. Results of Linkage Analyses in Affected Pairs of Siblings with Bronchial Hyperresponsiveness to Histamine.*

MARKER†	NO. OF PAIRS OF SIBLINGS	MEAN‡	P VALUE
Interleukin-9	10	0.61	0.14
D5S393	22	0.61	0.04
D5S500	35	0.58	0.09
D5S658	35	0.60	0.03
D5S436	35	0.64	0.009
FGFA	25	0.62	0.015
D5S434	34	0.56	0.08
CSF1R	20	0.60	0.05
D5S470	35	0.57	0.10
D5S410	20	0.53	0.31

*Histamine threshold value, ≤ 32 mg per milliliter.

†FGFA denotes fibroblast growth factor acidic, and CSF1R colony-stimulating-factor receptor 1.

‡Proportion of alleles that were identical by descent.

ly associated in epidemiologic studies.^{17-19,42-45} We also observed a very strong association between IgE levels and bronchial hyperresponsiveness, since more than 50 percent of the offspring with elevated IgE levels in our study had physiologic evidence of bronchial hyperresponsiveness (data not shown). The striking feature of this study is the coinheritation and colocalization of a gene that determines both bronchial responsiveness and serum IgE levels. Moreover, the evidence of the coinheritation of these traits in this family study provides a potential genetic mechanism to explain the relation between these variables in prior epidemiologic studies.^{17,18,43-45} In particular, we interpret these results as suggesting that there are one or more closely associated susceptibility genes on the same chromosome that are important in the development of bronchial hyperresponsiveness and the regulation of serum IgE levels. For traits to be coinherited in siblings, they must cosegregate with each other at meiosis. This implies genetic linkage to the same chromosomal region. If bronchial hyperresponsiveness and serum IgE levels are not

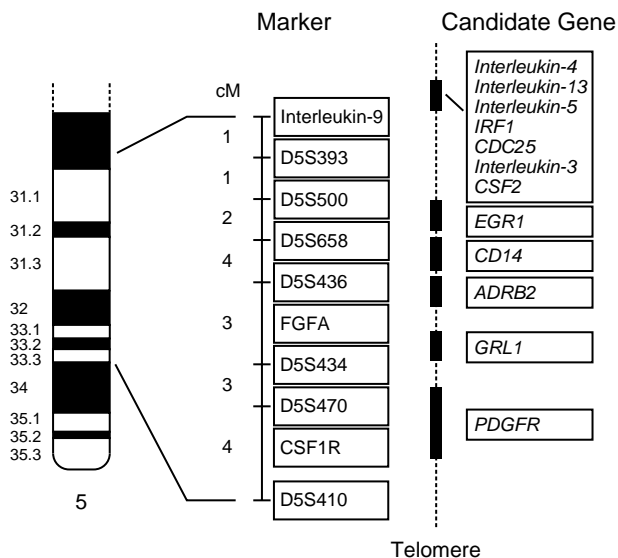


Figure 3. Map Showing the Relative Order of and Distance between the Polymorphic Genetic Markers Used and the Approximate Location of the Gene Candidates for Asthma, Bronchial Hyperresponsiveness, and Atopy Relative to the Markers Studied.

The map includes the following genes: interleukin-4, 13, 5, and 3; immune regulatory factor 1 (*IRF1*); cell division cycle 25 (*CDC25*); granulocyte-macrophage colony-stimulating factor (*CSF2*); early growth response gene 1 (*EGR1*); *CD14*; β_2 -adrenergic receptor (*ADRB2*); lymphocyte-specific glucocorticoid receptor (*GRL1*); and platelet-derived growth factor receptor (*PDGFR*). Bands 5q31-q33 extend from approximately interleukin-4 to D5S410. The distances reported are sex-averaged recombination fractions.³⁷ (The approximate location of and distances between gene candidates are derived from the Genome Data Base [recorded October 12, 1994] and the Cooperative Human Linkage Center Database.) Since the markers within colony-stimulating factor receptor 1 (*CSF1R*) and fibroblast growth factor acidic (*FGFA*) have not been incorporated into the published maps, we have placed them in their approximate location on the basis of our mapping data.

Table 3. Linkage Analysis of D5S436 with Bronchial Responsiveness as a Qualitative Trait in Pairs of Siblings.*

BRONCHIAL-HYPERRESPON-SIVENESS STATUS	NO. OF PAIRS OF SIBLINGS	MEAN†	P VALUE‡
Both negative	173	0.55	0.02
1 positive, 1 negative	114	0.39	<0.001
Both positive	35	0.64	0.009

*Histamine threshold value, ≤ 32 mg per milliliter.

†Proportion of alleles that were identical by descent.

