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Genetic and environmental interaction in allergy and asthma

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Asthma is an inflammatory disorder of the airways involving coordinate up-regulation of T_H2-type cytokines encoded in a cluster on chromosome 5q₃₁₋₃₃ on T cells and inflammatory cells. There is also a requirement for local airway susceptibility factors that, together with T_H2 polarization, results in hyperresponsiveness, variable airflow obstruction, and, over time, remodeling of the airway wall. Asthma has strong genetic and environmental components that interact both in the induction and subsequent expression of the disease phenotypes. Multiple genes are involved and probably interact. Whole genome screens are beginning to identify gene-rich regions of special relevance to asthma and atopy, although a novel disease-related gene has yet to be discovered from these. By contrast, there are a plethora of candidate genes whose function in relation to disease pathophysiologic mechanisms and response to treatment are known. Two examples are polymorphisms involving IL-4 receptors and the enzymes controlling cysteinyl leukotriene production. Abnormal signaling between the epithelium, which is in contact with the environment, and the underlying (myo)fibroblasts and dendritic cells indicating reactivation of the epithelial mesenchymal trophic unit, which is involved in fetal lung development and branching, provide a basis for asthma that encapsulates both T_H2 polarization and airway wall remodeling. (*J Allergy Clin Immunol* 1999;104:1139-46.)

Key words: Atopy, asthma, genetics, IL-4 and IL-13, IL-4 and IL-13 receptors, leukotrienes

Asthma is a complex disorder involving a combination of genetic and environmental interactions that culminate in a specific type of inflammation involving mast cells, eosinophils, and macrophages and polarization of T cell-mediated immunity toward enhanced production of cytokines encoded in a cluster on the long arm of chromosome 5. These include IL-4, IL-5, IL-9, IL-13, and GM-CSF, which orchestrate the isotype switching of B lymphocytes to produce IgE, maintain the persistence of T-helper 2 (T_H2) lymphocytes with their enhanced capacity to secrete cytokines of the IL-4 gene cluster and recruit and maintain the survival of mast cells, basophils, and eosinophils.¹

In contrast to the many animal models of T_H2 polar-

Abbreviations used

AIA:	Aspirin-intolerant asthma
Arg:	Arginine
BHR:	Bronchial hyperresponsiveness
Cyst-LT:	Cysteinyl leukotriene
DZ:	Dizygotic
Gln:	Glutamine
IL-4r:	IL-4 receptor
Ile:	Isoleucine
IRS:	Insulin receptor substrate
LO:	Lipoxygenase
LT:	Leukotriene
LTRA:	Leukotriene receptor antagonist
MZ:	Monozygotic
Prol:	Proline
PUFA:	Polyunsaturated fatty acid
Ser:	Serine
SPT:	Allergen skin prick test
STAT:	Signal transduction and activators of transcription
T _H 2 cell:	T-helper 2 lymphocyte
Val:	Valine

ization in the lung, which tend to be self-limiting, asthma is a chronic disorder characterized by exacerbations and remissions and an underlying bronchial hyperresponsiveness (BHR) of the airways to a wide variety of environmental factors.² In established disease a major part of the BHR can be separated from the inflammatory response and most likely represents structural changes to the airways with deposition of matrix proteins throughout the airway wall and "remodeling" of the formed elements including epithelial goblet cell metaplasia, smooth muscle hypertrophy, and an increase in microvessels and nerves.³ Whether these features occur as a consequence of or in parallel with the inflammatory response is not known, but increasingly in asthma it is becoming appreciated that many of these structural elements are themselves altered to produce cytokines, growth factors, and mediators that may contribute to the sustenance of the inflammatory response.⁴

ASTHMA PHENOTYPES

Although for therapeutic reasons it has become convenient to consider asthma as a single disease entity, this clearly is not the case, with many variants occurring.⁵ From a clinical standpoint, a minimal subdivision includes atopic asthma, cough variant asthma, brittle asthma, intrinsic asthma, aspirin-intolerant asthma (AIA), and occupational non-IgE-dependent asthma. When disease severity

