*Allergy 1997: 52: 256–273*
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ALLERGY
*ISSN 0105-4538*

**Review article**

# Susceptibility genes for allergy and asthma

Ruffilli A, Bonini S. Susceptibility genes for allergy and asthma. Allergy 1997: 52: 256–273. © Munksgaard 1997.

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Accepted for publication 22 November 1996

In studies of the genetics of allergy and asthma, it is possible to identify three different phases characterized by different methodological approaches and ultimate goals.

The first studies of *formal genetics* aimed at defining the heritability (excess risk for relatives) of allergy and asthma and selecting the best fitting model of inheritance (mono- or polygenic, dominant, codominant, recessive). Allergy and asthma and related traits, such as atopy, total serum IgE level, and bronchial hyperreactivity (BHR), were assessed in population, twin, and family studies. The results of these studies were often conflicting, although the hypothesis receiving strongest support was that of polygenic inheritance (1–7).

A second phase was stimulated by the advances in basic immunology which had clarified the role of the major histocompatibility complex (MHC; HLA in man) in immune recognition and by the studies reporting an association between several human diseases and specific HLA haplotypes (8). Interesting results in the field of allergy and *immunogenetics* were reported by Marsh (9), who documented the association between IgE and IgG antibody response to certain purified allergens and HLA class II alleles. On the other hand, studies on the association between HLA haplotypes and clinical allergy or sensitization to crude extracts were, in general, less convincing.

Recent progress in molecular biology and genetics has led to a third phase, aimed at directly *mapping on the chromosomes* susceptibility genes for allergy, asthma, and related traits. These studies involve complex methodologies and specific backgrounds, and the technical language of related papers is often difficult for clinicians.

The growing gap between basic and clinical scientists interested in the genetics of allergy and asthma is an obstacle to the global comprehension of a multifaceted problem. It is conceivable that molecular geneticists and statisticians may lose contact with the clinical phenotype while looking at sophisticated models of mapping and analysis, whereas doctors facing clinical aspects of these diseases come to simplistic extrapolations from evidence which, although sound, is confined to specific experimental models.

On the contrary, cooperation between clinicians and molecular geneticists is essential in tackling three main methodological issues related to the definition of allergy, asthma, and associated phenotypes and to the characterization of the study population.

Firstly, a clear definition of the clinical phenotypes of asthma and allergy and of the main disease-related traits is needed. The criteria commonly used to subdivide the study population are based on clinical phenotypes (asthma, rhinitis, conjunctivitis), or on disease-related traits defined by quantitative biologic parameters such as skin sensitization, total and specific IgE, BHR, and eosinophil count considered separately or cumulatively (e.g., atopy in studies where it is defined as the presence of high total IgE and/or skin test positivity [10–14]) or in conjunction with clinical phenotypes (e.g., atopic and nonatopic asthma).

Secondly, the overlapping among different clinical phenotypes should also be monitored, because, for example, a large variation in the extent of the overlapping between asthma and atopy can be introduced by the ascertainment criteria used to select the study population (15). In fact, regardless of the achievement of consensus on the definitions, the clinical phenotypes are heterogeneous with respect to the biologic traits (e.g., asthma includes both subjects with and without specific IgE). Similarly, each trait is present in patients with different clinical phenotypes as well as in normal subjects.

Thirdly, definition of the factors which can influence the clinical phenotypes and the disease-related traits is important. These factors, which should be monitored in the study population, include not only age, sex, and ethnic background but also environmental exposure which can modify the penetrance or mimic the effects (phenocopies) of predisposition genes. For example, it is well documented that the level of allergen exposure is important in determining the allergic phenotype and that infection by parasites (e.g., helminth) or viruses can modify the immunologic and tissue response.

Several reviews have recently been published on the genetics of allergy and asthma (16–22), including the study by Panhuysen et al. published in *Allergy* (23). This review aims to update information on the genetics of allergy and asthma from both the clinical and the genetic perspectives. This complex subject will be tackled under the following subdivisions:

1) a description of the main strategies currently used to map common disease genes
2) a working hypothesis correlating a broad spectrum of clinical phenotypes of allergy and asthma with postulated predominant pathophysiologic abnormalities
3) a review of the present status of the continually growing list of candidate genes and regions.

## Mapping strategies

Allergy and asthma, like coronary heart disease, Alzheimer's disease, diabetes, and hypertension, are common diseases which have a high prevalence in most human populations and show a clear familial aggregation. Genes controlling common diseases are susceptibility genes because the disease phenotype is usually controlled at more than one genetic locus and is also dependent on non-genetic factors which decrease gene penetrance and, in some cases, are sufficient to cause the disease (phenocopies).

Mapping common disease genes has proved to be difficult because there is no biunivocal relationship between a gene and the disease phenotype, as mutation at a specific locus is neither sufficient nor necessary to cause the clinical phenotype, and predisposing alleles may be present in nonaffected subjects and absent in patients (24). Heritability (the risk that a sibling from affected parents has the disease as compared to the risk of an unrelated matched individual from the same population; i.e., the relative risk for sibs) is much lower than in single-gene diseases: for example, it has been calculated that the relative risk is 500 for cystic fibrosis, 15 for type 1 diabetes, and only 2 for asthma (25).

As common diseases are multigenic, for mapping of disease genes, the effect of a single or a few genetic loci must be resolved from the complex of genes controlling susceptibility. Several strategies have been used for this purpose. In some cases, different clinical phenotypes correspond to mutation at different loci. For example, in Alzheimer's disease, mutations predisposing to the late- and to the early-onset disease have been mapped, respectively, at the amyloid precursor locus on chromosome 21 (a minor predisposing locus being at chromosome 19) and at a region of chromosome 14 (26). The selection of isolated communities as study populations can help to reduce the number of genes contributing to the development of a disease. In recently founded, genetically isolated communities, there is a high probability that a given disease involves the same genes in most of the patients because the founders introduced a limited number of alleles (founder effect), and polymorphism is further reduced by chance elimination of alleles over time (genetic drift) (27, 28).

### *Random genomic search and candidate gene approaches*

Random genomic search aims to screen the genome in order to identify regions linked with the disease traits. Candidate gene approach aims to screen limited chromosomal regions where genes that could be involved in the disease (potential candidates) have already been mapped. An example of random genomic search is the study by Cookson et al. (10) reporting the linkage between chromosome 11q13 markers and atopy, followed by the report that the gene encoding $Fc_{\varepsilon}R1$-β, a major candidate, mapped in that region (11). An example of candidate gene approach is the study by Marsh et al. (29), reporting the linkage between markers at chromosome 5q31–35 (a region which contains several potential candidates) and high serum total IgE level.

These approaches are complementary rather than alternative. If successful, both will lead to the identification of linked regions. When a linked

region has been identified through a random search, the next step is to search for a potential candidate gene (a candidate gene is a gene at a linked region which is postulated to influence the disease trait). It is obvious that the power of random genomic searches to detect regions of interest depends on the number and density of the markers used. This approach is likely to be used more frequently as the number of known markers is increasing, with the sequencing of the human genome, at a greater speed than the knowledge of disease mechanisms.

