

## Review article

# The genetics of asthma and atopy

Panhuysen CIM, Meyers DA, Postma DS, Bleecker ER. The genetics of asthma and atopy.

Allergy 1995; 50: 863–869. © Munksgaard 1995.

C. I. M. Panhuysen<sup>1</sup>, D. A. Meyers<sup>2</sup>,  
D. S. Postma<sup>3</sup>, E. R. Bleecker<sup>1</sup>

<sup>1</sup> University of Maryland at Baltimore, MD, USA; <sup>2</sup> Johns Hopkins University, Baltimore, MD, USA; <sup>3</sup> University Hospital, Groningen, The Netherlands

E. R. Bleecker, MD  
University of Maryland  
School of Medicine  
10 S. Pine Street, Suite 800  
Baltimore, MD 21201  
USA

Accepted for publication 25 July 1995

Asthma is a respiratory disease that is characterized by variable airways obstruction, airways inflammation, and bronchial hyperresponsiveness (BHR) (1). Most patients with asthma have clinical and serologic evidence of atopy. Even in children who are asymptomatic, BHR appears to be closely linked to an allergic diathesis, as reflected by the association of serum IgE level with BHR and asthma (2). These findings suggest a close relationship between asthma and atopy. There has been a recent increase in morbidity associated with asthma (3), and epidemiologic studies have provided strong evidence that asthma and allergic disorders are increasing both in prevalence and severity (4, 5). While the precise reasons for these changes are unknown, some evidence indicates that these rising trends are associated with increased levels of sensitization to common environmental allergens and early-life exposure to adjuvant factors including air pollutants and viruses in susceptible individuals (6).

Understanding the genetic mechanisms responsible for allergy and asthma has widespread public health consequences, as it may lead to improved preventive measures and new therapeutic approaches. This review will discuss the general approaches used in genetic studies and methodologic difficulties, as well as current findings that demonstrate the recent advances in understanding the genetics of asthma and atopy.

## Approaches in genetic studies

### *Familial aggregation*

Significant familial aggregation of the phenotypes associated with asthma and allergy has been described in numerous studies (7–9), but this does not always imply a genetic basis. Familial aggregation can be caused by common environmental factors or by an interaction of environmental and genetic factors that can influence the perceived pattern of inheritance.

In testing for familial aggregation, a comparison of disease frequencies in related individuals is performed, and the result is compared to the frequency in a group of controls, or to the disease frequency in the entire population. The excess risk for relatives can be expressed as the risk ratio ( $\lambda$ ), which is the relative's risk compared to the prevalence within the population. These risk ratios can be used to estimate the number of loci involved in the disorder (10, 11). In twin studies with monozygotic (MZ) and dizygotic (DZ) twin pairs, the difference between the disease frequency in MZ and DZ twins provides an indication of heritability, while the difference within MZ twins is an indication of environmental influence. Studies of adopted individuals provide a further opportunity to estimate the environmental and genetic components by comparing natural and adopted parents of affected individuals.

While studies of relatives are helpful in determining whether a genetic component is important, they usually do not provide insight into the mode of inheritance or the specific location of the disease genes in the genome.

#### *Segregation analysis and linkage studies*

There are two basic approaches to mapping genes for asthma and allergy that need to be considered: 1) complex segregation analysis followed by linkage analysis using the most parsimonious genetic model identified by the segregation analysis, and 2) linkage analysis using affected pairs of relatives without a specified model of inheritance (12, 13).

Segregation analysis tests explicit models of inheritance in families, using the qualitative or quantitative data on the trait, possible environmental factors, and family structure. It compares the observed number of affected individuals with the expected number, using various mendelian modes of inheritance, e.g., recessive, dominant, etc. The method of ascertainment of families is very important in segregation analysis. For example, the selection of families with an affected parent and an affected child would bias the results of the analysis in favor of a dominant model of inheritance. Thus, one needs to correct for ascertainment bias in this analytic method. The best-fitting model can be determined by comparing the likelihoods from the several models tested (i.e., dominant, recessive, polygenic, environmental model) with the likelihood of a general model. Models that significantly differ from this general model can be rejected. Estimates of gene frequency, penetrance of the disease in individuals, and heterozygosity or homozygosity for the disease gene can be obtained. This model and its estimates can be used in subsequent linkage analysis.