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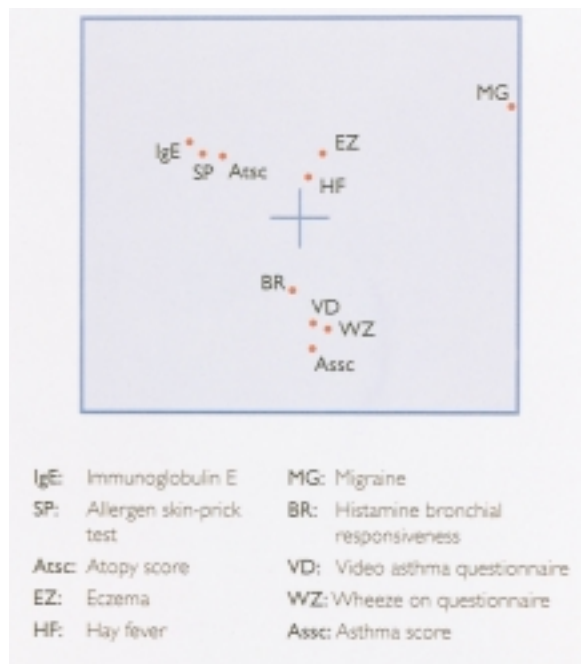


FIG 1. Eigenvector plot shows relationship between various clinical phenotypes and the summated scores for asthma and atopy derived by principal-component regression analysis.

and responsiveness to treatment are added to this categorization, the number of variations becomes very large. If these manifestations are controlled by specific genes and environmental interactions, then the true complexity of this disease becomes appreciated.

Atopy, the propensity to generate IgE against common environmental allergens, is the strongest single risk factor that has so far been identified for asthma, increasing the risk in those affected by 10- to 20-fold.⁶ Although atopy and asthma interact, they are not interchangeable. Thus, although a high proportion of children and young adults are atopic, even in countries with a high prevalence of atopy (eg, United Kingdom, Australia, and New Zealand) full-blown chronic asthma will develop in only 1 in 5 atopic patients. Moreover, in adults, especially at the severe end of the asthma spectrum, atopy diminishes as a risk factor.⁷

The phenotype of other chronic inflammatory diseases, such as Crohn's disease or psoriasis, presents little diagnostic uncertainty but, in the case of asthma, there is a lack of diagnostic precision. This has led to the use of intermediate phenotypes reflecting asthma and atopy, such as BHR, serum total and allergen-specific IgE, skin prick test (SPT) positivity, and circulating eosinophil counts. Although these provide quantitative measures, BHR, for example, can be assessed in many different ways (eg, histamine or methacholine provocation, exercise or cold air challenge, sulfur dioxide challenge, peak expiratory flow variability, etc), each measure describing different airway characteristics. In addition, there are numerous ways in which an individual can be designated atopic.

The danger in using intermediate phenotypes is the assumption that their genetic basis will be the same as that of the disease state. Several large epidemiologic studies have established that the presence of asthma corresponds to high serum levels of total IgE.^{8,9} However, when analyzed on a family basis, a tendency to be a high IgE producer proved to be only one factor related to the inheritance of asthma susceptibility and, in itself, had a limited ability to predict asthma inheritance.¹⁰

An alternative approach has been to pool multiple measures of asthma (eg, respiratory questionnaire, SPT, specific and total IgE) to generate summary scores using, for example, principal component regression analysis.¹¹ This method can also be used to construct a quantitative trait in the form of an asthma score in which the influence of atopy is removed¹² (Fig 1).

ASTHMA AS A GENETIC DISORDER

Although it has long been known that asthma and related atopic diseases cluster in families, the genetic basis for this has eluded definition. In 176 families a striking association has been shown between asthma in parent and offspring, hay fever in parent and offspring, and eczema in parent and offspring, suggesting that, in addition to genetic factors determining allergen sensitization, there are also important genetic factors that determine the end-organ in which this was expressed, a conclusion drawn from further large epidemiologic studies.^{13,14}

One method that can be used to great effect in complex disorders to determine the relative contribution of genes and the environment is to study the concordance of a trait in monozygotic (MZ) and dizygotic (DZ) twins, in which the former have identical genotypes and the latter share on average only half their genes. Thus a disease that has a strong genetic component will show a higher rate of concordance in MZ than in DZ twins. In a large survey of 7000 twin pairs, concordance rates for asthma, eczema, and hay fever were all substantially higher for MZ than for DZ twins.¹⁵ This observation has also been shown for BHR, SPT responses, and serum total and specific IgE.^{16,17} In a study deliberately designed to disaggregate genetic from environmental effects, both allergic disease and partial phenotypes were compared in MZ and DZ twins reared together and apart.¹⁸ Whether together or separated, MZ twins showed a greater concordance than DZ twins, indicative of a strong genetic contribution. This has been further strengthened by the findings in a recent 11,688 Danish twin pairs with use of additive and genetic and nonshared environmental modeling that 73% of asthma susceptibility was genetic and a substantial part of the variation liability of asthma was the result of environmental factors.¹⁹