When a candidate region has been identified, it is important to narrow it down to approximately 1 cM (corresponding to approximately 1 Mb), an area containing 30–50 genes, by using additional markers (high-resolution mapping) to allow cloning and sequencing. The next step is usually the identification of allelic variants at candidate loci and the comparison of the variant frequency between patients and controls. Finally, the formal proof that a mutated variant is causing the disease is reached by defining the functional or regulatory abnormality of the encoded polypeptide and its relationship to the disease phenotype.

*Linkage and allelic association analyses*

Two approaches, both based on genetic linkage, are used for mapping.

In *gametic* (or meiotic) *recombination mapping*, commonly known as *linkage analysis*, linkage is defined by meiotic cosegregation (coinheritance) of alleles at a marker locus with a disease trait, in family studies.

In *linkage-disequilibrium mapping* (also known as *allelic association analysis*), linkage is defined by a statistical association between a specific allele at a marker locus and a disease trait, in case-control studies. The underlying concepts, the study designs, and the resolution powers are different in these two approaches (30).

The choice of one rather than the other is usually dictated by the polymorphism and density of the markers available, the characteristics of the population, and the magnitude of the study group.

*Gametic recombination mapping* is based on gametic disequilibrium, which describes, in a simple mendelian model of inheritance, the tendency of alleles at two closely located loci to be inherited as a block (e.g., if a marker locus is close to a disease gene, the allele of the affected parent will tend to segregate with the disease phenotype). The study population consists of families with affected members. In gametic recombination mapping (linkage analysis), a measure of the strength of a linkage is given by the estimate of the recombination fraction ($\theta$) between two loci.

Statistical approaches to measure linkage can be parametric or nonparametric.

Parametric methods, such as likelihood methods (lod score statistics), require specification of genetic parameters as they test whether the inheritance pattern fits a specific model (the best-fitting model of inheritance is usually obtained by previous segregation analysis). The likelihood method of linkage analysis consists of estimating the recombination fraction and testing whether an observed estimate is significantly smaller than 1/2. The statistical criterion for concluding that two traits are linked is based on the odds ratio of the probability of observing the distributional pattern of the two traits in a given set of families under the hypothesis of linkage (at a given $\theta$) to the same probability under the hypothesis of no linkage ($\theta=1/2$). Usually, the decimal logarithm of the odds ratio (L, lod score) is reported at several values of $\theta$ to obtain the maximum value of L. Conventionally, a maximum lod score of 3 is required to assert a linkage. Parametric methods are used in mapping genes for mendelian diseases and in analyzing mendelian traits of complex diseases. In mapping complex disease genes, they may lead to misleading results if the model of inheritance (penetrance, dominance, recombination fraction) is misrepresented (31).

Nonparametric (allele-sharing) methods measure the increase in allele sharing between affected individuals in pedigrees and do not require specification of genetic parameters. Chi-square statistics are used to test whether the observed values deviate from those expected under the assumption of independent assortment. These methods and especially their simplest form, sib-pair analysis, are used frequently in mapping genes for common diseases partly because the high disease prevalence facilitates the recruitment of affected sibs (32). When a marker is associated with a disease in case-control studies, it is possible to use the transmission disequilibrium test, a nonparametric analysis based on the assumption that an associated allele is more frequently transmitted from a heterozygous parent to an affected sib than a nonassociated allele. This test uses chi-square statistics (33).

The power to detect linkage (the probability of rejecting the null hypothesis of no linkage) of a given study design depends on several parameters. This resolution power should be specified to ensure correct interpretation of the results and especially to interpret negative results in independent replications. The most relevant parameters are the composition and magnitude of the study group, the density and heterozygosity of markers, and genetic

parameters such as ethiologic heterogeneity (presence of multiple loci), the presence of phenocopies (due to nongenetic causes), the disease allele frequency, and the mode of inheritance. For example, it has been calculated that, if the affected-sib-pair method is used, with a disease having a prevalence of 1%, sample sizes needed to detect with a power of 80% a gene linked in 50% of the families (allowing for decreased penetrance, phenocopies, and heterogeneity and for recombination rates of up to 10% between the disease gene and the marker gene) are 60 and 120 pairs, under the hypotheses of recessive and dominant inheritance, respectively (34).

*Linkage-disequilibrium mapping* (allelic association analysis) can be used to map a gene when multiple allelic variants at a locus are available. Linkage disequilibrium is a consequence of gametic disequilibrium and reflects the fact that, if the recombination frequency between two linked loci is low, gametic disequilibrium in that region tends to be maintained in the population (35).

In linkage-disequilibrium mapping, the study population consists of patients and controls (to decrease the possibility of biases due to stratification in the general population, controls are usually internal to the families). The association is detected by chi-square statistics to show that the proportion of a specific allele significantly increases in patients as compared to controls. As genetic recombination tends to erode gametic linkage and the number of recombinations increases over time, linkage disequilibrium between two loci also depends on the population history and tends to extend over a larger distance in younger than older populations (27, 28).

It is obvious that, as the chances of recombination between the two loci are greater in the population than in a family, linkage-disequilibrium mapping has a higher resolution power than gametic recombination mapping. Whereas the latter defines regions which are approximately within 1–2 Mb of a marker, linkage-disequilibrium mapping can define regions within up to 50 kb of a marker. In general, the sample size necessary to provide evidence of linkage disequilibrium between two loci is much smaller than that necessary for gametic mapping over the same interval (36). In gene mapping, gametic recombination is normally used to identify regions of interest and linkage disequilibrium to confirm the involvement of the candidate loci and/or to reduce the candidate region to a size accessible to cloning and sequencing. For example, Cookson et al. (10) have utilized gametic recombination to detect linkage of allergy-related traits to chromosome 11q markers and linkage disequilibrium (association between disease phenotypes and alleles encoding variant polypeptides) to confirm the $Fc_{\varepsilon}R1$-β locus as a candidate (11). A comprehensive approach, where gametic mapping and linkage disequilibrium have been used in parallel, has been used by Doull et al. (36), who screened 12 highly polymorphic markers at nine chromosomal regions (containing potential candidate genes) for linkage/association with allergy-related traits. Linkage and association studies may yield contrasting results. For example, a marker allele associated with an increased disease risk in the population may not cosegregate with the disease phenotype if the disease expression requires other genetic or environmental factors, or if the sample is too small.

## Allergic and asthmatic phenotypes

In allergy and asthma, clinical phenotypes are very far from the resolution power best for genetic analysis; i.e., the biunivocal relationship between a defined phenotype and a specific gene. The reasons for such complexity are numerous and reflect the multiple pathophysiologic abnormalities underlying clinical symptoms and ultimately the organization of the inflammatory network, where single molecular species transmit multiple signals and undergo modulation through redundant influences.

