

5. Genetics of hypersensitivity

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Genetics provides the basis for the host response to a variety of environmental factors that can play a role in the generation of complex genetic diseases, such as asthma and atopy. An understanding of the genetic bases for these conditions is therefore essential to understand their pathophysiology. Studies of the genetics of asthma and atopy have suffered from several daunting challenges. These include the recognition that these are conditions caused by numerous genes, with each gene assuming variable roles in different individuals. In addition, each gene presumably contributes only a small percentage to a given individual's genetic risk of asthma. This has led to the current situation, in which studies often demonstrate a lack of replication that can be explained by their being insufficiently powered. Furthermore, the pathophysiologies of asthma and atopy are incompletely understood, and the lack of clearly defined phenotypes also contributes to the inadequacies of the current literature. Nonetheless, regions of the human genome have been reproducibly associated with asthma and atopy. These regions have undergone intense study, and many genetic variants within them have been implicated as asthma and allergy genes. In addition, through candidate gene approaches, several genetic polymorphisms have been convincingly linked to increased risks for the development of asthma and atopy. Many of these genes are associated with alterations in responsiveness to therapeutic agents used in the treatment of these conditions. These genetic studies have an exciting potential for individually tailoring the therapeutic regimen to a given subject's genotype. It is to be hoped that they will also define new targets for the next generation of asthma and allergy therapeutic agents. (J Allergy Clin Immunol 2003;111:S495-501.)

Key words: Allergy, genetics, candidate genes, single-nucleotide polymorphism

The idea that genetics plays a role in allergic disease and asthma has been recognized for the past 100 years. This genetic component was clear to asthma and allergy investigators as early as the first and second decades of the 20th century^{1,2} through observations that allergic subjects had a significantly higher incidence of family histories than did control subjects. After those early works, however, the lack of strong support for either dominant or recessive modes of inheritance led to a period during which the entire idea of inheritance of atopy was in ques-

Abbreviations used

SLO: 5-Lipoxygenase gene
ADAM-33: A disintegrin and metalloproteinase
CCL2: Monocyte chemoattractant protein 1 gene
CCL5: Eotaxin gene
LTC4S: Leukotriene C₄ synthase gene
SNP: Single-nucleotide polymorphism
STAT-6: Signal transducer and activator of transcription-6
TIM: T-cell integrin mucin-like (gene family)

tion. This led to the recognition that allergies and asthma represent examples of complex genetic disorders, disorders that have numerous contributing genes, each with variable degrees of involvement in any given individual. In addition to genetics, environmental exposures, including allergen exposure, secondhand cigarette smoke, pollutants, low birth weight, infectious agents, and numerous others, all contribute to the development of allergies and asthma through their ability to influence gene expression.

The contribution of genetics to these disorders was first identified by the analysis of twin studies.³⁻⁶ Twin studies are a useful means of generating evidence of a genetic contribution in disorders with contributions from both inherited and environmental influences. Twins raised in the same household, whether monozygotic or dizygotic, share many of the same environmental influences. Whereas monozygotic twins have identical genomes, dizygotic twins have, on average, only half of their chromosomes in common. Thus a higher concordance rate of a given condition in monozygotic twins provides evidence for the presence of genetic influences. These data provide the statistical information necessary to estimate the relative contribution provided by genetic, as opposed to environmental, factors in a complex genetic condition. Inspired by the pioneering work by Hopp et al,⁵ it was considered that approximately 50% of the risk for development of asthma might be related to the environment, with an equivalent risk associated with inheritable factors. Of further interest in these early studies was the trend toward a slightly greater tendency toward maternal inheritance of asthma and allergy than paternal inheritance, a phenomenon not readily explained by traditional Mendelian concepts of inheritance.

POSITIONAL CLONING

One approach to identifying disease-causing genes involves searching the entire genome with a technique termed *positional cloning*. This technique is based on the presence of highly polymorphic genetic markers with positions on a chromosome that are known. Markers

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close to the disease gene will statistically be coinherited with the disease when multiple families are analyzed. Typically, these approaches can only localize a marker to within approximately 10^6 bp of the actual gene. Identification of such a closely linked marker is then followed by "chromosomal walking" until the exact mutant gene is found. This is an enormous task, even with today's molecular biology techniques. With the completion of the human genome project, however, the more usual approach has been to access the latest map of the human genome and obtain a list of all of the genes localized to the chromosomal region where a linkage marker is identified. It is then possible to determine whether mutations, either in one of these genes or in adjacent regions that may influence gene expression, could be contributing to the development of allergies and asthma. Often obvious candidate genes can be identified within that region, and their roles in the genetics of allergy can be determined. However, the function of most of the genes identified through the human genome project is not known. Insofar as one of the major objectives of doing positional cloning is to identify previously undiscovered genes, these may be among the more interesting genetic discoveries.