Segregation analysis is a method for estimating the pattern of inheritance of a disease by observing how it is distributed through family pedigrees. Several different modes of inheritance have been proposed for elevated serum total IgE, including autosomal recessive, autosomal dominant, and polygenic inheritance.²⁰⁻²² Applica-

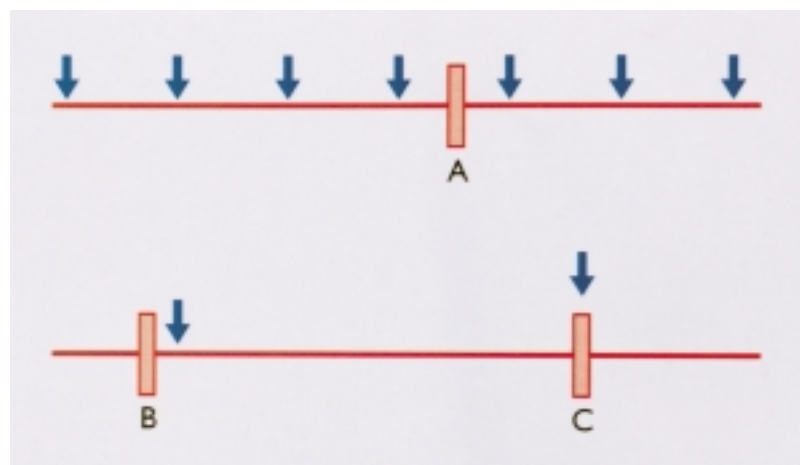


FIG 2. Different approaches to identify susceptibility genes: random genome search with microsatellite markers (*upper*), microsatellite markers close to a known gene (*lower left*), and mutation analysis of known gene or its promoter (*lower right*).

tion of more sophisticated segregation models to asthma and its partial phenotypes have shown that it is unlikely that any single gene predominates,²³ although for physician-diagnosed asthma in US Hispanics a major autosomal codominant gene has been proposed.²⁴

METHODS FOR DETECTING DISEASE SUSCEPTIBILITY GENES

In contrast to single-gene disorders, which are rare, subject to severe mutations and deletions, and exert a large phenotypic effect often independent of environmental factors, complex genetic traits such as asthma and related allergic disorders are common and result from mild mutations in multiple genes each of which has a small effect on the phenotype and requires subtle gene-gene (epistasis) or gene-environmental interactions for optimal expression. Two fundamental approaches are being used to discover susceptibility genes in asthma and atopy: linkage analysis with functional cloning and association analysis for mutations of “candidate” genes thought to be involved in disease pathogenesis.

LINKAGE ANALYSIS

Linkage analysis uses family data to follow the transmission of genetic information between or across generations to enable genes to be identified by their position on the genetic map; no prior knowledge of disease pathophysiological features is required. Linkage studies require families usually enriched with the disease, which must be accurately phenotyped. Depending on the approach, families can be nuclear families (ie, children and their parents), extended pedigrees, or inbred populations. Linkage analysis requires the saturation of the entire human genome at regular intervals with microsatellite markers comprising variable nucleotide tandem repeats whose precise position on the genetic map are known. Whole-

genome screens use 300 to 500 dinucleotide, trinucleotide, or tetranucleotide markers spaced 5 to 10 cM across the genome. The proximity of a marker to a disease-related gene is estimated by measuring the number of recombination events between them; the closer 2 loci are, the less chance they will be separated at meiosis (Fig 2). The significance of linkage is measured by the “lod score” (log of the odds ratio of the likelihood of a hypothesis of linkage to the likelihood of a hypothesis of no linkage). For example, for a lod score of 3, there is a 5% chance of a false-positive linkage. A lod score of 2.2 is suggestive of linkage, 3.6 significant linkage, and 5.4 highly significant linkage.²⁵