For didactic purposes, we suggest distinguishing four major pathophysiologic abnormalities, which are related to the clinical phenotypes of allergy and asthma:

1) enhanced allergen-specific IgE response
2) enhanced polyclonal IgE (and IgG4) synthesis
3) upregulation of inflammatory cells (increased number/releasability of mast cells, basophils, and mainly eosinophils
4) tissue (skin, lung, nose, and eye) hyperreactivity

These pathophysiologic abnormalities possibly undergo different genetic and environmental control (Fig. 1).

### *Enhancement of allergen-specific IgE response*

IgE antibody response to common allergens, as defined by positive response to skin tests, is usually considered to be a marker of atopy. The reported prevalence of skin test reactivity to common allergens in the general population (including nonsymptomatic subjects) is usually high. For example, in a large study of New Zealand children, Burrow et al. (37) reported that 46% of the subjects had skin test reactivity to one or more allergenic extracts. In addition, subjects without allergen-specific IgE may have IgG antibody to allergens (38) or be able to develop such a response upon administration of allergen by injection (39).

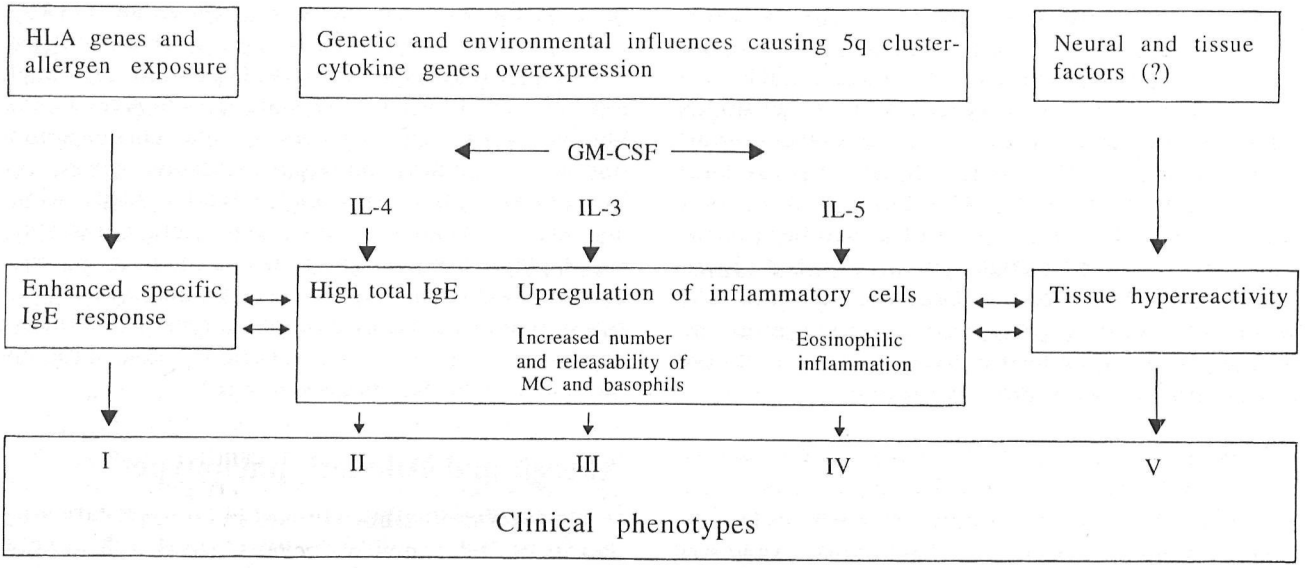



*Fig. 1.* Broad spectrum of allergic disease.

The cellular and molecular mechanisms controlling the immune recognition of antigens and antibody synthesis have been largely clarified: a crucial event is the formation of a ternary complex between T-cell peptide-specific receptors (TCR) and molecular complexes between peptides and the major histocompatibility complex (MHC; HLA in man) class II molecules. This event (cognate recognition) is the basis of the reported and well-documented association between specific HLA class II haplotypes and enhanced responsiveness to certain allergens (39, 40).

The power of a study to detect linkage/association of specific IgE with HLA class II genes may depend on the selection of the study population. For example, the selection of families through probands with clinical symptoms may increase the population prevalence of atopics with high total IgE in the study group, favoring overlapping between the effects of genes controlling total and

Table 1. Clinical phenotypes of asthma

**Type I**
*Example:* allergic asthma with monosensitization to grass
*Biologic traits:* low total serum IgE; early- but not late-phase reaction after bronchial allergen challenge; no eosinophilic inflammation out of season
*Diagnosis:* positive skin test/RAST; low ECP
*Treatment:* efficacy of cromones and bronchodilators; hyposensitization effective but often not needed

**Type II**
*Example:* allergic asthma in subjects with high sensitization to grass or sensitivity to perennial allergen
*Biologic traits:* high total serum IgE; late-phase reaction after bronchial allergen challenge; persistent eosinophilic inflammation
*Diagnosis:* positive skin test/RAST; high ECP
*Treatment:* cromones and topical steroids; indications for allergy avoidance and hyposensitization

**Type III**
*Example:* allergic asthma with multiple sensitization
*Biologic traits:* high total serum IgE; persistent eosinophilic inflammation and bronchial hyperreactivity
*Diagnosis:* etiologic diagnosis through skin test/RAST of limited values; positivity of inflammation markers; bronchial hyperreactivity
*Treatment:* cromones and topical steroids; hyposensitization of limited value

**Type IV**
*Example:* intrinsic asthma with high total serum IgE
*Biologic traits:* high total IgE; marked eosinophilic inflammation and hyperreactivity
*Diagnosis:* negative skin test/RAST but positivity of markers of allergic inflammation
*Treatment:* topical steroids

**Type V**
*Example:* exercise (only) induced asthma
*Biologic traits:* low total IgE; low ECP; bronchial hyperreactivity; negative skin test/RAST
*Diagnosis:* tests of nonspecific bronchial reactivity
*Treatment:* bronchodilators on request only

ECP: eosinophil cationic protein.

specific IgE. In addition to genetic factors, environmental conditions and, in particular, the level of allergen exposure play a significant role in the modulation of allergen-specific IgE level in atopics (41). Genetic and environmental confounding factors may explain why, in several studies, including studies on atopic twins, a significant genetic effect of HLA genes on specific IgE response has not been observed (42). These considerations suggest that linkage/association of HLA class II genes to specific antibody response may be stronger in study populations selected regardless of symptoms, with a well-controlled allergen experience.

*Enhanced polyclonal total IgE synthesis*

It is well known that a comparatively high level of total serum IgE (and IgG4) is usually associated with atopy, and increased levels of IgE (and IgG4) in secretions are observed in various forms of allergic diseases. However, high serum IgE levels are also present in some nonatopic subjects; for example, in some intrinsic asthmatics (43). Moreover, in many healthy subjects, in smokers (44), and in subjects with nonallergic diseases (such as some infections and proliferative and autoimmune diseases), high serum total IgE serum levels are not accompanied by the presence of IgE antibodies to common allergens.

