

I. Overview, epidemiology, and basic science of systemic allergic inflammation

Evidence for common genetic elements in allergic disease

Kathleen C. Barnes, PhD *Baltimore, Md*

Genetic research in allergic disease has focused primarily on asthma and its associated phenotypes (eg, total IgE), with very little attention given to the presence or absence of concomitant allergic diseases, especially allergic rhinitis and atopic dermatitis. Because asthma, allergic rhinitis, and atopic dermatitis share common systemic characteristics, it is reasonable to propose that a number of susceptibility genes could contribute to the allergic process regardless of the specific clinical phenotype. Consequently, the many genetic linkages previously reported for asthma may not be specific for asthma per se but rather may reflect an overall predisposition for allergic disease. Finally, epidemiologic data suggest that asthma and allergic rhinitis represent a continuum of disease, whereby those individuals with less severe disease will express rhinitis without asthma and those individuals with more severe disease express more than 1 phenotype. Alternatively, it is plausible that, in addition to the "allergic disease genes," there are "phenotype-specific genes" or possibly certain combinations of susceptibility genes (eg, gene-gene interactions) that contribute to the expression of asthma, allergic rhinitis, or atopic dermatitis. (*J Allergy Clin Immunol* 2000;106:S192-200.)

Key words: Allergic rhinitis, asthma, phenotype

It can be argued that, although a number of genes seem to be important for each of the clinical allergic phenotypes (eg, asthma, allergic rhinitis, and atopic dermatitis), other genes are associated with allergic disease in general. We hypothesize that there are different categories of genes that control the expression of allergic disease, which include, but are not limited to, (1) immune response genes, which determine the ability to produce specific (cognate) immune responses that are dictated in part by exposure to environmental factors, such as indoor allergens; (2) nonspecific (noncognate) immune response genes, which determine the overall propensity to synthesize IgE of any specificity; and (3) clinical phenotype-specific genes (eg, asthma, allergic rhinitis, or atopic dermatitis), which may be separable from those that

Abbreviations used

ASP: Affected sib-pair
BHR: Bronchial hyperreactivity
FCER1B: High-affinity IgE-receptor gene
MCC: Mast-cell chymase

determine overall atopic disease. Limited data are available to support or refute the hypothesis that there is a common genetic basis for allergic disease. My objective was to address 3 basic questions: (1) Do the linkage and association data support the hypothesis that there may be several categories of genes that contribute to the overall susceptibility of allergic disease? (2) Have appropriate studies been conducted to address this hypothesis? (3) Are there data to support the hypothesis that asthma and allergic rhinitis are essentially 1 continuum of airway disease?

GENETIC FEATURES RELATED TO SYSTEMIC ASPECTS OF ALLERGIC DISEASE

Features related to the systemic aspects of allergic disease (presented elsewhere in this volume) support our hypothesis that a common genetic basis is responsible for this complex trait and is independent of specific clinical phenotype (ie, asthma, allergic rhinitis, or atopic dermatitis). Perhaps the best example is the role of total IgE in allergic disease, a measurable phenotype for which a number of groups have reported evidence for linkage to several loci. A summary of linkage and association studies for asthma, allergic rhinitis, atopic dermatitis, and atopy is presented in Table I. The studies cited in this Table clearly demonstrate that some of the most replicated evidence for linkage between candidate loci for allergic disease and total IgE concentrations is found in the same regions for which reasonable evidence for linkage to asthma has been reported. Borecki et al¹ attempted to relate the genetics of IgE regulation to the different manifestations of allergic disease, using total IgE and clinical data from the 173 families studied previously by Gerrard et al.² Borecki et al showed that a major locus that determines high IgE levels markedly influences the development of different manifestations of atopic disease. Furthermore, when only asthma and atopic dermatitis were considered, the effect of a major gene was compatible with recessive inheritance.

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Reprint requests: Kathleen C. Barnes, PhD, Johns Hopkins University, 5501 Hopkins Bayview Circle, Baltimore, MD 21224-6821.