This type of parametric linkage analysis requires an a priori knowledge of the mode of inheritance of the disease or its partial phenotype, which, for asthma and allied allergic disorders, is not known. Under such circumstances nonparametric linkage analysis or allele sharing methods are more reliable but less powerful. Affected sib-pair analysis is most commonly used, which involves studying affected relatives in a pedigree to see how often a particular copy of a chromosomal region is shared identical by descent (ie, inherited from a common ancestor within a pedigree). For example, 2 siblings can share 0 or 2 copies of any locus. If the disease or partial phenotype is linked to a certain marker, then the affected siblings will inherit identical alleles of the marker more frequently than expected by chance alone. When assessed by a chi-square test a lod score of >3.6 is considered significant.²⁶

Association studies are case control studies based on a comparison of unrelated affected and unaffected individuals from a population. Although association can be performed for any random DNA polymorphisms, they are most meaningful when applied to functionally significant variations in genes having a clear biologic relationship to the trait. Positive association may occur under 3 circumstances: (1) the allele is contributing to the phenotype, (2) population (racial or ethnic) admixture, and (3) when

TABLE I. Summary of results from published whole-genome scans in asthma

Chromosome	CSGA 1 ²⁹	CSGA 2 ³⁰	British/Australian ²⁸	Hutterites ³¹	German Asthma Genetics Group ³²
2pter				BHR/asthma	IgE/RAST
2q22-33	Asthma, Hispanic	IgE (Der p 1)			
3p24.2-22				BHR/asthma	
4q35			BHR		
5p15	Asthma, African American				
5q23-33	Asthma, white	IgE (Der p 1)		Asthma	
6p21.3-23	Asthma, white	IgE (Der p 1)	IgE/Eos		Asthma, eosinophil, IgE/RAST
7p35			IgE/BHR		
8p23.3		IgE (Der p 1)			
9 (D9S925 and DS1784)				Asthma/BHR	Asthma, IgE/RAST
11p15	Asthma, white				
11q13			IgE/skin test		
12q13					Asthma
12q14-24.2	Asthma, white				
13q14.3-32.2	Asthma, Hispanic			Asthma	
14q11.2-13	Asthma, white	IgE (Der p 1)	Atopy	BHR	
16q24.1			IgE/BHR		
17p11.1-11.2	Asthma, African American				
19q13	Asthma, white			Asthma	
21q21	Asthma, Hispanic			Asthma/BHR	
Linkage criteria	$P < .01$	$P < .001$	$P < .001$	$P < .01$	$P < .01$

Der p 1, Principal house dust mite allergen; RAST, radioallergosorbent test for allergen specific IgE.

alleles at 2 loci are close together (linkage disequilibrium). An alternative type of case control is the transmission disequilibrium test, which avoids the confounding effects of an incorrectly matched control population and uses a trio design of 2 parents and 1 affected sibling.²⁷

GENOME SCANS IN ASTHMA AND ATOPY

A number of whole-genome scans for asthma have now been completed (Table I).²⁸⁻³² Although there is an emerging consensus for some chromosomal regions, in different populations there exist many where linkage has not been reproduced. Although this may represent true heterogeneity on the basis of racial differences, it is of concern that all the whole genome screens have been conducted on relatively small numbers of families (100-500), whereas it is predicted on statistical grounds that in excess of 1000 sibling pairs is needed to provide absolute confidence for linkage to a specific marker.²⁵ One possible way around this is to pool data from different studies either by meta-analysis or through establishing a voluntary network in which separate groups pool their results in a single analysis.³³

Even when a chromosomal region has been narrowed down to 1-2 cM, the task of identifying which gene (or genes) within this stretch of DNA is contributing to the disease phenotype is daunting. This requires the construction of physical maps of the region with use of overlapping genomic DNA clones and techniques such as

exon trapping and complementary DNA selection to identify genes in a given section of DNA. With the availability of integrated genetic and physical maps it is possible to obtain an inventory of genes mapping to the specified genetic interval and scan this for genes of known function (positional-candidate approach). Once a specific gene and its mutations have been identified, their expression can be assessed in diseased tissue by a combination of PCR and in situ hybridization and functional studies undertaken by overexpressing and underexpressing the gene in appropriate human cell lines and transgenic mice. At the time of writing, no candidate genes for asthma have yet been reported that have emerged from whole genome screens.

CANDIDATE GENES

A large number of mutations have been described for candidate genes that influence functions relevant to known disease mechanisms in asthma and allied disorders. In all cases, altering the level of expression or function of a specific protein accounts for only a very small component of the disease phenotype. Table II displays candidate genes that have found widest acceptance in different populations.