Total serum IgE can be considered a composite parameter, consisting of an allergen-specific and a polyclonally induced fraction. In allergic subjects, there is evidence that the enhancement of Ig constant region (CH) gene switching by the expression of IgE and IgG4 isotypes reflects an abnormal expression of the cytokines interleukin (IL)-4 and IL-13 (45) encoded at chromosome 5q31–5q33 (5q cytokine gene cluster) (46), leading to the predominance of a Th2-type cytokine profile (47).

In allergic subjects, the interaction between HLA class II genes controlling the response to specific allergens and genes influencing polyclonal, IgE overproduction cannot easily be analyzed. For example, the sensitization to multiple allergens which usually accompanies high total IgE levels probably does not reflect the presence of many HLA-predisposing alleles but is a result of polyclonal activation of allergen-specific B cells. Very little is known about total IgG4 levels, a variable which could be interesting as an additional marker of 5q cytokine gene cluster overexpression (42, 48).

*Upregulation of inflammatory cells*

Studies of late-phase reactions after allergen challenge, as well as biopsy and mediator studies of allergic organ tissues, clearly indicate that asthma and allergic diseases are characterized by different degrees of eosinophilic inflammation (49, 50). Mast cells, activated eosinophils, and CD4-positive cells with a Th2 functional phenotype are increased in number, altered in distribution between the subepithelium and the epithelium, and show increased releasability (51). The genetic control of eosinophilia, suggested by experimental animal models, has been poorly investigated in man up to now. Genetic influences on releasability *in vitro* have been reported in atopic twins (52). The localization of genes encoding several molecules involved in allergic inflammation, such as C-C chemokines (53) or adhesion molecules (54), has also been elucidated, thus suggesting new candidate regions for the study of the genetics of allergy and asthma.

Of the abnormalities shown in Fig. 1, the upregulation of inflammatory cells is certainly the most heterogeneous with respect to underlying genetic and pathologic mechanisms. A major common factor is probably the overexpression of the 5q clustered cytokines, leading to a generalized Th-2 cytokine profile (IL-5-driven eosinophil differentiation, activation, recruitment, and survival and IL-3-driven mast-cell and basophil differentiation) (55).

*Tissue hyperreactivity*

Studies of target organ challenge with nonspecific stimuli (such as histamine) suggest that an increased responsiveness, independent of that induced by allergic inflammation, may represent a distinct basic abnormality.

The mechanisms leading to this basal hyperreactivity are still largely unexplored. Neural influences might well be important in this area. Nerve–mast-cell interactions (56), neuropeptides (57), and the complex neuroendocrine immune network (58) are new, relevant subjects for studies of genetic and environmental modulation of end-organ hyperreactivity. In asthma, for instance, genetic control of BHR, as suggested by experimental data, is strongly supported by the gaussian distribution of this variable in the general population (59).

Table 1 shows the relationship of these traits to clinical asthma, atopy (skin test sensitization), and inflammation as well as the usual therapeutic approaches.

Although close relationships exist among the pathophysiologic abnormalities reported in Fig. 1 (for example, total and specific IgE response influence each other, high sensitization increases the severity of inflammation and enhances tissue reactivity, etc.), their relative predominance can identify at least five different clinical phenotypes on the spectrum of allergic diseases (Fig. 1). The comprehensive spectrum of phenotypic abnormalities

represented in Table 1 may aid in the selection of patients for a genetic study. For instance, we suggest that it may be useful to subdivide asthmatic patients into five phenotypes having distinct pathologic and clinical features (Table 1), whereas their aggregation would probably introduce confounding factors and decrease the resolution power of genetic analyses. In fact, van Herwerden et al. (15), analyzing separately the subsets of asthma with and without atopy, have argued that chromosome 11q13 markers are linked with asthma even in the absence of atopy, a contention that could not be verified in other studies where asthma phenotypes had not been disaggregated. Moreover, Marsh et al. (29), who reported the linkage between high total IgE level and chromosome 5q markers, increased the power of their linkage analysis by selecting a subset of the study population with high total IgE but without atopy.

Finally, we suggest that, especially in asthmatic patients, different response to treatments with a well-defined major pharmacologic activity may represent an additional criterion of classification which may help to resolve the heterogeneity of phenotypes into discrete metabolic abnormalities.

## Candidate genes and regions

The identification of potential candidates for susceptibility to asthma and allergy is important in order to focus linkage analysis on selected chromosomal regions (candidate gene approach) and to narrow to specific loci fine mapping at candidate regions identified through genomic searches.

The most obvious criterion is to select genes whose products are known to mediate the immunoinflammatory reactions and airway tissue damage in asthma and allergy. Among these genes, those encoding the cytokines which characterize the T-helper (TH)-cell subsets TH2 (IL-4, IL-5, IL-10, and IL-13), and TH1 (IL-2, interferon-gamma [IFN-γ], and tumor necrosis factor-beta [TNF-β]) play a major role (60). Many cell types, in addition to TH cells, express these cytokines in response to various stimuli. The increased expression of TH2 cytokines is a crucial factor in determining the phenotypes of asthma and allergy (61–64).

Of the TH2 cytokines, IL-4 and IL-13 have largely overlapping biologic activities, are expressed at the sites of allergen challenge in patients with asthma, and deliver one of the main signals for the switch of the Ig CH gene to epsilon in B cells (65–67). IL-5, which is produced mainly by activated T cells and allergically triggered mast cells, is a major survival and differentiation factor for eosinophils, and its expression is enhanced in patients with bronchial asthma (68). IL-15, a newly identified cytokine, has T-cell and B-cell growth factor activity similar to that of IL-2 and can induce IL-5 production by T cells (69).

Many of the genes encoding TH2 cytokines are clustered at chromosome 5q31–35 (from centromere: IL-13, IL-4, IL-5, IL-3, IL-9, and IL-2 β-chain) (46). Candidate regions containing loci encoding cytokines and cytokine receptors potentially involved in susceptibility to allergy and asthma also include 12q22–24 (IFN-γ) (70), 16p12 (IL-4R) (71), 4q31 (IL-15) (72), and 6q16–22 (IFN-γ-R) (73).

The genes encoding factors regulating cytokine gene expression are also important candidates. These include the activator protein (AP)-1, which may mediate the inhibitory effect of glucocorticoids on cytokine expression (74), the nuclear factor (NF)-kB, whose expression is activated by specific cytokines (75), and T-cell-specific transcription factors such as NF-AT (76, 77).