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TABLE I. Summary of linkage and association studies for asthma, allergic rhinitis, atopic dermatitis, and "atopy"

Locus*	Candidate genes	Asthma†	Allergic rhinitis	Atopic dermatitis	Atopy‡
2pter	Unknown	Wjst et al, 1999 ⁴⁴			Wjst et al, 1999 ⁴⁴
2q33	CD28, IGBP5	CSGA, 1997 ⁵⁷			
3p24.2–p22	CCR4	Ober et al, 1998 ⁵⁸			
4q35	IRF2	Daniels et al, 1996 ⁴⁵			Daniels et al, 1996 ⁴⁵
5p15	Unknown	CSGA, 1997 ⁵⁷			
5q23–q33	IL3, IL4, IL5, IL13, IL9, CSF2, GRL1, ADRB2, CD14	CSGA, 1997 ⁵⁷ ; Ober et al, 1998 ⁵⁸ ; Postma et al, 1995 ⁶⁰ ; Noguchi et al, 1997 ⁶¹		Kawashima et al, 1998 ⁶²	Palmer et al, 1998 ⁴⁶ ; Doull et al, 1996 ⁵⁵ ; Noguchi et al, 1997 ⁶¹ ; Marsh et al, 1994 ⁶³ ; Meyers et al, 1994 ⁶⁴ ; Hisawa et al, 1998 ⁶⁵
6p21.1–p23	HLAD, TNFA	Wjst et al, 1999 ⁴⁴ ; CSGA, 1996 ⁵⁷			Wjst et al, 1999 ⁴⁴ ; Daniels et al, 1996 ⁴⁵ ; Hizawa et al, 1998 ⁶⁵ ; Caraballo & Hernandez, 1990 ⁶⁶
7p15.2	TCRG, IL6	Daniels et al, 1996 ⁴⁵			Daniels et al, 1996 ⁴⁵
7q35	TCRB				Noguchi et al, 1998 ⁶⁷
9q31.1	TMOD	Wjst et al, 1999 ⁴⁴			Wjst et al, 1999 ⁴⁴
11p15	Unknown	CSGA, 1997 ⁵⁷			
11q13	FCER1B, CC16/CC10	Daniels et al, 1996 ⁴⁵ ; Doull et al, 1996 ⁵⁵ ; van Herwerden et al, 1995 ⁵⁶		Folster-Holst et al, 1998 ⁶⁸	Daniels et al, 1996 ⁴⁵ ; Palmer et al, 1998 ⁴⁶ ; Cookson et al, 1989 ⁵⁰ ; Young et al, 1992 ⁵¹ ; Shirakawa et al, 1994 ^{52,53} ; Hizawa et al, 1995 ⁵⁴ ; Doull et al, 1996 ⁵⁵
12q14–q24.33	STAT6, IFNG, SCF, IGF1, LTA4H, NFYB, BTG1	Wjst et al, 1999 ⁴⁴ ; Barnes et al, 1999 ⁴⁷ ; Barnes et al, 1996 ⁴⁸ ; CSGA, 1997 ⁵⁷ ; Ober et al, 1998 ⁵⁸ ; Wilkinson et al, 1998 ⁶⁹	Barnes et al, 1999 ⁴⁷		Wjst et al, 1999 ⁴⁴ ; Barnes et al, 1996 ⁴⁸ ; Nickel et al, 1997 ⁴⁹
13q14.3–qter	TPT1	CSGA, 1997 ⁵⁷ ; Kimura et al, 1999 ⁷⁰			Daniels et al, 1996 ⁴⁵ ; Hizawa et al, 1998 ⁶⁵ ; Leaves et al, 1999 ⁷¹
14q11.2–q13	TCRA/D, MCC	CSGA, 1997 ⁵⁷		Mao et al, 1996 ³¹	Moffatt et al, 1994 ⁷² ; Mansur et al, 1999 ⁷³
14q32	IGHG				Oxelius et al, 1998 ⁷⁴
16p12.1	IL4R				Deichmann et al, 1998 ⁷⁵
16q22.1–q24.2	Unknown	Daniels et al, 1996 ⁴⁵			Daniels et al, 1996 ⁴⁵
17p11.1–q11.2	C-C chemokine cluster	CSGA, 1997 ⁵⁷			
19q13	CD22	CSGA, 1997 ⁵⁷ ; Ober et al, 1998 ⁵⁸			
21q21	Unknown	CSGA, 1997 ⁵⁷ ; Ober et al, 1998 ⁵⁸			
Xq28/Yq28	IL9R	Holroyd et al, 1998 ⁷⁶			

CD, Cell differentiation antigen; IGBP, insulin-like growth factor-binding protein; CCR, C-C chemokine receptor; IRF, interferon regulatory factor; CSF, colony-stimulating factor; GRL, glucocorticoid receptor; ADR, adrenergic receptor; TCR, T-cell receptor; TMOD, tropomyosin-binding protein; STAT6, signal transducer and activator of transcription 6; SCF, stem-cell factor; IGF, insulin-like growth factor; LTA4H, leukotriene A4 hydrolase; NFYB, the β subunit of nuclear factor- κ B; BTG, B-cell translocation gene; TPT1, tumor protein, translationally controlled 1; IGHG, immunoglobulin heavy chain G.