The past 15 years have opened the door to positional cloning with linkage studies within families as a means of identifying markers that may be linked to allergies and asthma. Several problems, however, have limited the value of these studies. These include the confounding influences of genetic heterogeneity, incomplete penetrance, and the importance of both genotype-environment and gene-gene interactions. Positional cloning studies optimally require unambiguous phenotypes. However, the absence of exact definitions of asthma, atopic dermatitis, and other atopic diseases has contributed to the frustrating lack of replication observed in linkage studies. A more useful but still problematic approach has been to perform linkages to what are termed *intermediate phenotypes* that may be better quantified. These intermediate phenotypes include bronchial hyperresponsiveness, airway function, skin test reactivity to inhalant allergens, total and specific IgE levels, and so on. The inability to unambiguously phenotype family members and the lack of general consensus as to how these available measures should be performed and interpreted have contributed to the current confusion, wherein a genetic linkage to a particular trait shown in one study is often unconfirmed in a second study or alternatively shows a positive linkage but to a distinct trait. Many genome-wide searches have also been inconclusive, because they were underpowered with respect to the number of families in the genetic analysis. Asthma and allergies represent the cumulative influence of many, perhaps dozens, of genes. Different genes presumably act in different families and different individuals. In addition, each gene presumably contributes only a small percentage of a given individual's genetic risk for development of asthma. Because of these issues, thousands of families need to be studied to draw conclusive evidence for a role for a given genetic marker. This represents a daunting

task, and the failure to properly power these studies has contributed to the disappointing results obtained from positional cloning research. Nonetheless, during the past decade at least 18 to 20 genome screens with a variety of intermediate phenotypes have been reported.⁷⁻⁹ These studies have given us hints and have identified genetic markers that are linked with allergies and asthma. The earliest genome-wide search was performed by Moffatt et al¹⁰ at Oxford. With the technology available at the time, these investigators performed linkage analyses to a very limited number of polymorphic DNA markers to either allergen-specific IgE or a high total serum IgE. Their analysis showed a linkage to chromosome 11q when linked to maternal but not paternal phenotype. As has been typical of these genetic studies, significance of this linkage to chromosome 11 has been controversial, insofar as several other groups were unable to confirm these data.¹¹⁻¹⁵ Analysis of 11q demonstrated that this marker mapped near the gene for the β chain of the high-affinity IgE receptor (Fc ϵ RI). Whereas the α and γ chains of the high-affinity IgE receptor are sufficient for sending signals to the cell for activation, the β chain is important as an amplification mechanism for this signaling pathway and permits mast cell activation in the presence of fewer cross-linked IgE molecules. These authors have suggested that base exchanges in the cytoplasmic region of the β chain may be the disease-causing mutations.

Several more extensive genome-wide searches have now been reported.^{7,8,16} The National Heart, Lung, and Blood Institute funded the multicenter Collaborative Study on the Genetics of Asthma. Their initial genome screen involved three racial groups (blacks, whites, and Hispanics),¹⁶ and more recently this group has reported information on individuals of Hutterite ancestry.⁸ Together, these studies have uncovered approximately 15 separate promising linkages, including several in previously unsuspected regions of the human genome. Several of the more promising linkages have been confirmed by competing investigators in different populations (summarized in Table I). These include a locus on chromosome 2 near the IL-1 cluster that includes the genes for CD28 and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and the major histocompatibility complex (MHC) complex on chromosome 6. Not surprisingly, the chromosome 5 cytokine gene cluster that includes the genes for IL-3, IL-4, IL-5, IL-9, IL-13, and granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as the gene for leukotriene C₄ synthase, has been linked to allergies and asthma. Genome-wide searches have also supported presence of potential allergy and asthma genes on chromosome 12 in association with IFN- γ and signal transducer and activator of transcription-6 (STAT-6). Other important loci may be present on chromosomes 13 and 19. Many of the reported putative sites of asthma susceptibility genes may ultimately prove to be false-positive results. Similarly, it would not be surprising if ultimately even more asthma susceptibility genes were to be identified. Multiple genes are involved in the pathophysiology of allergies and asthma, each of

which may individually be contributing only a small percentage of the total genetic predisposition toward these conditions. To date, the application of positional cloning to the identification of genes in complex genetic disorders has been disappointing, and this disappointment has led to greater attention to detection of polymorphisms in candidate genes.