The difficulty encountered in attempting to resolve allergy- and asthma-related phenotypes at the level of a single gene or a few genes probably depends on the complexity and multiplicity of the mechanisms regulating TH1/TH2 cytokine balance. The shift in favor of the expression of TH2 cytokines by T cells and other cell types can be caused by a number of factors, both genetic and environmental, and through several different metabolic pathways (62, 63). In addition, TH2 cytokines can influence allergy-related parameters through several pathways. For example, the predominance of the T-helper-cell subset with TH2 cytokine profile, which helps B-cell IgE synthesis, can reflect microenvironmental modification (e.g., by cytokines produced by other cell types, hormones, or growth factors) (62), but also TCR interaction with certain peptide-class II molecule complexes on antigen-presenting cells (APC) (78, 79). Similarly, IL-4 and IL-13 may induce Ig CH genes to switch to epsilon through different pathways, T-cell-dependent or T-cell-independent (e.g., CD40 engagement) (65). TH1/TH2 cytokine balance is also influenced by environmental factors whose effect, according to several studies, is crucial at the time before and around birth, when the allergic adult phenotype is defined (80, 81). The characteristic pleiotropic function of cytokines (a single cytokine influences different processes and hence different phenotypic traits), as well as their participation in the generation of regulatory cascades (63), adds further obstacles to the establishment of a biunivocal relationship between genes and phenotypes.

Candidate genes also include TCR and MHC genes which are involved in the cognate recognition of allergens. TCR alpha and delta loci map at chromosome 14q12 (82, 83), beta loci at

chromosome 7q35) (84), and gamma loci at chromosome 7p15 (85), whereas the HLA complex maps at chromosome 6p21.3, in a region also including TNF-α and -β (86).

Regions containing genes involved in predisposition or protection can be pinpointed by positive or negative association of allergy with clinically unrelated genetic diseases, a finding which may indicate contiguity of the loci involved or reflect common genetic etiology. As the number of mapped disease genes is increasing, this contribution may become more important in time. For example, the positive association of alpha thalassemia with an X-linked mental retardation syndrome has been explained by a mutation at a locus which encodes a regulatory protein acting on several contiguous genes, including the α-globin genes (87). A decreased prevalence of asthma has been observed in subjects heterozygous for a frequent allele at the cystic fibrosis transmembrane regulator protein locus (chromosome 16p), which in homozygous condition is the main cause of the disease (88). The prevalence of asthma is also lower in heterozygous carriers of familial Mediterranean fever, a disease common among North African Jews (89). It has also been observed that bronchial asthma occurs seldom or in a mild form in diabetic patients and that in diabetic rats sensitized against ovalbumin the cell yields from bronchoalveolar lavage after antigen challenge are lower than in normal controls (90).

The identification of candidate genes in man may be helped by studies with mouse and rat models, where asthma-like phenotypes have been described and inbred strains are available. Homology maps between the mouse and human chromosomes are available, and linkage at certain regions is conserved in evolution. In mice, high IgE antibody production is inherited as a dominant autosomal trait (91). The gene or genes responsible for high/low IgE responsiveness have not been identified, although one hypothesis is that inability to produce IgE is associated with the absence of CD4+ NK1.1+ T cells, a T-cell subset which produces IL-4 upon stimulation with superantigen or with anti-CD3 antibody, and which could be important in the initiation of the immune response (92). In mice, it has been shown that the tendency to produce a TH1- or TH2-type response to certain peptides (93, 94) and to produce IFN-γ in response to several antigens (95) is influenced by MHC genes. More recently, it has been reported that the genetic susceptibility of certain inbred mouse strains to *Leishmania* infection, mediated by a predominant TH2 response, reflects an impaired ability of T cells to produce IL-12 upon antigen stimulation rather than an overexpression of TH2 cytokines (96). The genetics of mouse phenotypes related to human allergy has also been investigated. In the A/J and C57BL/6J strains (which have an asthmatic and a normal phenotype, respectively), De Sanctis et al. (97) reported the linkage of asthma traits to markers at chromosome 2 (near the IL-1 β-chain locus) and at chromosome 15 (near the IL-2β receptor, IL-3$\beta_1$ and IL-3$\beta_2$, and platelet-derived growth factors loci). In the C57BL6 and DBA/2 strains, Levitt & Mitzner (98) reported a modest linkage of atracurium-induced bronchoconstriction (atracurium is a nondepolarizing muscular blocker which induces rare idiosyncratic bronchospasm in man) to chromosome 13 markers (a region homologous with human chromosome 5q). Huang et al. (99) described airway hyperresponsiveness to acetylcholine, a feature of asthma, in mice homozygous for a null mutation in the gene encoding the beta 6 subunit of integrin beta, suggesting that this protein, expressed only in epithelial cells, might contribute to the development of inflammatory diseases of the lungs and skin.

*Chromosome 5q31–5q33*

This region contains a cluster of genes encoding TH2 cytokines (from the centromere, IL-13, IL-4, IL-5, IL-3, and IL-9) (46) and many other potential candidates, including the $\beta_2$-adrenergic receptor ($\beta_2$-ADR), a transmembrane molecule involved in signal transduction which is a target in the pharmacologic treatment of asthma (100). Other candidate genes encode transcription factors, such as IFN regulator factor-1 (IRF-1), which controls IFN-inducible gene expression (101), and the early growth factor response-1 (EGR-1), which specifically links B-cell receptor signal transduction to the induction of intercellular adhesion molecules important for T-cell-dependent B-cell activation and for B-cell function as APC (102). The 5q31–5q33 region also contains genes encoding factors and receptors for the growth, differentiation, and survival of macrophages, such as granulocyte macrophage colony-stimulating factor-2 (CSF-2) (103), the receptor for colony-stimulating factor-1 (CSF-1), which binds CSF-1, a regulator of the survival, proliferation, and differentiation of mononuclear phagocytes, and the macrophage marker CD14, whose expression is increased in extrinsic allergic alveolitis (104).

Marsh et al. (29) analyzed 5q31–5q33 markers for linkage to total serum IgE level and to antibody response to common allergens. The study group consisted of 11 large families (349 sib pairs), selected from an isolated Pennsylvania Amish community for having at least one child with atopy (defined as the presence of detectable serum IgE

to inhalant common allergens). Of the eight markers used, four were linked to high total serum IgE level, but not to allergen-specific IgE (the *P* value showed two peaks at IL-4-R1 and at D5S399 marker loci) ($P<0.0069$ and $<0.0020$, respectively). That the linkage was to the total IgE level only was confirmed by showing that the association was more significant in a subset of 128 nonatopic sib pairs ($P<0.000\,004$ for IL-4R1 and $<0.000\,78$ for D5S399). The authors suggested that the differential gene control between total and allergen-specific IgE observed reflected the difference between the underlying mechanisms, as the first parameter depends mainly on polyclonal B-cell activation and the second on immune recognition of allergens mediated by cognate T–B-cell interaction (28).

Meyers et al. (105) analyzed a 6-Mb region, telomeric to IL-9 and including the $\beta_2$-ADR, for linkage to total serum IgE and to BHR, using eight markers. The study population consisted of 92 Dutch families, selected through parents who had participated in an earlier study on symptomatic asthma, and who, at that time (1962–70), had been tested for skin test reactivity, eosinophil count, pulmonary function, and BHR. Evidence of linkage of region markers to high total serum IgE level was obtained by sib-pair and lod score analysis. The most significant linkage was to the marker D5S436 (lod score=3.56 at q=0.09; $P<0.0003$ in the sib-pair analysis). Segregation analysis suggested recessive inheritance of high total IgE levels with a gene frequency of 0.41 for the low IgE allele. A subsequent report (106) documented the linkage of D5S436 ($P<0.009$ in the sib-pair analysis) and adjacent markers to BHR. The serum total IgE level appeared to be influenced by other genetic/environmental factors, in addition to those common to BHR, as, in sib pairs concordant for total IgE levels, BHR values were not correlated, whereas, in sib pairs concordant for BHR, total IgE levels were correlated. Additional support of the hypothesis of a second major locus regulating total IgE level unlinked to the 5q locus came from segregation analysis (107).