‡P value for linear regression (T = 4.7, df = 320, P = 0.000002).

linked (i.e., these traits are determined by genes on separate chromosomes), they should be inherited independently of each other. In contrast, serum total IgE levels were highly correlated in pairs of siblings concordant for bronchial hyperresponsiveness (Fig. 1). Since these traits appear to be coinherited, they should map to the same chromosomal region.

Mapping of Bronchial Hyperresponsiveness to Chromosome 5q31-q33

Linkage analysis was used to identify a genetic location for bronchial hyperresponsiveness. Because bronchial hyperresponsiveness mapped to a major gene for atopy, we examined chromosomal regions reported to be important in the regulation of serum IgE levels. Candidate regions for atopy have been described through linkage analyses.^{20,21,46-48} Previous studies have suggested that atopy and bronchial hyperresponsiveness in the current study population are not linked to a genetic locus on chromosome 11q.³¹ However, there is evidence of a major gene for atopy on chromosome 5q31-q33.^{20,21} Therefore, to determine the chromosomal location of a gene or genes governing susceptibility to bronchial hyperresponsiveness, which would be coinherited with a major gene for atopy, we performed linkage analyses between bronchial hyperresponsiveness and genetic markers on chromosome 5q. Analyses of affected pairs of siblings demonstrated statistically significant evidence of linkage between bronchial hyperresponsiveness and D5S436, D5S658, and several other markers located nearby on chromosome 5q31-q33 (Table 2). These data strongly support the hypothesis that one or more closely spaced genes on chromosome 5q31-q33 determine susceptibility to bronchial hyperresponsiveness and atopy.

Candidate Genes for Asthma on Chromosome 5q31-q33

Chromosome 5q31-q33 was originally examined because it is especially rich in genes that are implicated in bronchial inflammation associated with asthma (Fig. 3).^{24-28,49-51} Granulocyte-macrophage colony-stimulating factor, fibroblast growth factor acidic, other colony-stimulating factors and receptors, the lymphocyte-specific glucocorticoid receptor 1, and the β_2 -adrenergic receptor map to this area.²⁴ A cluster of cytokines, interleukin-3, 4, 5, 9, and 13, are also tightly linked and map to this region.²⁴⁻²⁸ These cytokines have overlapping ef-

fects on the growth and proliferation of B cells and other cells associated with allergic inflammation.⁴⁹⁻⁵¹ Interleukin-9 enhances interleukin-4–dependent synthesis of immunoglobulin, and interleukin-13 regulates the expression of CD23, an IgE surface-antigen–binding factor.^{26,28} One of the limitations of our study is that we cannot exclude any of these candidates. However, further mapping with genetic markers through this region may provide evidence in the future of linkage disequilibrium and should facilitate the positional cloning of a specific candidate gene.^{29,52} Moreover, although our data strongly support the localization to chromosome 5q31-q33 of genetic factors important to susceptibility to asthma, we cannot yet establish whether these linkages are due to a single gene, nor can we offer a precise location for the gene or genes on chromosome 5q31-q33. Further studies aimed at identifying a specific genetic model for bronchial hyperresponsiveness and asthma will be useful in this regard.

Implications for the Clinical Assessment of Asthma

Our findings have potential implications for the role of bronchial hyperresponsiveness in the clinical assessment of asthma. We found evidence that elevated levels of IgE are coinherited with bronchial hyperresponsiveness, yet bronchial responsiveness was not correlated in siblings concordant for elevated serum total IgE levels (\log_{10} value, >2) (Fig. 2). These data imply that serum total IgE levels can be influenced by multiple genetic and environmental factors that may not be common to the development of bronchial hyperresponsiveness. Because allergy is prevalent, it is likely that certain factors affecting serum total IgE levels are not common to the development of asthma. Moreover, because bronchial hyperresponsiveness is a known risk factor in asthma,^{2,3} one interpretation of these data is that bronchial hyperresponsiveness may be a more specific measure of susceptibility to asthma than serum total IgE levels. Since these measurements were made simultaneously, discordance between pairs of siblings for bronchial hyperresponsiveness would represent an inability to detect this risk factor despite concomitant environmental exposure in these subjects resulting in elevated serum total IgE levels. This latter explanation seems less likely in our view, since numerous studies suggest that these traits are generally expressed together in asthma.^{17-19,42-45}

CONCLUSIONS

This study mapped bronchial hyperresponsiveness to a region of chromosome 5q31-q33 previously reported as one site for a major locus regulating serum total IgE.^{20,21} These data provide strong evidence of one or more susceptibility loci on chromosome 5q31-q33 that contribute to bronchial hyperresponsiveness and atopy and that are closely associated with bronchial inflammation critical in the pathogenesis of asthma. The coinheritance and genetic colocalization of essential components of asthma generate many important new questions about the molecular basis of susceptibility to

this disorder. However, replication of our findings in other populations, including those identified randomly, will be useful to allow their generalization and to guide future studies on the molecular relations between these risk factors and the development of asthma.

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