
Susceptibility Loci Regulating Total Serum IgE Levels, Bronchial Hyperresponsiveness, and Clinical Asthma Map to Chromosome 5q*

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Asthma is a chronic inflammatory disorder of the airways. This chronic inflammation is responsible for increased airways hyperresponsiveness to a variety of stimuli and for the recurrent symptoms and airflow limitation characteristic of asthma. The close association between bronchial hyperresponsiveness (BHR) and asthma has been well established, since virtually all asthmatics demonstrate BHR. It has been shown that BHR may precede the development of asthma and constitutes a risk factor for the development of asthma. Animals studies have suggested that BHR is genetically determined. In humans, twin studies have suggested a heritable component to BHR, with higher concordance levels in monozygotic compared to dizygotic twins. However, BHR is complex genetically and is not likely to be inherited as a simple mendelian trait.

Allergy and asthma are also complex genetic disorders that do not follow a simple mendelian pattern. It is likely that multiple interactions from numerous genes, combined with environmental influences, are involved. Although discovering the genetics underlying asthma and allergy is difficult, it appears they are closely interrelated, with most asthmatics having clinical and serologic evidence of atopy. In addition, a very close relationship has been reported between total serum IgE levels and BHR, and children with elevated IgE levels have an increased risk of developing BHR and asthma even when other allergic factors are controlled.

We performed linkage analysis on data from 92 families from the Netherlands, ascertained through a parent with asthma who was first studied approximately 25 years ago. From 1991 to 1995, these probands were reevaluated and their spouses, children, and grandchildren (over 8 years of age) studied. All 92 families were studied clinically, using the following: (1) standardized respiratory questionnaire; (2) pulmonary function testing; (3) bronchial responsiveness to inhaled histamine using the method of Devries et al; (4) intradermal skin tests; (5) total serum IgE; (6) specific IgE levels to house dust mite and grass mix; and (7) total peripheral blood eosinophil counts. These data were used for segregation analysis for total serum IgE, which demonstrated recessive inheritance of high IgE levels, with the identification of at least two independent major loci contributing to the variance in IgE levels observed in this population.

Genotyping was conducted on the 84 families for whom DNA was available. Since there are a number of candidate genes on chromosome 5q31-33 that regulate IgE production and the cellular responses that are likely to be involved in bronchial inflammation associated with BHR and asthma, families were genotyped for markers in this region. Linkage analysis of total serum IgE levels was performed using the sib-pair method. This method is based on sharing of marker alleles identical by descent in sibling pairs and is not dependent on the genetic model from the segregation analysis. In the presence of linkage, siblings who are identical by descent for the marker would be expected to have similar IgE levels, and those not sharing marker alleles would be expected to have a larger difference in their IgE levels. In addition, 2-point lod scores were calculated using the genetic model of recessive inheritance of “high” IgE levels obtained from segregation analysis. By sib-pair analysis, significant evidence was observed for the highly polymorphic marker D5S436 (Table 1). In addition, evidence for linkage for the flanking loci, D5S393 and CSF-1R, was observed. The results of the lod-score analyses for IgE were similar. The highest lod (3.61) was obtained for D5S436 with 9% recombin-

Table 1—Results of Linkage Analysis for log[IgE], BHR, and the Asthma Phenotype

<table>
<thead>
<tr>
<th>Marker</th>
<th>Sib-Pair Log[IgE]</th>
<th>Sib-Pair BHR p Value</th>
<th>LOD (θ)</th>
<th>LOD (θ) Log[IgE]</th>
<th>LOD (θ) Log[IgE] p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin-9</td>
<td>0.047</td>
<td>0.013</td>
<td>1.13 (.07)</td>
<td>0.013</td>
<td>0.013</td>
</tr>
<tr>
<td>D5S393</td>
<td>0.013</td>
<td>0.02</td>
<td>1.93 (.10)</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>FGFA</td>
<td>NS*</td>
<td>0.02</td>
<td>0.82 (.17)</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>D5S436</td>
<td>0.00004</td>
<td>0.009</td>
<td>3.61 (.9)</td>
<td>0.009</td>
<td>0.009</td>
</tr>
<tr>
<td>CSF-1R</td>
<td>0.028</td>
<td>0.05</td>
<td>0.98 (.11)</td>
<td>0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*NS=not significant, p>0.05.
Evidence suggests a close relationship between atopy and pulmonary function. In particular, there is a strong association between airway responsiveness and serum IgE levels. To further explore the relationship between BHR and allergy (IgE levels), we tested the hypothesis that BHR would map to the same region where we have evidence for a locus that regulates total serum IgE on chromosome 5q. The sib-pair analysis for BHR as a qualitative trait conducted with each of the markers is reported in Table 1. The sib-pair data for BHR are highly significant with the marker D5S393. However, D5S393 and D5S412 were also identical by descent in a significant number of sibling pairs with similar airway response phenotypes. When we evaluated linkage between BHR as a quantitative trait (ie, using the actual provocative concentration of substance causing 20% fall in FEV_1 values for histamine provocation) and D5S436, the p value was 0.0002 (p value for linear regression: p=0.000002; T=-4.7; degrees of freedom=320). These data confirm the close genetic relationship between IgE and BHR. Moreover, we found that high IgE was co-inherited with BHR and markers on 5q, but the converse was not true. In summary, these data suggest that a genetic locus (or loci) in the vicinity of the interleukin complex (closest to D5S436) determines a significant amount of the observed biologic variability in bronchial responsiveness. This relationship remained significant even when total serum IgE levels were included as a covariate.

Furthermore, using an algorithm based on BHR, symptoms, smoking, FEV_1, and reversibility, we found evidence for linkage of asthma to markers on 5q by affected sib-pair analysis (p<0.05) and by lod score analysis with a dominant model for the asthma phenotype (D5S658 lod=3.64). These results demonstrate the colocalization of a major gene(s) for asthma, BHR, and IgE levels to chromosome 5q31-33 in an area rich with cytokine genes. This suggests that there is at least one and possibly multiple important loci for susceptibility to allergic asthma in this region and justifies efforts towards identification of such genes, such as fine mapping and positional cloning.

REFERENCES

3 Levitt RC, Mitzner W. Expression of airways hyperreactivity to acetylcholine as a simple autosomal recessive trait in mice. FASEB J 1988; 2:2605-08

Association of the Gln 27 β2-Adrenoceptor Polymorphism and IgE Variability in Asthmatic Families*

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Two common N-terminal polymorphisms have been described in the β2-adrenoceptor resulting in amino-acid substitutions at positions 16 and 27. We have previously described an association of the Gln27 β2-adrenoceptor polymorphism with lower airway reactivity in asthmatic subjects. The aim of the current study was to investigate the possibility that this polymorphism is associated with markers for allergic disease in families multiplex for asthma.

Three hundred forty-five individuals were genotyped for β2-adrenoceptor polymorphism from 60 families selected by an asthmatic proband and characterized for markers of allergic disease. The allelic frequencies were as follows: Arg16, 33%; Gly16, 67%; Gln27, 54%; Gln27, 46%. Nonparametric linkage analysis revealed an association between total sex- and age-adjusted IgE levels and Gln27 (p=0.0088, r=0.171[95% confidence interval 0.043-0.301]). No significant association between the Gln27 β2-adrenoceptor polymorphism and asthma score or atopy score was found in this population. In addition, no

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