A potential candidate locus for susceptibility to asthma at chromosome 5q31–31 is the $\beta_2$-ADR. $\beta_2$-ADRs are transmembrane proteins which, upon binding agonists, activate G protein-mediated signal transduction. $\beta_2$-ADR agonists are used in pharmacologic treatment of asthma to relax airway smooth muscle and to protect the airways from constrictor stimuli in challenge tests. A relationship between defects in the receptor function and asthma has not been proved, but a series of recent reports postulates a function of $\beta_2$-ADR in the modification of BHR and in the definition of certain asthmatic phenotypes (108–114). Reishaus et al. (112) described three common allelic variants of $\beta_2$-ADR, with the substitutions Gln27/Glu and Arg16/Gly and the double substitution Gln27/Glu+Arg16/Gly. They also reported that the variant frequency did not differ between patients (51 subjects) and controls (56 subjects), but, when the patients were subdivided according to the use of therapeutic agents, there was a modest excess of subjects with Gly16 ($P<0.03$) in the subset on corticosteroid and immunization therapy. Subsequent studies documented that the mutations altered agonist-promoted receptor downregulation, which was enhanced in the variant Gly16 and in the double variant and decreased in the variant Glu27, as compared to the wild type (108, 109). The authors then attempted to correlate these characteristics with the asthma phenotype of the patients. Prompted by a former report of a characteristic pattern of nocturnal decrease in $\beta_2$-ADR expression in patients with nocturnal asthma (111), they compared variant prevalence between patients with nocturnal and with diurnal asthma (23 and 22 patients, respectively) and reported a significant excess of subjects homozygous for the Gly16 variant in the former ($P<0.0001$), a finding which they attributed to the enhanced agonist-promoted downregulation characteristic of this variant (112). Finally, in a study group of 65 patients with mild to moderate asthma and on oral steroid therapy, they investigated whether the resistance of the Glu27 variant to downregulation was correlated with a decreased lower airway reactivity in asthmatic patients with this genotype, and reported an increase in the geometric mean of methacholine provocative dosage in subjects homozygous for Glu27 ($P<0.035$), as compared to subjects homozygous for the wild-type receptor (114). It is difficult to evaluate the latter report, given the modest statistical significance and also because the proportion of subjects with the double mutation, previously reported to be associated with increased downregulation (108), was not indicated.

### *Chromosome 6p21.3*

The major histocompatibility complex (MHC; HLA in man) is a family of highly polymorphic genes located at chromosome 6p21.3. MHC class II products are membrane proteins involved in the presentation of peptides to CD4+ T-helper cells. HLA class II alleles are associated with several autoimmune diseases (reviewed by Kostyu [8]), with antibody response to certain autoantigens (115, 116), to hepatitis B virus surface antigen (117), and to numerous allergens (5, 9, 17). In allergic subjects, antibody response to several pollen allergens, to mold allergens (*Alternaria*), and to

insect allergens (chironomids) (118–127) is associated with class II alleles. The strongest association is that between HLA-DR2 and IgG and IgE antibody response to Amb a 5, a minor *Ambrosia* allergen of little clinical relevance, as reported by Marsh et al. (118–120). Absence of antibody response to the bee-venom allergen mellitin (128), and to mountain-cedar pollen allergens (129), is also associated with class II alleles. Recent studies reporting the linkage of HLA-DR and -DQ loci to responsiveness to the mold allergen Alt a 1 and to the cat allergen Fel d 1 (130) have confirmed the results of the association studies.

The contribution of HLA class II genes to the risk of developing allergy is generally modest but is more significant in the subset of patients who are monosensitized and/or have low serum total IgE levels (121, 126, 127).

The relationship between class II genes and asthma has also been studied. A decreased prevalence of DPB1*0401 in asthmatic patients has been reported in two independent studies (131, 132). The primary association may be with atopy, as suggested by the study of Caraballo & Hernandez (133), who reported the linkage of class II loci with asthma ($P<0.0001$) in patients with skin test positivity to the mite *Dermatophagoides farinae*, but not in patients with intrinsic asthma.

In mouse inbred strains, the ability to mount an antibody response of any isotype to certain antigens is inherited as a dominant trait and cosegregates with defined MHC class II alleles (reviewed by Berzofsky [134]). Of more specific interest to allergists is a series of recent reports which suggest that MHC genes control TH1/TH2 subset balance in the mouse response to certain peptides (93–95) and to the hapten trinitrophenyl (135). It has also been reported that the guinea pig asthma phenotype is associated with MHC class II alleles (136).

The control of MHC genes on specific immune responsiveness to protein antigens is believed to reflect MHC-dependent restriction of T-helper-cell response (134). It has been argued that this restriction may reflect the ability/inability of MHC allelic products to bind peptides deriving from antigen processing, or on the presence/absence in the available T-helper-cell repertoire of TCRs specific for the peptide-class II product complex (117). It is possible that additional mechanisms (e.g., constraints in T–B-cell reciprocal interaction) are also important (134).

Two additional potential candidate genes map within the HLA region: the closely linked lymphokines TNF-α and TNF-β. TNF-α is a mast-cell-derived cytokine which upregulates the expression of IL-6, is a major mediator of inflammation, and is present in the bronchial lavage fluid of patients with diseases associated with eosinophilia. TNF-β plays a role in the destruction of tumor cells and virally infected cells and is an upregulator of TNF-α expression (137–139). A preliminary report in two large British and Australian study groups indicates that a TNF-β promoter polymorphism, known to be associated with upregulation of TNF-β gene expression, is significantly increased ($P<0.003$) in subjects with asthma, regardless of atopy (140). Another candidate for susceptibility to asthma is the endothelin-1 (EDN-1) locus, which maps distal to the HLA region and encodes a peptide with potent vasoactive properties (141).