For linkage analysis, DNA marker data are used together with data on the trait and family structure. The purpose of linkage analysis is to delineate major gene(s) by demonstrating cosegregation of the disease with polymorphic DNA markers. A polymorphic marker is usually not a specific disease-related gene but a chromosomal marker with multiple alleles that can be characterized in all family members and followed through different generations. Using this method, one can test the hypothesis that the asthmatic/allergic children inherited the same marker allele from their asthmatic/allergic parent, and that the unaffected offspring inherited the other allele. There are two general approaches to linkage analysis: performing a genome-wide search and studying specific chromosomes identified because of specific candidate genes. In a genome-wide search, polymorphic markers that are distributed relatively uniformly throughout the genome are examined. The relation-

ship of these markers to the disease or trait is used to determine linkage to a specific chromosomal region.

The maximum likelihood method of linkage analyses (LOD score) is dependent on having a specific model of inheritance, usually acquired through segregation analysis. Results of these analyses are expressed as a LOD score, which is the logarithm of the odds. For mendelian disorders, a  $\text{LOD} \geq 3.0$  (odds 1000:1) at a specific recombination fraction is considered to be significant evidence of linkage (13, 14). There are alternative methods to test for genetic linkage without knowing the model of inheritance. For example, sib-pair analysis, which tests for deviation from the expected mendelian distribution of haplotypes shared by descent among affected sibs, is a common method. In complex disorders such as asthma and allergy, it is very important to replicate the results of linkage analysis in multiple studies. Since there may be false associations between phenotypic characteristics and chromosomal markers during a genome-wide search, replication of results in different population samples is needed. Once linkage is confirmed in complex genetic disorders such as asthma or clinical allergic disease, finding the actual gene is a complex process that calls for close integration of clinical approaches and disease identification, and genetic analysis by techniques that include linkage disequilibrium and molecular and physical mapping with detection of mutations (15) (Fig. 1).

#### **Methodologic issues in studies on asthma and allergy**

Although the many studies published on the genetics of asthma and allergy support the concept that these conditions have a significant familial predisposition, there is little or conflicting information on the mode of inheritance and less on the physical mapping and sequencing of the disease genes. While genes for mendelian disorders such as cystic fibrosis have been localized and cloned, complex genetic

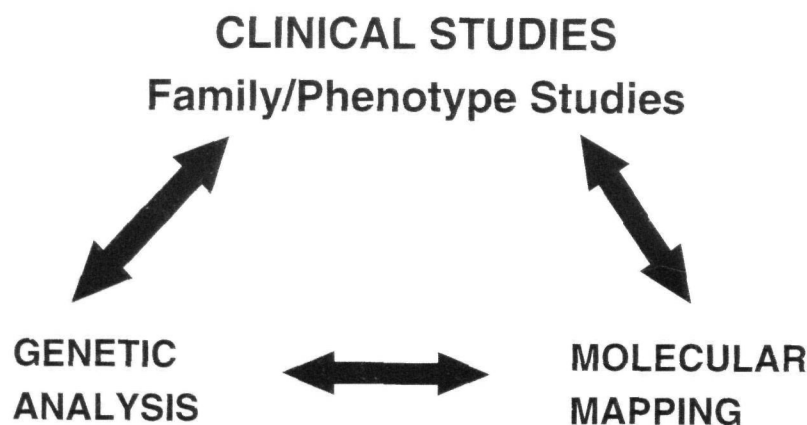


Fig. 1. Approaches to studies on genetics of asthma and bronchial hyperresponsiveness.

disorders such as asthma and allergy are far more complicated. In contrast to cystic fibrosis, a disease with a specific history and laboratory test (16), asthma and allergy are multifactorial diseases with varied phenotypic expressions. Thus, defining the asthma and allergic phenotypes is a central issue in detecting the genetic components of these conditions.