*Includes the full regions for which evidence of linkage has been observed.

†In general, asthma was defined as a qualitative (yes/no) trait in most studies^{45,46,55,56,60,76}; the definition of asthma included BHR as either a qualitative or a quantitative trait (eg, log_e slope).

‡The definition for atopy includes individual measurements or a composite measurement of total IgE, sIgE (RAST or skin prick test). The study by Hizawa et al⁶⁵ reported novel evidence for linkage to sIgE response to Der p and 2 novel regions, 2q21–q23 and 8p23–p21; but these findings have not been replicated by others.

The case is less clear for the role of allergen-specific IgE and allergic disease. Some researchers have speculated that the association between asthma and specific IgE is simply evidence that the allergic diathesis underlies most, and possibly all, of asthma.³ However, in a large controlled study in Australia, Duffy et al⁴ observed differences in the categories of specific allergens in terms of their importance as causal or consequential to asthma. By studying monozygotic and dizygotic twins, they observed that allergic sensitization to predominantly perennial indoor allergens (eg, house dust, cockroach, cat) caused asthma in susceptible individuals, whereas allergic sensitization to grass pollens and molds was an epiphenomenon, in which the genetically determined allergic process caused both asthma and the expression of sensitization to specific aeroallergens. These findings correspond, to some degree, to historic studies that associated single or groups of closely related major histocompatibility complex class II molecules in the HLA-D subregions (ie, DR, DQ, or DP) of the human major histocompatibility complex (located on chromosome 6p21.3) with specific immune response to very restricted phenotypes (eg, immune responsiveness to the major allergen of short ragweed, Amb a 5; $M_r = 5000$). The initial work was conducted by Marsh et al,⁵ who demonstrated that in all but 2 of approximately 80 white IgE responders to Amb a 5, class II restriction was limited to individuals carrying HLA-DR2 and Dw2 (DR2.2). This was significantly higher than the frequency of this haplotype among nonresponders (approximately 22%). Numerous studies⁶⁻¹² confirmed the findings of Marsh et al, most notably for other grass pollens (giant ragweed, perennial rye), but a few studies have also supported this finding for the mite allergens Der p 1 and Der p 2.

Another argument for a common genetic role in the systemic nature of allergic disease is, at least in the case of asthma and allergic rhinitis, the existence of features that are common in both upper and lower airways. For example, both upper and lower airway allergic inflammation involve a similar array of inflammatory mediators and a cellular infiltrate predominantly characterized by eosinophilia.¹³⁻¹⁹ In addition, several physiologic phenomena related to allergen exposure occur in both the upper and lower airways, including early and late responses and increased responsiveness to nonantigenic stimuli. These facts have weakened the conventional notion that the 2 atopic disorders are separate entities and have contributed to the idea that asthma and allergic rhinitis are perhaps "a continuum of inflammation within one common airway."²⁰ The strongest evidence in support of this hypothesis is the coexistence of the allergic clinical phenotypes. It has been reported that 60% to 80% of individuals with allergic asthma have coexisting rhinitis.^{21,22} In a recent study by Kapsali et al,²³ who used a highly sensitive and standardized tool, 98.9% of all individuals with atopic asthma who were surveyed had allergic rhinitis. It has been estimated that approximately 40% of infants with atopic dermatitis will experience the development of asthma by the age of 3 to 4 years.²⁴ In other

reports, 35% of patients with asthma had concurrent manifestations of atopic dermatitis,²⁵ and approximately 20% to 38% of patients with allergic rhinitis had asthma.^{21,22}

A final and yet most intriguing case for a common genetic basis for the allergic phenotypes is the thought-provoking work by Becker et al.²⁶ They identified 18 distinct "clusters" of susceptibility candidate loci that are common to many of the autoimmune and immune-mediated diseases, including asthma. By comparing linkage results from 23 genome-wide scans of 5 human diseases (asthma, Crohn's disease, familial psoriasis, multiple sclerosis, and type-I diabetes mellitus) and 6 murine diseases, they found that approximately 65% of the human linkages mapped into 18 different clusters. These clusters included a number of regions for which linkage to asthma has been replicated or originally determined in candidate gene studies and in other genome-wide scan studies, including 11q13, 12q21.1-q24, and 13q. These findings suggest the existence of shared genes that may be important for primary or secondary regulation of immune system disorders.