CANDIDATE GENE STUDIES

The understanding that whole-genome screens may not be the best way to analyze the genetics of asthma and atopy has led to use of candidate gene studies. Candidate genes include all of the numerous biochemical markers that are known to either be abnormally regulated or otherwise function inappropriately to produce allergies and asthma (Table II). Candidate gene studies consist of aggressively studying a narrow region of the genome with numerous polymorphic markers that saturate the region of interest in a fashion that would not be practical with a genome-wide scan.¹⁵ Several statistical techniques are used in these candidate gene approaches. In association studies, a particular gene thought to have pathologic consequences is examined for its variance in predicted frequency in populations with and without the suspected syndrome. This approach can confirm candidates as being important to the genetics of atopy and asthma, but it ignores the contributions of other unknown and unbiased loci that may be important. A tool that has been used to enhance the power of association studies and maintain some of the power of linkage studies has been to perform transmission disequilibrium testing. This involves assessing the frequency with which a potential disease-causing allele is transmitted to an affected offspring from either parent.¹⁷

Recently, the structure of the human genome has been broken into haplotype blocks. The identification of these haplotype blocks will further enhance the concept of linkage disequilibrium and recombination hot spots that potentially control inheritance of a wide variety of shared traits associated with these haplotype blocks. These haplotype blocks can be incorporated into the transmission disequilibrium testing and association studies to enhance the power of genetic analyses looking for association of portions of the genome with particular complex traits.¹⁸ This approach may be a promising first step in genetic analysis.

A recent study has demonstrated the utility of positional cloning techniques when combined with candidate gene analyses to potentially identify asthma and allergy genes. A genome-wide scan performed on 460 families identified a relatively strong linkage of asthma and bronchial hyperresponsiveness with markers on chromosome 20p13. A subsequent survey of 135 polymorphisms in 23 genes within this region identified the gene for ADAM-33 as being significantly associated with asthma, according to both association and transmission disequilibrium analyses.¹⁹ ADAM-33 is a protease active at the cell surface and is part of the matrix metalloproteinase family. Its role in asthma is speculative, but expression of this protein on epithelium, smooth muscle, and inflam-

TABLE I. Linkages with asthma and allergy

Chromosome	Candidate genes or products
1p	IL-12 receptor
2q	IL-1, cytotoxic T lymphocyte-associated antigen 4, CD28
3p24	B-cell lymphoma-6 (STAT-6 binding inhibition) Chemokine cell receptor 4
5q23-35	IL-3, IL-4, IL-5, IL-9, IL-13, GM-CSF <i>LTC4S</i> Macrophage colony-stimulating factor receptor β_2 -Adrenergic receptor Glucocorticosteroid receptor <i>TIM1</i> , <i>TIM3</i>
6p21-23	MHC TNFs Transporters involved in antigen processing and presentation (<i>TAP1</i> and <i>TAP2</i>) Large multicatalytic proteolytic particles
7q11-14	T-cell receptor γ chain, IL-6
11q13	High-affinity IgE receptor (Fc ϵ RI) β chain Clara cell protein 16 Fibroblast growth factor 3
12q14-24	IFN- γ Stem cell factor Nitric oxide synthetase (constitutive) β Subunit of nuclear factor Y (transcription factor for HLA genes) Insulinlike growth factor 1 Leukotriene A ₄ hydrolase STAT-6 (IL-4 STAT)
13q21-24	Cysteinyl leukotriene 2 receptor
14q11-13	T-cell receptor α and δ chains Nuclear factor κ B inhibitor
16p11-12	IL-4 receptor
17p12-17	CC chemokine cluster
19q13	CD22, transforming growth factor β_1
20p13	ADAM-33

matory cells may alter the response of lymphocytes and inflammatory cells to cytokines by altering turnover of receptor proteins. It also might alter growth factor expression and remodeling responses in the basement membrane to damaged epithelium and smooth muscle of the airway.²⁰ These highly speculative functions of ADAM-33 need to be confirmed, but the genetic evidence suggesting ADAM-33 as a target in asthma has begun to be accumulated.