Various standard approaches have been used to examine allergic phenotypes in epidemiologic and genetic studies. These approaches include the measurement of total and specific serum IgE levels as well as quantitative and qualitative results from various skin test panels for common allergens. These studies require standardization of techniques and the purity of allergens. In population-based studies, total serum IgE has been shown to correlate with the clinical expression of allergy as well as with BHR and asthma (2, 17). Recently, skin test responses have been shown to be closely related to BHR and asthmatic symptoms in a similar population-based sample (8).

The assessment of the asthma phenotype is far more complicated and difficult to quantify. There have been numerous attempts to develop comprehensive definitions during the last 35 years (19–21). While current definitions of asthma now emphasize the importance of inflammatory mechanisms in addition to physiologic changes associated with asthma, often they are not helpful for early identification or for the differentiation of asthma from other closely related conditions. Usually in genetic family studies, individuals are classified as either affected or unaffected (dichotomous). In common complex disorders such as asthma and allergy, there will be a group of clearly affected individuals, e.g., defined by specific clinical criteria. In addition, there may often be another large group of individuals who cannot be specifically classified because they have some, but not all, of the characteristics of the condition under investigation. Since one uniform phenotype defining asthma may not exist, investigators have used different, subjective or more concrete definitions of asthma: a reported prior doctor diagnosis of asthma (22, 23), questionnaire data (24, 25), the presence of BHR (26), or combinations of the above. Some investigators include the atopic status in their definition of asthma by separating intrinsic and extrinsic asthma (8, 9). All these different approaches may make it very difficult to compare the results of various epidemiologic and genetic studies.

An important issue in genetic studies in asthma is the close association between asthma and atopy (2, 22) that permits evaluation of closely related heritable factors in both conditions. However, despite the close relationship between asthma, high total serum IgE, and atopy, these traits cannot be simply

interchanged. The same is true for asthma and BHR; though virtually all asthmatic subjects show BHR, not all subjects with BHR have asthma. BHR may precede the expression of asthma and indeed constitute a risk factor (27), or it may be present in association with chronic obstructive lung disease (COPD) (28). However, both total serum IgE levels and BHR are useful measurements that can be analyzed in genetic family studies as quantitative traits. The value of a quantitative trait is that all family members can provide useful information for genetic analysis. In contrast, dichotomous traits such as the presence or absence of asthma provide useful information in a much smaller percentage of the population.

Another obstacle in family studies is that the clinical expression of asthma and atopy may vary with age (29, 30). The clinical expression of asthma may change from a disease initially triggered by allergen exposure and viral infections in childhood (31) to more irreversible airways obstruction with less variability in older patients, who may have been exposed to various environmental agents such as tobacco smoke and air pollutants (32). Furthermore, it is well known that both IgE levels and the diameter of allergy skin tests increase from birth into young adulthood, followed by a decrease with aging. This may cause bias when family members from different generations are studied.

Besides the genetic components of asthma, there are many environmental factors associated with the expression of the disease, such as breast-feeding, viral respiratory infections in early childhood, exposure to allergens, and parental smoking, especially maternal smoking during pregnancy (33–35). It is difficult to assess accurately and control for these known factors in genetic studies, and there may be additional unknown factors. Asthma appears to be of multifactorial origin, closely related to BHR and allergic status, and influenced by multiple genes and environmental factors.

## Studies on asthma and atopy and their phenotypic expressions

### *Familial aggregation*

Several studies have reported an increased frequency of asthma and atopy in first-degree relatives of asthmatic subjects compared to control subjects (7, 8, 36), illustrating familial aggregation of these traits.

### *Twin studies on asthma and atopy*

Edfors-Lubs (25) performed a twin study with 7000 same-sex twins born between 1886 and 1925. The concordance for self-reported asthma in MZ twin pairs was 19.0%, while it was 4.8% in DZ twins,

comparable to the prevalence in the whole twin population (3.8%). The results of this and other twin studies, such as the study performed in 3800 twin pairs from the Australian twin register (24) and the studies reported by Hopp et al. (26), show significant differences between MZ and DZ twin pairs, providing evidence of a genetic component in the development of asthma and atopy. The latter group also found evidence of heritability of phenotypes associated with asthma and allergy, i.e., BHR, skin test responses, and total serum IgE (7, 27).