INHERENT DIFFICULTIES IN GENETIC STUDIES OF ALLERGIC DISEASE

Defining the disease phenotype is crucial in dissecting the genetic components of a complex trait (such as allergic disease) and is an important first step in designing a genetic epidemiologic study. As suggested by Lander and Schork,²⁷ fine-tuning the definition of a given disease enables the geneticist to analyze a trait that "is more nearly Mendelian in its inheritance pattern" and, therefore, more homogeneous. Defining the clinical phenotype has been 1 of the major challenges in genetic studies of allergic disease. For example, there is no quantitative marker specific for asthma and no gold standard against which to validate the diagnostic usefulness of physiologic measures, such as bronchial hyperreactivity (BHR).²⁸ This is even more applicable to allergic rhinitis and atopic dermatitis, in which there are no physiologic measurements on which to base an absolute diagnosis and in which diagnosis is based primarily on subjective symptoms (eg, runny, stuffy nose; pruritus). This is in contrast with other complex diseases in which quantitative traits, or a series of measurable "biomarkers," have proved useful in teasing out susceptibility genes. Examples include prostate-specific antigen in prostate cancer, fasting insulin and C-peptide in non-insulin-dependent diabetes mellitus,²⁹ and spinal bone-mineral density in osteoporosis.³⁰

Yet another challenge is that the clinical phenotypes of allergic disease tend to be moving targets; disease is quite often episodic, and the natural history can change substantially during the course of an individual's lifetime. For example, asthma is characterized by both acute and chronic airway inflammation (most typically IgE-mediated) or as allergic inflammation in response to aeroallergens. In defining the asthma phenotype, we focus on symptoms of acute inflammation and the associated increase in smooth muscle contraction, mucus hypersecretion, and vascular permeability. However, none of

these features vary substantially from what is observed after structural and functional changes over time, as in the case of chronic airway inflammation. In older patients, the diagnosis of asthma can also be confounded by other pulmonary diseases, such as chronic obstructive pulmonary disease or the effects of heavy smoking. This is a classic example of phenocopy, in which the case looks like a trait of interest (eg, asthma) but is actually something different. Phenocopies result in false-positive cases, which can seriously hamper the outcome of the analysis. Frequently, analysts are faced with the difficult task of classifying the subjects of an equivocal diagnosis into a definitive category (ie, asthmatic or normal) or removing the subjects from the analysis altogether. The pattern is similar for allergic rhinitis and atopic dermatitis.

Finally, the high rate of coexistence of the 3 clinical phenotypes, as described earlier, has potentially complicated the search for phenotype-specific genes. In most genetic studies of asthma, probands (the primary affected subjects in a family or the individuals through whom the families were selected) have been selected by the use of a reasonably stringent definition of asthma, but with virtually no attention given to concomitant allergic rhinitis or atopic dermatitis. In other words, in the final genetic analysis, probands with asthma are treated only in the same manner as probands with asthma and allergic rhinitis or probands with asthma and atopic dermatitis. Considering that there may be specific genes for lower airway disease (asthma) plus more generic genes for the overall genetic propensity for atopy, it becomes clear that the populations we have selected and characterized do not, as a whole, fit the criteria of narrowing the phenotype to a Mendelian-like, monogenic trait, as outlined by Lander and Schork.²⁷ One exception to this trend is an association study conducted in Japan by Mao et al,³¹ in which they recruited equal numbers of patients with only 1 of the following clinical disorders: atopic asthma, nonatopic asthma, allergic rhinitis, or atopic dermatitis (an equal number of control subjects were included). Although a significant association between eczema and a polymorphism at the BstXI site in the gene encoding the proinflammatory serine protease mast-cell chymase (MCC) on chromosome 14q11.2 was found, there was no association with any of the other phenotypes. Interestingly, approximately 98% of dermal mast cells produce MCC, whereas only about 7% of bronchial and pulmonary mast cells produce MCC.^{32,33} This was 1 of the first examples of studies that controlled for coexisting disease and concluded that a candidate gene (in this case, an identified variant) was associated with risk for 1 phenotype, but not the other 2.