GENETIC POLYMORPHISMS

It is thought that the vast majority of genetic variants that contribute to complex genetic disorders probably represent the contribution of base exchange mutations in individual DNA bases, termed *single-nucleotide polymorphisms* (SNPs). Other genetic mechanisms, including deletions and transpositions, may also play a role. SNPs occur in approximately 1 in 1000 bp throughout human genomic DNA. Because there are 4.2 billion bases within the human genome, that would suggest that there are at least 4 million SNPs that contribute to all of our individual characteristics, including height, weight, person-

TABLE II. Candidate genes of atopy and allergy

	Examples
Cytokines influencing allergic phenotype	
Eosinophil growth, activation, and apoptosis-inhibiting factors	IL-5, IL-3, GM-CSF, eotaxin, RANTES
Mast cell growth factors	IL-3, IL-9, IL-10, nerve growth factor, stem cell factor, transforming growth factor β
Histamine-releasing factors	Monocyte chemoattractant protein 1, monocyte chemoattractant protein 3, RANTES
IgE isotype switch factors	IL-4, IL-13
Inhibition of IgE isotype switch	IFN- γ , IL-12, IL-18, IL-23
Lipoxygenase pathway metabolism	5LO, 5-lipoxygenase-activating peptide, leukotriene C ₄ synthase
Pro-inflammatory cytokines	IL-1 α , IL-1 β , TNF- α , IL-6
Anti-inflammatory cytokines	Transforming growth factor β , IL-10, interleukin-1 receptor antagonist
Receptors	
Antigen receptors	T-cell receptors (α/β , γ/δ), B-cell receptor (Ig, κ/λ light chain)
IgE	Fc ϵ RI β chain, Fc ϵ RII (CD23)
Cytokine gene receptors	IFN- γ receptor β chain, macrophage colony-stimulating factor receptor, IL-1 receptor, IL-4 receptor, TNF receptors
Adhesion molecules	Virus-like agent 4, vascular cellular adhesion molecule 1, intercellular adhesion molecule 1, leukocyte functional activating molecule-1, TIM1, TIM3
Corticosteroid receptor	Glucocorticoid receptor-heat shock protein 90
Neurogenic receptors	β_2 -Adrenergic, cholinergic receptors
Nuclear transcription factors	Activating protein-1, nuclear factor of interleukin-2, octamer transcription factor-1, STAT-1/2, GATA3, T-box expressed in T cells, nuclear factor κ B, inhibitor of nuclear factor kappa B, nuclear factor of activated T cells, STAT-4, STAT-6, BCL-6

TABLE III. Useful links between polymorphisms and disease

- Change in gene causes relevant alteration in function or level of gene product.
- Association study has adequate power.
- Mechanism is biologically plausible.

ality, eye color, hair color, and so on. SNPs are usually silent, with no effect on either gene structure or gene expression. Most interest has focused on the contributions of SNPs in the coding sequence of genes, termed

coding SNPs, that impact protein structure. However, SNPs that occur in gene promoters and enhancers or in sequences that influence chromatin structure may modify gene expression and thereby also have important genetic effects. The importance of SNP biology has led to a consortium of biotechnology and pharmaceutical companies working to develop a complete SNP map of the human genome.

To prove that a given SNP is directly contributing to the disease process, certain criteria have to be addressed. These concepts are summarized in Table III. First, the polymorphism needs to cause a relevant alteration in either the function or level of expression of the candidate gene product. Second, the SNP variant needs to have a linkage study done with adequate power to confirm its association with the disease. Finally, the most stringent criterion for linking SNPs to disease would be to examine the gene mutation in an animal model in which the natural gene has been knocked out and replaced with the relevant variants of the human gene. A full accounting of the potential role of SNPs in asthma and atopy is not yet available. However, this approach has been analyzed in a hypertension study, in which 75 candidate genes were plausibly identified and 874 SNPs have been identified within those genes.²¹ Approximately 44% were coding SNPs, and 24% had the possibility of altering one of these proteins.²¹ One would expect that the genetics of asthma and atopy would be just as complex.

CANDIDATE GENES OF ASTHMA AND ALLERGY

Candidate genes of asthma and allergic disease include the numerous genes that regulate IgE production and the proliferation and maturation of allergic effector cells, including eosinophils and mast cells (Table II). Many of these genes are clustered on the long arm of chromosome 5, including the genes for IL-3, IL-4, IL-5, IL-9, IL-13, and GM-CSF.²² Additional genes in this area that may be relevant to asthma include those for the corticosteroid receptor, the macrocyte colony-stimulation factor receptor, the β_2 -adrenergic receptor, and leukotriene C₄ synthase.²³ Although these cytokines themselves are not polymorphic, mutations within nearby regions of DNA that are responsible for regulating transcription may influence their tendency to be produced after allergen exposure, thereby contributing to the development of asthma and allergies. Several studies have reported linkages of polymorphisms present on chromosome 5q with asthma and atopy.^{24,25} Marsh et al²⁴ found evidence for genetic linkages with high-IgE phenotype (but not specific IgE) for several markers within a narrow region of 5q near the IL-4 locus. Similar results were obtained from the study by Meyers et al,²⁵ who demonstrated highly significant linkages with total IgE; in contrast to Marsh et al's study,²⁴ however, their most significant linkage markers were nearer the IL-9 and β_2 -adrenergic receptor loci. These authors subsequently reported a separate linkage with bronchial hyper-

responsiveness within this gene cluster.²⁶ Follow-up studies on different populations have both confirmed²⁷ and failed to confirm^{15,28,29} strong linkages between asthma and this chromosome 5 cluster, so the ultimate significance of these findings has yet to be established.