In many cases it is highly likely that several mutations involving a number of components of a particular metabolic or physiologic pathway are needed to fully manifest the effect of a candidate gene. For example, for IL-4 a

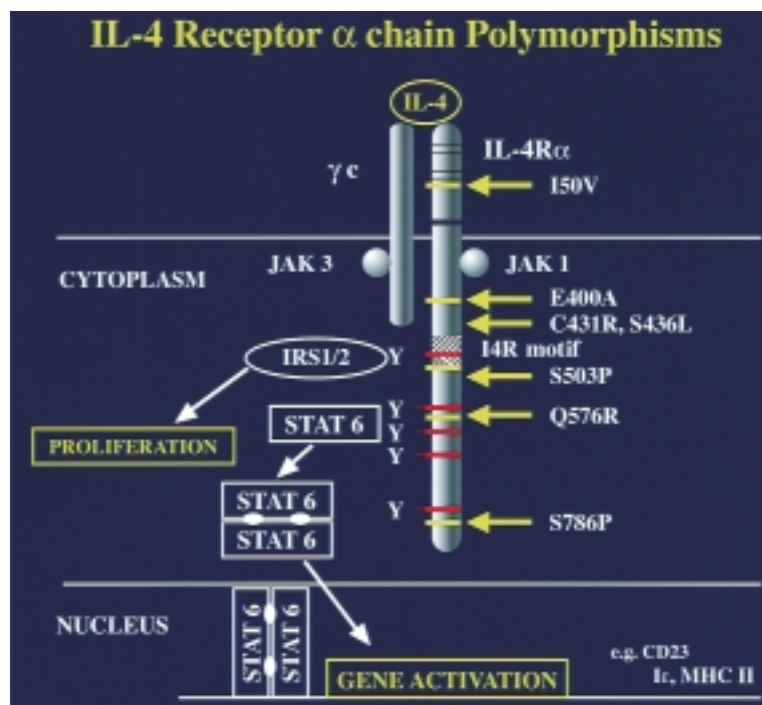


FIG 3. IL-4 activates a number of signaling pathways, including signal transduction and activators of transcription (STAT) 6 and IRS (insulin receptor substrate) 1 through IL-4 receptor (IL-4R). IL-4R is composed of α chain (IL-4R α) and γ (γ c) α chain; however, other forms do exist because of formation of heterogeneous structures with a component of α γ chain, which is shared with the IL-2 β IL-13 receptor (IL-13 α_4). Signal transduction through IL-4R is thought to involve activation of IRS1/2 and STAT6, which leads to cell proliferation and activation of gene transcription. A number of polymorphisms have been identified within the IL-4R α gene and several of these result in amino acid coding changes. Several of these polymorphisms have been shown to have effects on IL4 signal transduction. However, the precise effects of each polymorphism and combinations of these polymorphisms are still unclear.

TABLE II. Candidate genes in asthma and allergy and their chromosomal locations

Candidate	Chromosome location	Function
IL-3	5q31-33	Eosinophil and basophil growth factor
IL-4	5q31-33	IgE switching, T _H 2 polarization, up-regulation of VCAM-1, induction of mucus genes
IL-9	5q31-33	Mast cell growth factor
β_2 -Adrenoceptor	5q31-33	Cyclic AMP-dependent signaling
LTC ₄ synthase	5q35	Cysteinyl Leukotriene generation
MHC class II	6p21.3-23	Antigen recognition
TNF- α	6p21.3-2.3	Pleiotropic cytokine
5-Lipoxygenase	10q11.2	Leukotriene synthesis
Fc ϵ RI β chain	11q13	Regulation of IgE signaling
CC16 (CC10, uteroglobin)	11q12-13	Lung anti-inflammatory protein
NOS-1	12q24.3	Neural nitric oxide production
TCR α chain	14q11.2	Antigen-driven immune responses
IL-4 α	16p12	IL-4 signaling
TGF- β_1	19q13.1-13.3	Increased IgE synthesis, profibrotic cytokine

VCAM-1, Vascular cell adhesion molecule-1; LTC₄, leukotriene C₄; Fc ϵ RI, high-affinity receptor of IgE; NOS-1, nitric oxide synthase-1; TCR, T-cell receptor.