GENETICS OF ALLERGIC DISEASE: WHAT WE KNOW TO DATE

To date, evidence of linkage to more than 22 loci of 15 autosomal chromosomes and the pseudoautosomal region of Xq/Yq has been reported from numerous candidate gene studies (Table I).³⁴ Several genome-wide screens for asthma and/or atopy have also been complet-

ed, and more are on the way, including collaborations with the biotechnology and pharmaceutical industry. Most candidate gene studies have selected loci of interest on the basis of the mapping of T_H2-type cytokines (eg, the IL-4 gene cluster), receptors (eg, the high-affinity IgE receptor), and "recognition" genes (eg, the HLA-D complex). More recently, researchers have considered genes encoding transcription factors (eg, signal transducer and activator of transcription 6) and other mediators of inflammation (eg, 5-lipoxygenase). In independent studies, the most reproducible linkages included the IL-4 gene cluster on 5q31-q33, the HLA-D region on 6p21, the region that encodes the high-affinity IgE-receptor gene (FCER1B) on 11q13, and a large region on chromosome 12q14-q24.33 that encodes several candidates for allergic disease, including signal transducer and activator of transcription 6, IFN- γ , stem-cell factor, and nitric oxide synthase 1. The C-C chemokine cluster on 17q11.2 has also been an attractive candidate region.

However, conclusions drawn from most of these linkage studies are speculative at best. Each of the regions in which significant and reproducible evidence of linkage has been identified contains multiple candidate genes. The best evidence for linkage in any 1 of these regions tends to extend over relatively large portions of the chromosome, to 10 centimorgan (cM) (1 cM = approximately 1 million bp) or more, rendering pinpointing of any specific locus difficult. This is confounded further by the limitations of the methods used. Statistical approaches commonly used for linkage analysis or association tests for genotype data generated by microsatellite markers do not usually allow accurate determination of the specific gene of interest, but only narrow the region of peak linkage score, which may still include hundreds of genes. This is true even in the case of fine mapping with the aim of localizing a gene to a region less than 1 cM.

The limited work that has been conducted so far on allelic variants in candidate genes for allergic disease has been devoted to loci, for which there was preliminary evidence of linkage. Many of the published studies have not been replicated in other populations. Most of the candidate genes studied so far are major players in the T_H2 response/upregulation of IgE (eg, cytokines, chemokines, receptors). For example, Rosenwasser et al³⁵ obtained evidence, in families with asthma, that a polymorphism in the IL-4 promoter (C-589T) is associated with elevated total serum IgE levels. Their finding has been supported by some³⁶⁻³⁸ and refuted by others.³⁹ There are similar reports on CD14 (C-159T) on 5q,⁴⁰ IL-10 on 1q32 C-571A,⁴¹ the transforming growth factor beta (TGF- β) gene on C-509T,⁴¹ a polymorphism in FCER1B (E237G) on 11q13,⁴² and the regulated on activation, normal T-cell expressed and secreted gene (A-401G) on 17q.⁴³

EVIDENCE FOR COMMON LINKAGES

The published studies on the genetics of allergic disease have focused mainly on the asthma phenotype or some measure of "atopy," which typically includes total and/or