#### *Studies on the genetics of atopy*

Atopy can be defined in several ways as one or a combination of the following: positive skin tests, elevated total serum IgE level, positive specific serum IgE level, the presence of eosinophilia, and self-reported symptoms and signs of atopic disease (eczema, hay fever). Hopp et al. were unable to demonstrate significant difference between MZ and DZ twin pairs with regard to allergic symptoms based on a questionnaire (26), although they reported a genetic component for clinical atopy parameters.

Defining atopy as a positive skin test, and/or elevated total serum IgE, and/or elevated specific IgE, Cookson and coworkers reported (37–40) that atopy was linked to a marker on chromosome 11q, using an autosomal dominant model of inheritance. Their LOD score results varied from 10 to 3.38 (38, 39). Although these results strongly suggest the presence of at least one major gene for atopy on chromosome 11q, other independent investigators have been unable to confirm this finding (41–46).

#### *Studies on the genetics of bronchial hyperresponsiveness (BHR)*

An increased incidence of BHR has been described in nonasthmatic parents of patients with asthma compared to healthy controls (7, 36, 47), suggesting a heritable component of BHR. In a twin study (26) Hopp et al. estimated the hereditary component of BHR in response to methacholine as 66%. Townley et al. were the first group to report the results of segregation analysis on bronchial responsiveness to methacholine (48). These investigators reported a bimodal distribution of bronchial responsiveness in their population. Nevertheless, they were unable to exclude genetic or environmental factors, and therefore they concluded that the bimodal distribution of the bronchial response was not due to segregation at a single autosomal locus. Longo et al. reported a bimodal distribution of bronchial reactivity to inhaled carbachol in 80 nonasthmatic parents of asthma patients. They concluded that the BHR that exists in asthma families indicates an autosomal

dominant pattern of inheritance with an incomplete penetrance, which, in combination with environmental factors, results in the development of asthma (36).

#### *Studies on IgE*

Total serum IgE can be affected by several factors including allergic exposure and parasitic infection, as well as age, sex, and smoking status. A significant correlation between parents' and children's total serum IgE levels suggests the presence of one or more genes (23, 49, 50). Previous segregation analyses on families do not agree on the model of inheritance. However, several studies have found evidence of recessive inheritance of high total serum IgE levels (51–54). Martinez et al. reported evidence of codominant inheritance in a large sample of families (55). It is important to note that this does not represent conflicting results, but rather reflects the inability to distinguish between two or three underlying distributions which display substantial overlap.

#### *Linkage studies*

At the moment, there are two chromosomal candidate regions of major interest: the human homolog region of the mouse  $\beta$ -chain of the IgE receptor on chromosome 11q, and the region at chromosome 5q with multiple candidate genes that directly or indirectly regulate IgE production. This latter region includes the interleukin (IL)-4 group of cytokines (IL-4, IL-5, IL-3, GM-CSF), IL-9, IL-13, and other cellular growth factors such as FGFA.

Cookson and coworkers suggested maternal inheritance of atopic IgE responsiveness on chromosome 11q (39, 40) since more affected sib pairs shared the maternal allele than the paternal allele. Moreover, genetic linkage to chromosome 11q was primarily detectable in maternal-derived alleles, by the affected sib pair method (56). Shirakawa et al. (57) have recently reported an association between atopy and mutations in the  $\beta$  subunit of the high-affinity IgE receptor (Fc epsilon R1- $\beta$ ) on chromosome 11q. They reported a gene frequency far too low to explain the high existing population prevalence of atopic diseases, providing further arguments for polygenic control of atopy.

Recently, Marsh et al. described evidence of linkage of a locus for total serum IgE levels to chromosome 5q in an isolated population consisting of 11 Amish pedigrees with an LOD score of 1.84 (58). These investigators did not report evidence favoring one single model of inheritance of total serum IgE levels. Meyers et al. reported evidence of recessive inheritance of high IgE levels in 92 Dutch families consisting of 539 individuals (53). They furthermore