polymorphism at -589 involving a C→T substitution in the promoter region on chromosome 5q31 results in increased transcription of IL-4 and therefore increased responsiveness to IL-4 (eg, by enhanced IgE production).³⁴ Clearly, there may be other functionally active polymorphisms influencing IL-4 secretion. Moreover, at least 12 common polymorphisms have also been

described in the coding region of the IL-4 receptor gene on chromosome 16p12.1, 5 of which lead to amino acid changes of the gene product (Fig 3).³⁵ Some of these (eg, isoleucine [Ile] 50 valine [Val]) increase,³⁶ some (eg, serine [Ser] 503 proline [Prol]) decrease³⁷ STAT6 activation, whereas others appear to have no effect on IL-4 signalling.³⁸ The role of glutamine (Gln) 576 arginine (Arg)

is not clear.^{36,38,39} When 2 or more IL-4R polymorphisms occur together (eg, Ser 503 Prol and Gln 576 Arg, STAT6 phosphorylation is reduced and IRS1/2 phosphorylation is increased.³⁷ If the level of IL-4 secretion is also increased (eg, in the -589 promoter polymorphism), then any genetic effects mediated through the IL-4R or IL-13 receptor are likely to be magnified.

Another example of gene-gene interaction may occur in the leukotriene pathway. The cysteinyl leukotrienes LTC₄, LTD₄, and LTE₄ are critical mediators of airway narrowing, microvascular leakage, mucus secretion, and eosinophilia in bronchial asthma.^{40,41} The terminal enzyme for cysteinyl leukotriene (Cyst-LT) synthesis is LTC₄ synthase encoded on chromosome 5q35. We have shown that in patients with aspirin-intolerant asthma (AIA) the expression of this enzyme in mast cells and eosinophils is increased 5-fold in parallel with enhanced Cyst-LT production.⁴² This might explain why such patients find particular benefit from being treated with Cyst-LT₁ receptor antagonists (LTRAs) such as montelukast.⁴³ An A→C polymorphism at the -444 position of the LTC₄ synthase promoter has been shown to be strongly associated with AIA (odds ratio 3.89).⁴⁴ This base substitution creates an extra activator protein-2 transcription factor binding site, leading to increased enzyme transcription. We have also shown that the A/A or A/C allele is also found more commonly in patients with severe asthma and is accompanied by a greater ability to produce LTC₄ on ex vivo activation of the peripheral blood eosinophils and a tendency toward enhanced responsiveness to the antileukotriene drug zafirlukast.⁴⁵ 5-Lipoxygenase (5-LO) is the first committed enzyme in the biosynthesis of leukotrienes. A series of naturally occurring mutations have been discovered within the glucocorticoid-rich transcription factor binding region in the promoter of the 5-LO gene.⁴⁶ These involve deletion of 1, deletion of 2, or addition of 1 zinc finger (Sp1/Egr2) binding sites. When transfected, the mutant alleles result in reduced Sp1/Egr2 binding, and reporter gene transcription is reduced by 20% and 40% compared with the wild-type sequences.⁴⁷ In 236 patients with asthma, only those possessing mutant 5-LO alleles were relatively resistant to treatment with the 5-LO inhibitor ABT-761; the mean FEV₁ improved by ~5% compared with ~15% for the wild-type and heterozygotes.⁴⁸ Thus, if there were mutations both of the cysteinyl LT₄ synthase and 5-LO in favor of greater LTC₄ production, then a subtype of "leukotriene-dependent" asthma can be envisaged. With the recent cloning and expression of the Cyst-LT₁ receptor,⁴⁹ variation in expression, ligand binding, or transduction signaling may further the appearance of leukotriene dependence. Such mechanisms may help explain the responder-nonresponder phenomenon that is emerging in clinical studies of asthma involving LTRAs.^{43,50}

GENE BY ENVIRONMENT INTERACTIONS

Although asthma and related allergic disorders are closely linked to atopy, there are other important gene-

environmental interactions that are of central importance in the clinical expression of disease. In the case of asthma, exposure to oxidant air pollutants (eg, ozone, NO_x, particulates, tobacco smoke) has been linked to worsening disease.⁵¹ Respiratory virus infections, especially those caused by rhinoviruses and coronaviruses, account for the majority of asthma exacerbations in children and adults.^{52,53} Because both these environmental factors operate by increasing the activation of proinflammatory transcription factors in epithelial and inflammatory cells (eg, nuclear factor-κB),⁵⁴ genetic factors regulating this cascade are likely to be of considerable importance in determining susceptibility to exacerbations of continuing disease.