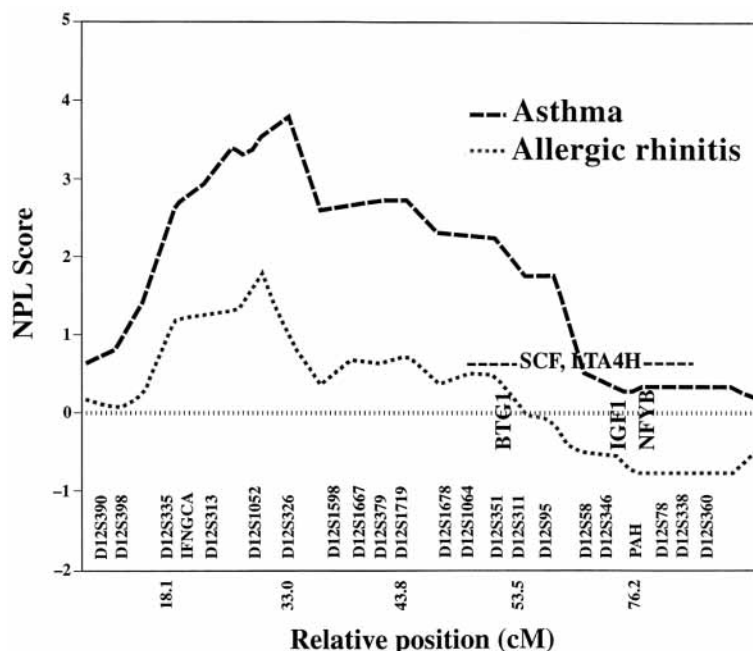


FIG 1. Multipoint identify-by-descent-affected relative analysis of chromosome 12q markers in 33 Barbadian kindreds for asthma and allergic rhinitis. The x axis illustrates the map positions of the markers with the use of the Kosambi mapping function for both Cri-Map 2⁷⁷ and GENEHUNTER (Version 1.0)⁷⁸ under the "fixed" option and the locus order indicated by the physical map of Krauter and others.⁷⁹ The y axis is the nonparametric linkage (NPL) score. The horizontal, small-hatched line indicates a level of significance at $P < .05$.

specific IgE measurements. Table I demonstrates the virtual absence of findings for linkage and/or association for the phenotypes of allergic rhinitis and atopic dermatitis. This is undoubtedly not because of negative findings for allergic rhinitis and atopic dermatitis at the loci listed but because of negative findings that are not regularly published, making comprehensive comparisons difficult. However, it is important to note that the studies shown for these 2 clinical phenotypes are the only published studies to date that focused on allergic rhinitis (12q14–q24.33) and atopic dermatitis (5q23–q33, 11q13, and 14q11.2–q13).

Some interesting conclusions can be drawn from the data in Table I regarding the hypothesis that there are common genes for allergic disease, regardless of the clinical phenotype, plus, possibly, specific genes for certain clinical phenotypes. In the large German genome-wide scan study, in which subjects were selected for asthma, the 4 regions with the strongest evidence for linkage for asthma (2pter, 6p21.1–p23, 9q31.1, and 12q14–q24.33) were the same regions for which the best evidence for linkage to total and specific IgE was observed.⁴⁴ In another genome-wide screen of 2 populations selected for atopic asthma, Daniels et al⁴⁵ found evidence for linkage to traits that are associated with both asthma (as a qualitative trait and slope on the dose-response curve) and atopy (total or specific IgE measurements) at 4 of the same loci (ie, 4q35, 7p15.2, 11q13, and 16q22.1–q24.2), but their evidence for linkage to markers in 6p and 13q was only for the atopy traits. Similarly, Palmer et al⁴⁶

found evidence for linkage to the quantitative traits of total and specific IgE to markers in 5q and 11q, but they did not observe evidence for linkage to a quantitative trait (eg, bronchial hyperresponsiveness) specific for asthma to either of these regions. Hence, it is plausible that none of the linkages reported in these 10 regions are specific for asthma but rather implicate 10 loci that are important in an overall genetic propensity for the expression of allergic disease.

This can be specifically illustrated in our own data on chromosome 12q14–q24.33 and an ongoing study in over 500 subjects from 33 multiplex families in Barbados, the West Indies. Using affected sib-pair (ASP) analysis, we observed significant evidence for linkage to asthma in a relatively large region (more than 30 cM; $P < .05$ –.002). The best evidence for linkage was at a CA repeat polymorphism in the first intron of IFN- γ in 12q21.1 ($P = .002$).⁴⁷ Evidence of linkage to allergic rhinitis was observed in the same region, at a proximal marker and the same marker (D12S313, $P = .006$; IFNGCA, $P = .01$, respectively). The same pattern was observed with multipoint linkage analysis (asthma: D12S326; nonparametric linkage score, 3.8; $P = .0008$; and allergic rhinitis: D12S1052; nonparametric linkage, 1.8; $P = .036$; Fig 1).

The Barbados population was recruited through an asthmatic proband; however, the families are large and complex, and there are a number of patients with allergic rhinitis, whom we have also characterized (39% of the population for whom information regarding allergic rhini-