observed linkage to a marker D5S436 on chromosome 5q31-q33, with a LOD score of 3.56, and a sib pair *P* value of 0.0003. Since a significant residual component was present in that study, two locus segregation and linkage analyses were performed. Evidence was found of a second major locus, unlinked to the locus on 5q (59). The first locus on chromosome 5q accounted for more than 50% of the variation in the total serum IgE level, while the second locus explained another 19% of the variation in these asthma families. Further studies are necessary to determine the chromosomal location of this second locus. These investigators have also reported linkage of BHR to markers in the same region on chromosome 5q31-33 (60), as shown in Fig. 2. These findings support the importance of this region in regulating aspects of the allergic and asthmatic phenotype. A mutation in the  $\beta_2$ -adrenergic receptor ( $\beta_2$ AR), localized at 5q, has been reported that could be responsible for part of the clinical heterogeneity in asthma (61). Asthma patients with this mutation were more likely to be steroid dependent. The same mutation had no consequences for subjects in the control group.

Two other regions have been linked to characteristics of the asthmatic and allergic phenotype. These are regions coding for the T-cell receptor (TCR) proteins, important because of their central function in the recognition of foreign antigens. Most of the TCR is made up of  $\alpha$  and  $\beta$  chains. The  $\alpha$  chain gene, consisting of the  $\delta$  chain region, is located at chromosome 14, while the  $\beta$  chain is coded at chromosome 7. Moffatt et al. described a genetic linkage from a sib pair analysis between TCR  $\alpha/\delta$  on chromosome 14 and specific IgE responses to common inhaled allergens in two independent populations. No linkage to TCR- $\beta$  was detected (62).

### Future directions

It will be a major challenge to identify the genes for complex multifactorial diseases such as asthma and allergy. Significant progress has been made in the

last decade. Linkage of loci for two important components of the asthma phenotype, total serum IgE and BHR to chromosome 5q, has been reported. Future research will focus on four major areas:

- 1) replication of the role of maternal inheritance of atopy reported on 11q
- 2) development of genetic models, such as multi-locus models, to investigate the inheritance of the complex genetic traits involved in asthma and allergy
- 3) completion of a genome-wide search for other linkages
- 4) fine mapping of the area(s) of interest on chromosome 5q because of the potential importance of this linkage.

These findings will be useful in analyzing the complex genetic relationship among susceptibility to BHR, allergic disorders, and asthma. Additional studies replicating previous studies and positional cloning studies will further define the genes important in the regulation of inflammatory processes in asthma and allergy. These combined genetic and clinical studies will lead to improved therapies and better techniques for early diagnosis of these disorders.

### Acknowledgments

The authors gratefully acknowledge support from the Dutch Asthma Funds and the National Institutes of Health (USA).

### References

1. HOLGATE ST, BEASLEY R, TWENTYMAN OP. The pathogenesis and significance of bronchial hyperresponsiveness in airway disease. *Clin Sci* 1987; 73: 561-72.
2. SEARS MR, BURROWS B, FLANNERY EM, HERBISON GP, HEWITT CJ, HOLDAWAY MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med* 1991; 325: 1067-71.
3. GERGEN PJ, WEISS KB. The increasing problem of asthma in the United States. *Am Rev Respir Dis* 1992; 146: 823-4.
4. PEAT JK, VAN DEN BERG RH, GREEN WF, MELLIS CM, LEEDER SR, WOOLCOCK AJ. Changing prevalence of asthma in Australian children. *BMJ* 1994; 308: 1591-6.
5. NINAN TK, RUSSEL G. Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years apart. *BMJ* 1992; 304: 873-5.
6. BURR ML. Epidemiology of clinical allergy. *Monogr Allergy* 1993; 31: 1-8.
7. HOPP RJ, BEWTRA AK, BIVEN R, NAIR NM, TOWNLEY RG. Bronchial reactivity pattern in nonasthmatic parents of asthmatics. *Ann Allergy* 1988; 61: 184-6.
8. SIBBALD B, TURNER-WARWICK M. Factors influencing the prevalence of asthma among first degree relatives of extrinsic and intrinsic asthmatics. *Thorax* 1979; 34: 332-7.
9. SIBBALD B, HORN MEC, BRAIN EA, GREGG I. Genetic factors in childhood asthma. *Thorax* 1980; 35: 671-4.
10. RISCH N. Linkage strategies for genetically complex traits. I. Multilocus models. *Am J Hum Genet* 1990; 46: 222-8.
11. RISCH N. Linkage strategies for genetically complex traits. II. The power of affected relative pairs. *Am J Hum Genet* 1990; 46: 229-41.