The complex cellular events that are linked to altered stress responses at the mucosal surface on exposure to pollutants or respiratory viruses are only just being revealed, but key among them is the ability of the epithelium to protect itself from such insults by antioxidant pathways.^{6,53} These include glutathione peroxidase, glutathione synthase, and xanthine oxidase.⁵⁵ In susceptible mice genetic linkage has shown that ozone-induced lung inflammation is directed by genes encoded on chromosome 17, including the strong candidate TNF-α, a pleiotropic cytokine generated during oxidant-induced cell injury.⁵⁶

There are numerous studies linking asthma with a reduced antioxidant status.^{57,58} Because antioxidants may also be provided in the diet (eg, vitamins A, E, and C), asthmatic subjects defective in endogenous antioxidant-generating capacity may be especially susceptible to dietary deficiencies.⁵⁷⁻⁵⁹

A similar case can be made for another dietary link to asthma. Both in animals and in in vitro studies in humans omega-3 polyunsaturated fatty acid (PUFA)-enriched diets has been shown to reduce allergen-induced inflammatory responses and Cyst-LT generation, respectively.^{60,61} On this basis, it has been suggested that supplementation of the diet with omega-3 fatty acids in the form of fish oil might protect asthmatic patients by reducing the capacity to generate Cyst-LTs. Unfortunately, clinical trials with diet supplementation have been disappointing both with allergen provocation and in clinical asthma.⁶¹⁻⁶³ However, Broughton et al⁶⁴ have recently shown that only those patients who have high urine secretions of LTE₄ responded favorably to omega-3 fatty PUFA dietary supplementation, whereas in those who were low excretors the asthma deteriorated or was unchanged rather than improved. Because urinary LTE₄ excretion is a measure of the activity of the 5-LO pathway,^{39,43} it is possible that responders and nonresponders to this dietary intervention could be determined by prior genotyping.

It has been suggested that reduced exposure to bacteria or their products during early infancy is a key factor in programming the immune response toward an allergic phenotype.⁶⁵ Thus children brought up in livestock farming communities have a substantially lower risk for development of allergies.⁶⁶ It is suggested that exposure to bacteria or their products (eg, endotoxin) polarizes the immune response toward a protective T_H1 phenotype by

enhanced IL-12 (or IL-18) production by professional antigen-presenting cells such as dendritic cells,⁶⁷ thereby providing a negative signal for T_H2 polarization by enhanced IFN- γ production. The lower prevalence of allergic disease in formerly communist countries and the subsequent increase that has been observed since reunification has also been cited as supporting the "hygiene hypothesis" of allergic disease, as has the increased urban-to-rural gradient of allergic sensitization in African communities.⁶⁸ However, what is notable about the changes in prevalence being observed in the former Eastern Bloc countries and in Africa is that allergic sensitization has increased but asthma and BHR has not.⁶⁹ This adds further evidence to the view that asthma and allergy are not equivalent or even linearly related and that local organ-derived factors are important. The recent description of a polymorphism of CD14, the endotoxin receptor that is linked to the development of atopy in children, is of great interest⁷⁰ and will encourage a search for other candidate gene polymorphisms linked to susceptibility to early life infection, including IFN- γ , natural resistance-associated macrophage protein-1, natural resistance-associated macrophage protein-2, and the mannose-binding protein.

INTEGRATED MODEL FOR EPITHELIAL-MEDIATED ALLERGIC DISEASE

Although genetic and environmental factors that operate to direct the immune response toward the T_H2 phenotype are fundamental to understanding the origin and pathogenesis of allergic diseases, genetic and the environmental factors that direct this response to selected organs are of key importance. Eczema is a strong predictor of asthma persistence and, in chronic severe disease, there is evidence for gastrointestinal epithelial permeability and inflammation. Therefore the epithelium may play a particularly important role in directing the inflammatory and remodeling responses in chronic allergic disease. Subepithelial deposition of interstitial (repair) collagens, impaired epithelial proliferative responses to damage, enhanced inflammatory and cytokine growth factor secretion, and evidence for altered subepithelial myofibroblast function in asthma suggest a fundamental abnormality in the epithelial-mesenchymal trophic unit that is involved in fetal lung development.^{71,72} Abnormal signaling between the epithelium and myofibroblast and to dendritic cells provides a basis for asthma that encapsulates both T_H2 polarization and airway wall remodeling. Whether this hypothesis can be sustained will require research at the gene by environment interface and its application to disease as it occurs in humans.

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