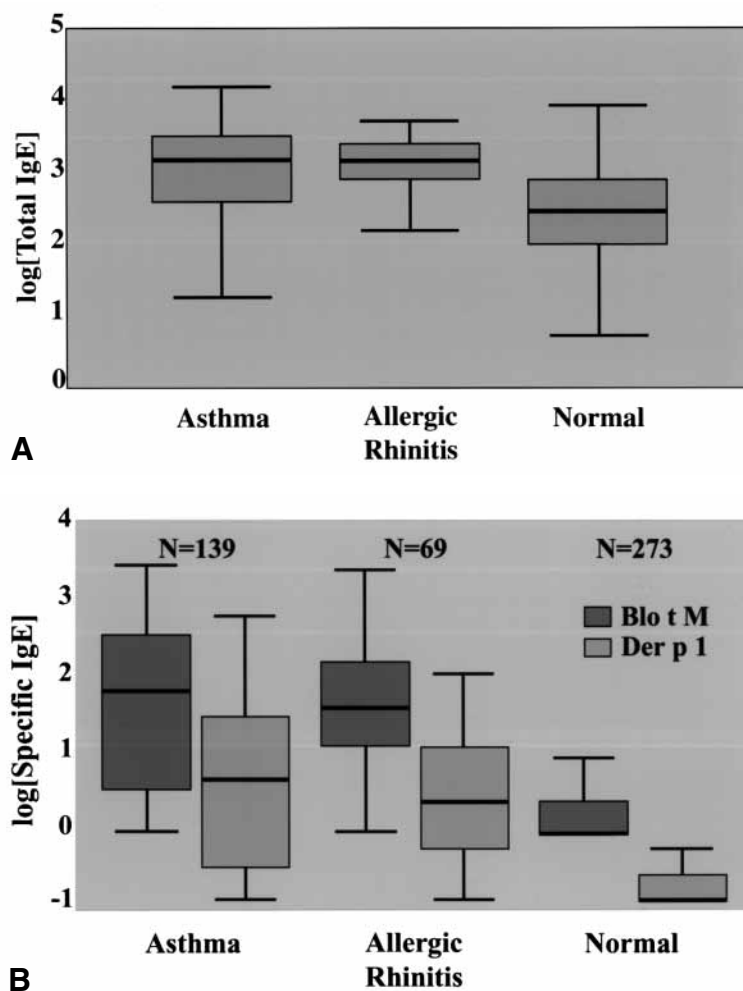


FIG 2. A, Box plot of log [total serum IgE] in individuals with asthma, in individuals with no asthma but with allergic rhinitis, and in normal individuals in 33 Barbados kindreds. **B**, Box plot of specific IgE to the major allergen of *Blomia tropicalis* (Blo t M) and *Dermatophagoides pteronyssinus* (Der p 1) in individuals with asthma, in individuals with no asthma but with allergic rhinitis, and in normal individuals in 33 Barbados kindreds.

tis was available were defined as having “allergic rhinitis”). When we adjusted for asthma in the ASP analysis on allergic rhinitis (ie, eliminated sib-pairs with allergic rhinitis who also had asthma), the level of significance at marker D12S313 increased ($P = .0006$). This finding suggests that the locus on 12q is not specific for asthma but may possibly indicate an allergic rhinitis locus. We cannot, however, make this conclusion with certainty because the adjustment significantly reduced the number of ASPs. On the other hand, other groups, including our own, have also provided evidence for linkage to this region for total IgE.^{44,48,49} Descriptive data of the 2 groups in Barbados (with asthma and with allergic rhinitis but without asthma) lend further support to the possibility that the 12q locus is a more general candidate for atopy, or the upregulation of IgE, rather than for airway disease. We compared log [total serum IgE] levels among patients with asthma and with allergic rhinitis with no asthma and a group of subjects without asthma or allergic rhinitis. The

results indicated nearly identical mean IgE levels among the patients with asthma (mean, 3.03 ± 0.69) and allergic rhinitis (mean, 3.13 ± 0.39) that were significantly higher than among control subjects (mean, 2.42 ± 0.68 ; Fig 2, A). The same pattern was observed for specific IgE measurements to the major allergens of *Blomia tropicalis* (Blo t M; a common storage mite in Barbados) and *Dermatophagoides pteronyssinus* (Der p 1; Fig 2, B).

Another important finding taken from the various linkage and association studies on allergic disease is shown in Table I. Notably, a number of studies have provided convincing evidence that a locus in 11q13 is important in the upregulation of IgE.^{45,46,50-55} Of the 6 published studies that focused on markers in this region and that included subjects who had been phenotyped for asthma, only those groups who defined asthma with the use of the quantitative trait BHR have shown evidence of linkage.^{45,55,56} The 3 genome-wide scan studies, which analyzed asthma as a qualitative trait, reported no evidence