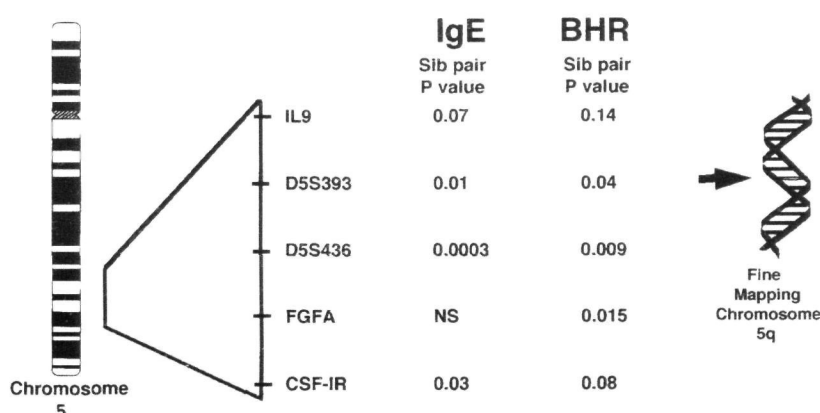


Fig. 2. Summary of results for linkage analysis for total serum IgE and bronchial hyperresponsiveness (BHR).

12. MEYERS DA, POSTMA DS, PANHUYSSEN CIM, AMELUNG PJ, LEVITT RC, BLEECKER ER. Genetics of asthma and COPD. V. Bronchitis. POSTMA DS, GERRITSEN J, eds. Assen, The Netherlands: Van Gorcum, 1994.
13. OTT J. Analysis of human genetics. Revised ed. Baltimore, MD: Johns Hopkins University Press, 1991.
14. MORTON NE. Sequential tests for the detection of linkage. *Am J Hum Genet* 1955; 7: 277-318.
15. DRACAPOLI NC, HAINES JL, KORF BR, et al. Genetic mapping. In: Current protocols in human genetics. John Wiley, 1994.
16. BYE MR, EWING JM, QUITTELL LM. Cystic fibrosis. *Lung* 1994; 172: 251-70.
17. BURROWS B, SEARS MR, FLANNERY EM, HERBISON GP, HOLDAWAY MD. Relationship of bronchial responsiveness assessed by methacholine to serum IgE, lung function, symptoms, and diagnosis in 11-year-old New Zealand children. *J Allergy Clin Immunol* 1992; 90: 376-85.
18. BURROWS B, SEARS MR, FLANNERY EM, HERBISON GP, HOLDAWAY MD. Relationship of bronchial responsiveness to allergy skin-test reactivity, lung function, respiratory symptoms, and diagnosis in 13-year-old New Zealand children. *J Allergy Clin Immunol* 1995; 95: 548-56.
19. CIBA GUEST SYMPOSIUM. Terminology, definitions, and classification of chronic pulmonary emphysema and related conditions. *Thorax* 1959; 14: 286-99.
20. AMERICAN THORACIC SOCIETY. Definitions and classification of chronic bronchitis, asthma, and pulmonary emphysema. *Am Rev Respir Dis* 1962; 85: 762-8.
21. MEDICAL RESEARCH COUNCIL. Definition and classification of chronic bronchitis for clinical and epidemiological purposes. *Lancet* 1965; *i*: 775-9.
22. BURROWS B, MARTINEZ FD, HALONEN M, BARBEE RA, CLINE MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med* 1989; 320: 271-7.
23. LEBOWITZ MD, BARBEE R, BURROWS B. Family concordance of IgE, atopy, and disease. *J Allergy Clin Immunol* 1984; 73: 259.
24. DUFFY DL, MARTIN NG, BATTISTUTA D, HOPPER JL, MATHEWS JD. Genetics of asthma and hay fever in Australian twins. *Am Rev Respir Dis* 1990; 142: 1351-8.
25. EDFORS-LUBS M. Allergy in 7000 twin pairs. *Acta Allergol* 1971; 26: 249-85.
26. HOPP RJ, BEWTRA AK, WATT GD, NAIR NM, TOWNLEY RG. Genetic analysis of allergic disease in twins. *J Allergy Clin Immunol* 1984; 73: 265-70.
27. HOPP RJ, TOWNLEY RG, BIVEN R, BEWTRA AK, NAIR NM. The presence of airway reactivity before the development of asthma. *Am Rev Respir Dis* 1990; 141: 2-8.
28. TASHKIN DP, ALTOSE MD, BLEECKER ER, et al. The Lung Health Study 3. The Lung Health Study: airway responsiveness to inhaled methacholine in smokers with mild to moderate airflow limitation. *Am Rev Respir Dis* 1992; 145: 301-10.
29. O'CONNOR GT, SPARROW D, WEISS ST. The role of allergy and nonspecific airway hyperresponsiveness in the pathogenesis of chronic obstructive pulmonary disease. State of the Art. *Am Rev Respir Dis* 1989; 140: 225-52.
30. ROORDA RJ, GERRITSEN J, VAN AALDEREN WMC, et al. Follow-up of asthma from childhood to adulthood: influence of potential childhood risk factors on the outcome of pulmonary function and bronchial responsiveness in adulthood. *J Allergy Clin Immunol* 1994; 93(3): 575-84.
31. BOUSHY HA, HOLTZMAN MJ, SELLER JR, NADEL JA. Bronchial hyperresponsiveness. *Am Rev Respir Dis* 1980; 121: 389-413.