### *Chromosome 11q13*

The chromosome 11q13 region received attention when, in a random genomic search with a limited number of markers, Cookson et al. (10) reported the linkage of the region marker D11S97 to atopy, in a study group of seven large families (the reported load score was 5.6 at $\theta=0.1$, but the major contribution came from a single family) (10). Subsequent reports (11, 142–144) analyzed a larger population of 64 nuclear and extended families, recruited partly from clinics through a proband with atopic asthma or rhinitis and partly through advertisement. Of the subjects, 63% were atopic, according to the broad definition used (positive skin test or RAST and/or elevated total serum IgE level), and 79% had symptoms (57% had asthma) (142). The linkage of atopy with D11S97 and other centromeric 11q13 markers was confirmed but could be detected only in families recruited through clinics (143). The initial hypothesis that atopy is inherited as an autosomal dominant trait (145), which conflicted with the results of several previous segregation and linkage studies (1–7, 146), was abandoned. The postulated susceptibility allele was inherited from the maternal chromosome, as shown by the fact that when the data were analyzed by the affected sib-pair method, the linkage was detected in siblings sharing maternal but not in those sharing paternal alleles. Moreover, with the lod score method, the load score increased from 3.88 (at $\theta=0.25$) to 5.21 under the hypothesis of unequal rates of maternal and paternal recombination. As excess sharing of maternal alleles occurred regardless of the atopic status of the mother, the authors suggested maternal expression of imprinted genes (paternal imprinting (144, 147). The mapping of the locus encoding the β-chain of the high-affinity IgE receptor ($Fc_\varepsilon RI\beta$) at the 11q13 region was also reported (11). The presence of the $Fc_\varepsilon RI\beta$ locus at this region had been suggested by the presence of the locus encoding the proliferation/differentiation factor CD20 (148), which, in the mouse, was linked to the $Fc_\varepsilon RI\beta$ locus (11).

$Fc_\varepsilon RI\beta$ is expressed as either $(\alpha)-(\gamma)_2$ trimer or $(\alpha)-(\beta)-(\gamma)_2$ tetramer and plays a central role in the initiation of the allergic response. Its cross-linking on the mast-cell surface leads to cell activation and to the synthesis and release of mediators of anaphylaxis and IL-4 (reviewed by Ravetch & Kinet [149]). The β-chain is not essential for ligand binding nor for signal transmission, but contains an antigen receptor activation motif (ARAM), which binds an Src family tyrosine kinase, regulating the phosphorylation of several substrates (150). Very recently, it has been shown that, whereas the gamma-dimer functions as an autonomous activation module, the beta-unit functions as a signal amplifier (151). The candidate region was subsequently narrowed to the interval between cCI11-319ca and the centromeric microsatellite marker $Fc_\varepsilon RI$-bca (mapping within the intron 5 of $Fc_\varepsilon RI\beta$) (152). A long-range restriction map, spanning 2.8 Mb and including $Fc_\varepsilon RI\beta$ and CD20 loci defining the order and distance between closely spaced markers was obtained, and a genetic linkage map based on a model of maternal inheritance was presented (153, 154).

The linkage of chromosome 11q D11S97 and $Fc_\varepsilon RI$-bca markers to atopy and the maternal mode of inheritance was confirmed in four large Japanese families with members with severe atopy (maximum two-point lod score of 9.35, under the assumption of unequal rates of maternal and paternal recombination) (155, 156). Collee et al. (157), in 26 nuclear families with sib pairs with asthma and atopy, reported increased sharing of parental alleles at D11S97 ($P<0.01$) and at PYGM ($P<0.001$) marker loci (but not at $Fc_\varepsilon RI$-bca locus), whereas no significant difference was observed in the proportion of maternal and paternal alleles. A partial confirmation also came from van Herwerden et al. (15), who, in a large Australian study group, recruited for asthma and/or atopy from a general population screening (123 affected sibling pairs), analyzed the linkage of $Fc_\varepsilon RI$-bca to BHR, high total IgE, and atopy. Their conclusions are partially different from those of Cookson's group, in that the marker was not linked to atopy in the subset of atopics without BHR and excess of maternal alleles was not observed. Other groups, generally in small populations, did not detect linkage of atopy with D11S97 and $Fc_\varepsilon RI$-bca or with closely located 11q13 markers (150–162). In general, it is difficult to evaluate the failure to confirm a reported linkage in a different population, because, even if the resolution power of the two studies is comparable and similar criteria of ascertainment are used, the relative frequency of disease-associated alleles may vary among different study populations.

In order to identify allelic variants of the $Fc_\varepsilon RI\beta$ polypeptide, the seven exons of the $Fc_\varepsilon RI\beta$ genes from several atopic patients were screened for missense mutations, leading to the identification of three polypeptide variants with the substitution Ile181/Leu, the double substitution Ile181/Leu + Val183/Leu (both in the fourth transmembrane domain of the polypeptide), and the substitution Glu237/Gly (close to the ITAM motif) (12–14). In an Oxford clinic patient sample (163 patients, unselected for atopy), Shirakawa et al. (12) reported a prevalence of 15.3% for the Leu181 variant (Leu183 was not found) which was associated with high total serum IgE level ($P<0.01$) and with positive RAST to grass ($P<0.03$) (but not to mite). They also reported that, in 10 families selected through young atopic asthmatic probands, Leu181 was highly associated with atopy ($P<0.0001$) and maternally inherited. Hill et al. (13) analyzed 1004 members of 230 young nuclear families from the general population of Busselton, Australia, and reported a prevalence of 4.5% of the Leu181/Leu183 (Leu181 was not found) and a prevalence of atopy of 45%. Leu181/Leu183 was associated with positive skin prick test reaction to house-dust mite (HDM) and to grass pollen ($P<0.0001$ and $<0.03$, respectively) and with BHR ($P<0.03$) only when maternally inherited (no significant association with high total IgE level was observed). In a recent paper, Hill et al. (14) reported that, in the same study population, the variant Gly237 had a prevalence of 5.3% and was associated with increased wheal diameter in the skin test response to grass pollen and HDM ($P<0.0004$ and $<0.04$, respectively) and to BHR ($P<0.0009$), but not to high total IgE level. In a Japanese population of 14 extended and nuclear families recruited through atopic asthmatic probands and in 120 unrelated random individuals, Hizawa et al. (158) reported the association of a variant at the marker locus D11S97 with high total IgE level in the families and in the population ($P<0.001$ and $<0.05$, respectively).

Other groups have been unable to find the Leu181 and Leu181/Leu183 variants in their study populations. Hizawa et al. (163) did not detect Leu181 in their Japanese family study population. Hall et al. (164) did not detect either variant in the screening of 65 asthmatic subjects, and Martinati et al. (165) did not detect Leu181 in 45 Italian families and in 42 children with atopic asthma.

Another candidate is the CC10 gene, which has recently been mapped at chromosome 11q13. Its product is the Clara cell, a 10-kDa protein which has anti-inflammatory and immune-modulating properties, as it inhibits phospholipase A, the rate-limiting enzyme in the synthesis of prostaglandin and leukotriene mediators, and which may be important in modulating inflammation within the airways (166).

Table 2. Linkage between chromosomal region markers and allergy-related traits (family studies)

| Region (marker) | Candidate locus | Linked trait | (References) |
|---|---|---|---|
| 6p21.3 | HLA | Allergen-specific IgE | (9, 38, 39, 118–130) |
| 5q31–33 | Several loci | Total serum IgE | (28, 105–107) |
| | | BHR | (105–107) |
| 11q13 | $Fc_eR1$-β | Atopy* | (11, 12, 142–145) |
| | | BHR, total serum IgE | (15) |
| | | Asthma, atopy* | (176) |
| 13 (D13S153) | | Atopy | (176) |
| 16 (D16S289) | | Atopy*, asthma | (176) |
| 4 (D4S426) | | Total serum IgE*, atopy* | (176) |
| 14 | TCR-α, TCR-δ | Specific IgE Ab, total IgE | (178) |

* Linkage to maternal meiosis.