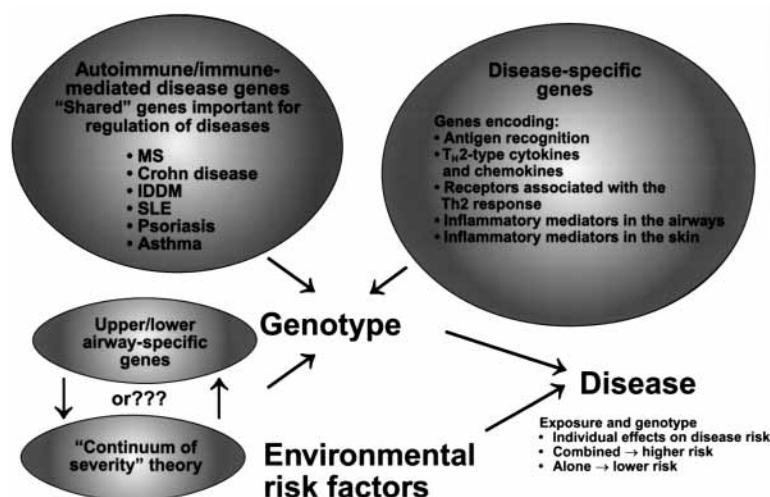


FIG 3. This model illustrates the possible genetic basis for allergic disease. *MS*, Multiple sclerosis; *IDDM*, insulin-dependent diabetes mellitus; *SLE*, systemic lupus erythematosus.

for linkage at this locus.^{44,57,58} It is not unreasonable therefore to conclude that perhaps this region contains loci important for different phenotypes that are associated with allergic disease, including lung function phenotypes and IgE phenotypes.

THE GENETIC BASIS FOR ALLERGIC DISEASE: PROPOSING A NEW MODEL

A possible model for the interpretation of the genetic basis of allergic disease is summarized in Fig 3. On the basis of the findings of Becker et al,²⁶ there exists a set of "immune-mediated disease genes" that are important for the primary and/or secondary regulation of diseases of the immune system. Interestingly, this set includes primarily those complex traits that are generally regarded as T_H1 -type diseases, with the exception of asthma, which we have traditionally regarded as etiologic T_H2 -type. The findings of Becker et al raise the question of whether there is a component of asthma, and, by association, of allergic disease, in general, that is T_H1 in nature.

A second set of genes is classified as disease-specific. In this cluster, we envision different groups of genes that are associated with different categoric phenotypes of allergic disease (eg, asthma, allergic rhinitis, and eczema). Also within this group, we predict several distinct groups of major genes (eg, genes encoding T_H2 -type cytokines and chemokines) that are involved in the differential expression of each of these phenotypes, such as the overall upregulation of IgE and/or inflammatory responsiveness.

Another cluster of genes (Fig 3) is specific for airway inflammation and hyperreactivity. In this case, it is possible to consider some combination of genes that is specific for airways and/or associated with severity. This is based on the notion that (1) asthma and allergic rhinitis represent a continuum of total airway disease, whereby

those patients with less severe disease will express rhinitis without asthma and those patients with more severe disease will express both phenotypes; or (2) alternatively, there are common genes associated with both asthma and allergic rhinitis, with additional genes (eg, modifiers) that determine the ultimate risk for asthma. It is perhaps worth considering the model of cystic fibrosis, wherein hundreds of mutations on a single gene lead to a host of different phenotypes.

Finally, environmental influences are key components of the complex mosaic that determines the expression of allergic disease. Developing atopy to a particular allergen requires appropriate exposure and the subsequent development of a specific IgE antibody response in a genetically susceptible host. For such an allergen to be important in asthma requires chronic low-dose exposure typically found in the indoor environment. The effect of gene-environment interactions on complex traits (such as allergic disease) can be partitioned into at least 2 categories: (1) the effect of a given environmental exposure on the risk of disease in people with different genotypes, and (2) the effect of a particular genotype on the risk of disease in people with exposure to different environmental factors.⁵⁹ Fig 3 represents a synergistic effect of genes and the environment proposed for allergic disease.

In summary, the very limited data that have been published suggest that many of the linkages and associations between candidate loci and phenotypes that are related to allergic disease are not necessarily specific for asthma, allergic rhinitis, or atopic dermatitis. The extension of such an approach to other diseases of the immune system²⁶ suggests that it is not unreasonable to speculate that genes that are part of a more generalized pathway of the immune response or the inflammatory network may ultimately play a central role in the overall pathophysiologic factors of allergic disease, whereas other (potentially minor) genes may be critical in the specific clinical phenotype.

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