32. POSTMA DS, DE VRIES K, KOETER GH, SLUITER HJ. Independent influence of reversibility of air-flow obstruction and non-specific hyperreactivity on the long-term course of lung function in chronic air-flow obstruction. *Am Rev Respir Dis* 1986; 134: 276-80.
33. SCHWARTZ J, GOLD D, DOCKERY DW, WEISS ST, SPEIZER FE. Predictors of asthma and persistent wheeze in a national sample of children in the United States. *Am Rev Respir Dis* 1990; 142: 555-62.
34. BURR ML, MISKELLY FG, BUTLAND BK, MERRETT TG, VAUGHAN-WILLIAMS E. Environmental factors and symptoms in infants at high risk of allergy. *J Epidemiol Commun Health* 1989; 43: 125-32.
35. ARSHAD SH, HIDE DW. Effect of environmental factors on the development of allergic disorders in infancy. *J Allergy Clin Immunol* 1992; 90: 235-41.
36. LONGO G, STRINATI R, POLI F, FUMI F. Genetic factors in nonspecific bronchial hyperreactivity. An epidemiologic study. *Am J Dis Child* 1987; 141: 331-4.
37. COOKSON WOCM, HOPKIN JM. Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q. *Lancet* 1989; *i*: 1292-5.
38. HOPKIN JM, COOKSON WOCM, YOUNG RP. Asthma, atopy and genetic linkage. *Ann N Y Acad Sci* 1991; 629: 26-30.
39. MOFFATT MF, SHARP PA, FAUX JA, YOUNG RP, COOKSON WOCM, HOPKIN JM. Factors confounding genetic linkage between atopy and chromosome 11q. *Clin Exp Allergy* 1992; 22: 1046-51.
40. COOKSON WOCM, YOUNG RP, SANDFORD AJ, et al. Maternal inheritance of IgE responsiveness on chromosome 11q. *Lancet* 1992; 340: 381-4.
41. HIZAWA N, YAMAGUCHI E, OHE M, et al. Lack of linkage between atopy and locus 11q13. *Clin Exp Allergy* 1992; 22: 1065-9.
42. RICH SS, ROITMAN-JOHNSON B, GREENBERG B, ROBERTS S, BLUMENTHAL MN. Genetic evidence of atopy in three large kindreds. No evidence of linkage to D11S97. *Clin Exp Allergy* 1992; 22: 1070-6.
43. LYMPANY P, WELCH K, MACCOCHRANE G, KEMENY DM, LEE TH. Genetic analysis using DNA polymorphism of the linkage between chromosome 11q13 and atopy and BHR to methacholine. *J Allergy Clin Immunol* 1992; 89: 619-28.
44. LYMPANY P, WELCH K, COCHRANE GM, KEMENY DM, LEE TH. Genetic analysis of the linkage between chromosome 11q13 and atopy. *Clin Exp Allergy* 1992; 22: 1085-92.
45. AMELUNG PJ, PANHUYSSEN CIM, POSTMA DS, et al. Atopy and bronchial hyperresponsiveness. Exclusion of linkage to markers on chromosome 11q and 6p. *Clin Exp Allergy* 1992; 22: 1077-84.
46. BRERETON HM, RUFFIN RE, THOMPSON PJ, TURNER DR. Familial atopy in Australian pedigrees: adventitious linkage to chromosome 8 is not confirmed nor is there evidence of linkage to the high affinity IgE receptor. *Clin Exp Allergy* 1994; 24: 868-77.
47. BRUDERMAN I, COHEN R, SHACHOR J, HOROWITZ I. Bronchial response to methacholine in parents of asthmatic children. *Chest* 1987; 91(2): 210-13.
48. TOWNLEY RG, BEWTRA MD, WILSON AF, et al. Segregation analysis of bronchial response to methacholine inhalation in families with and without asthma. *J Allergy Clin Immunol* 1986; 77: 101-7.
49. GERRARD JW, HORNE S, VICKERS P, et al. Serum IgE levels in parents and children. *J Pediatr* 1974; 85: 660-5.
50. MEYERS DA, BEATY WB, FREIDHOFF LR, MARSH DG. Inheritance of serum IgE (basal levels) in man. *Am J Hum Genet* 1987; 41(1): 51-62.
51. GERRARD JW, RAO DC, MORTON NE. A genetic study of immunoglobulin E. *Am J Hum Genet* 1978; 30: 46-58.