*Chromosome 14q12*

The T-cell receptor complex (TCR/CD23) is composed of multiple subsunits and delivers one of the two signals essential for T-cell-mediated induction of B-cell isotype switch to IgE (65). The subunits include TCR-α–β or, less frequently, γ–δ chains which confer to the complex the property of specific recognition of HLA class II molecule-peptide complexes on the membrane of APC. The TCR repertoire derives from the somatic assembly of TCR α, β, γ, and δ genes from constant (C), variable (V), diversity (D), and joining (J) segments and from their clonal expression. Studies in man and in mice suggest that the cytokine profile of T-helper cells may be correlated to the TCR V gene expressed (166) and, conversely, that certain microenvironmental cytokines can influence the preferential expansion of T-cell clones with certain TCRs (167). A restriction of the TCR repertoire and the preferential usage of certain Vβ and Vα families has been reported in the response to some allergens (168–171), as well as to certain autoantigens, but a role of genetic factors has not been demonstrated (172).

TCR allelic polymorphisms have been identified, and there is evidence that, perhaps in synergy with HLA class II alleles, they contribute to genetic susceptibility to certain autoimmune diseases (173–175). Moffatt et al. (175) investigated whether TCR alleles contribute to susceptibility to allergy. Two TCR-α and two TCR-β microsatellite polymorphisms were assessed for linkage to high total serum IgE level and to allergen-specific IgE in Australian and British study groups (66 nuclear and five extended British families identified through probands with asthma or rhinitis and 88 Australian nuclear families from the general population of Busselton). TCR-α gene cluster maps at chromosome 14q12 and includes part of the Vδ gene; TCR-β gene cluster maps at chromosome 7q35. Although there were minor differences between the two study populations, when analyzed cumulatively, TCR-α locus markers were linked to IgE antibody response to Der p 1 and Fel d 1 ($P<0.0002$ and 0.000 06, respectively). There was also a significant linkage to Der p 2- and grass-allergens-specific IgE antibody and to high total serum IgE level ($P<0.02$, 0.002, and 0.002, respectively).

*Genomic searches*

Doull et al. (36) have recently reported the results of a genomic search aimed at detecting linkage/association at nine regions selected because they contained potential candidate loci (11q13–13.5, 16p12.1–11.2, 19q13.3–13.4, 1q.21–23, 9p22, 13q22–24, 22q13, 5q 23–31, and 6p21.3). Twelve highly polymorphic markers were screened for linkage to atopy, total serum IgE, and BHR in a study group of 131 British families, selected for children aged 11–14 years, regardless of allergy. No evidence of linkage was obtained, but the presence of susceptibility genes at chromosome 5q and 11q candidate regions was confirmed. A chromosome 5q marker allele was associated with high serum total IgE level ($P<0.025$), but not with BHR, and two 11q13.5 marker alleles were associated with BHR ($P<0.003$) and with high total serum IgE level ($P<0.023$), respectively (the finding of an association in the absence of linkage is not unusual and may reflect the greater sensitivity of linkage-disequilibrium mapping).

More recently, Daniels et al. (176) reported the results of a random genome-wide search and the identification of new linked regions (potential candidates are not indicated). In a study population consisting of 80 nuclear families from a general population sample from Busselton, Australia, unselected for atopy, 269 markers were screened for linkage to total serum total IgE, skin test, peripheral blood eosinophil count, BHR, and atopy

Table 3. Association between alleles at marker loci and allergy-related traits (case-control studies)

| Region | Marker/ allele | Associated trait | *P* | (References) |
|---|---|---|---|---|
| 11q13 | $Fc_{\varepsilon}R1$-β/L181 | Total serum IgE | <0.01 | (12) |
| | | RAST to grass | <0.03 | |
| | | Atopy | <0.0001 | |
| | $Fc_{\varepsilon}R1$-β/L181/L183 | ST to HDM | <0.0001 | (13) |
| | | ST to grass | <0.03 | |
| | | BHR | <0.03 | |
| | $Fc_{\varepsilon}R1$-β/G237 | Ab to grass | <0.0004 | (14) |
| | | Ab to HDM | <0.04 | |
| | | BHR | <0.0009 | |
| | D11S97 | Total serum IgE | <0.001 | (159) |
| | D11S527/68 | BHR | <0.0003 | (36) |
| | D11S534/253 | Total serum IgE | <0.003 | (36) |
| 6p21.3 | TNF-β promoter polymorphism | Asthma | >0.003 | (176) |
| 5q31–35 | IL-9/118 | Total serum IgE | <0.0003 | (176) |

ST: skin test positivity.

(defined by a combination of skin test and RAST reactivity and high total IgE level). Regions showing evidence of linkage were reanalyzed with additional markers. The markers which showed again evidence for linkage ($P<0.001$) were tested in a second population of 77 nuclear and extended British families (previously used to map atopy on chromosome 11q13 (106, 107). Chromosome 11 $Fc_{\varepsilon}RI$-bca and a chromosome 16 marker were linked to asthma ($P<0.005$ and $P<0.05$, respectively), and a chromosome 13 marker was linked to atopy ($P<0.005$). When maternal meiosis only was considered, chromosome 11 $Fc_{\varepsilon}RI$-bca and chromosome 16 markers were linked to atopy ($P<0.0001$ and <0.001, respectively) as well as to asthma ($P<0.000\,01$ and <0.001, respectively), and a chromosome 4 marker was linked to atopy ($P<0.05$) and to high total IgE level ($P<0.001$). The extent of the maternal effect to several chromosomal regions makes the initially advanced hypothesis of paternal imprinting (144, 147) unlikely and favors an explanation based on the influence of immunologic interactions between mother and child on the adult phenotype.

Table 2 summarizes the results of linkage analyses and lists the candidate chromosomal regions and genes. Table 3 summarizes the results of several studies on the association between variants at marker loci and allergy traits. As it is possible that reported linkage/association with the postulated candidate genes reflects linkage disequilibrium with other closely located loci, it is important to detect polymorphic variants, in order to achieve finer recombination mapping and to associate structural and/or regulatory abnormalities of the encoded polypeptides with allergy and asthma traits.

Taken together, these studies indicate that a single trait is controlled at more than one locus, as it is associated with or linked to different chromosomal regions. The identification of candidate regions at chromosomes 11q13 and 5q31–33 is confirmed by several independent studies, but not by others. These contrasting results probably reflect the presence of many susceptibility genes, each having a relatively modest effect. For resolution of the effect of single genes, a useful strategy is to study genetically isolated communities, such as the population of the south Atlantic island of Tristan de Cunha (28) or the Amish communities (29), because in these populations the polymorphism is reduced (by the founder effect and genetic drift), and the number of loci involved in allergy and asthma may be relatively small.

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