52. MEYERS DA, BEATY TH, COLYER CR, MARSH DG. Genetics of total serum IgE levels: a regressive model approach to segregation analysis. *Genet Epidemiol* 1991; 8: 351-9.
53. MEYERS DA, POSTMA DS, PANHUYSSEN CMI, et al. Evidence for a locus regulating total serum IgE level mapping to chromosome 5. *Genomics* 1994; 23: 464-70.
54. DIZIER MH, HILL M, JAMES A, et al. Detection of a recessive major gene for high IgE levels acting independently of specific response to allergens. *Genet Epidemiol* 1995; 12: 93-105.
55. MARTINEZ FD, HOLBERG CJ, HALONEN M, MORGAN WJ, WRIGHT AL, TAUSSIG LM. Evidence for mendelian inheritance of serum IgE levels in Hispanic and non-Hispanic white families. *Am J Hum Genet* 1994; 55(3): 555-65.
56. SANDFORD AJ, SHIRAKAWA T, MOFFATT MF, et al. Localisation of atopy and  $\beta$  subunit of high-affinity IgE receptor (Fc epsilon RI) on chromosome 11q. *Lancet* 1993; 341: 332-4.
57. SHIRAKAWA T, LI A, DUBOWITZ M, et al. Association between atopy and variants of the  $\beta$  subunit of the high-affinity immunoglobulin E receptor. *Nature Genet* 1994; 7: 125-30.
58. MARSH DG, NEELY JD, BREAZEALE DR, et al. Linkage analysis of IL4 and other chromosome 5q31.1 markers and total serum immunoglobulin E concentrations. *Science* 1994; 264: 1152-6.
59. XU J, LEVITT RC, PANHUYSSEN CMI, et al. Evidence for two unlinked loci regulating total serum IgE levels. *Am J Hum Genet* 1995; 57: 425-30.
60. POSTMA DS, BLEECKER ER, AMELUNG PJ, et al. Genetic susceptibility to asthma: bronchial hyperresponsiveness co-inherited with a major gene for atopy. *N Engl J Med* 1995; 333: 894-900.
61. REISHAUS E, INNIS M, MACINTYRE N, LIGGETT SB. Mutations in the gene encoding for the  $\beta_2$ -adrenergic receptor in normal and asthmatic subjects. *Am J Respir Cell Mol Biol* 1993; 8: 334-9.
62. MOFFATT MF, HILL MR, CORNELIS F, et al. Genetic linkage of T-cell receptor  $\alpha/\delta$  complex to specific IgE responses. *Lancet* 1994; 343: 1597-1600.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.