Because of the reported linkages of allergies and asthma with the chromosome 5 region, which includes the genes for IL-4 and IL-13, and with mutations within the IL-4 gene itself, analyses were performed with chromosome 16 markers flanking the IL-4 receptor gene that is used by both of these cytokines.³⁰ Significant linkage of chromosome 16p with enhanced IgE responsiveness of maternal but not paternal alleles was found in two independent populations and confirmed by transmission disequilibrium testing.⁷ Significant linkages have also been made with polymorphisms within or flanking the IL-13 receptor α gene on the X-chromosome. Increased IgE synthesis that linked to a promoter polymorphism in the IL-10 gene located on chromosome 1 has also been observed in asthmatic probands.³¹ This polymorphism has also been linked in numerous studies examining autoimmune diseases.

It is intriguing to note that there are genetic variants of the genes for IL-4, IL-13, IL-4 receptor α , and IL-13 receptor $\alpha 1$ that have been linked with asthma and atopy and may contribute to either high or low outputs of these cytokines and their receptors. Combining high output of IL-4 and IL-13 with gain-of-function variants in IL-4 and IL-13 receptor represents an example in which gene-gene interactions may be important in the development of asthma. These polymorphisms may contribute to an overproduction of T_H2 cells and thus a predisposition toward the development of atopy and asthma.^{24,32-35} Recent studies have identified variants in additional candidate genes within the human chromosome 5q 31-33 complex, *TIM1* and *TIM3* (TIM stands for *T-cell integrin mucin-like*). *TIM1* and *TIM3* encode receptors that influence the development and function of T_H2 and T_H1 lymphocytes, respectively. Polymorphisms that control varying expression of these genes may thereby influence immune deviation of T helper cells.^{36,37} Of interest is the fact that *TIM1* is the hepatitis A virus receptor.³⁶ This may be related to the reported ability of hepatitis A virus infection to protect against the development of asthma. It is speculated that engagement of the *TIM1* receptor by hepatitis A virus may protect against the development of T_H2-directed immunity.³⁸⁻⁴⁰

Chromosome 12 is a particularly strong candidate region with several genes in close association, including those for interferon- γ , nitric oxide synthetase, stem cell factor, insulinlike growth factor 1, the β subunit of nuclear factor Y, and STAT-6 (Table I). With this candidate region approach, both asthma and total IgE levels have been linked with chromosome 12q in several separate populations.⁴¹⁻⁴³ Further support for a role of STAT-6 in asthma susceptibility is derived from the observation that the transcription factor B-cell lymphoma-6 is an inhibitor of IL-4's biologic activity through its ability to interfere with the binding of STAT-6 to its DNA-recognition

motif. The gene for B-cell lymphoma-6 is present on chromosome 3p24, an area linked with asthma in the collaborative study.⁸

Additional candidate regions include immune response-regulating genes on chromosome 6, such as the MHC class I and class II alleles. The MHC determines both whether an immune response develops to a specific antigen and the intensity of that response.⁴⁴⁻⁴⁶ Linkages to MHC are likely only to explain a heritable basis for the specific immune response to a given allergenic epitope, rather than the development of asthma or allergies. For example, allergic responses to the ragweed antigen Amb a 1,⁴⁷ the rye grass antigens Lol p I and II,⁴⁸ and the mite antigen Der p 1^{49,50} have been linked with specific MHC class II loci. Several other genes within the MHC locus have obvious relevance to immune function and may also influence atopic and asthmatic phenotype. These include the tumor necrosis factor genes and genes involved in antigen processing and presentation, including those associated with proteolysis of antigens (large multicatalytic proteolytic particles) and with transport of antigenic peptides to MHC class I molecules (transporters involved in antigen-processing and presentation, *TAP1* and *TAP2*). These genes are known to be polymorphic,^{51,52} and this variability may contribute to disease susceptibility.⁵³

Just as it might be predicted that MHC genes could influence the intensity of the immune response to a specific allergen, it has also been proposed that the T-cell receptor genes may similarly contribute to the genetic component of allergy. The structure of the T-cell receptor determines the affinity of the interaction of the T-cell with allergen and thus contribute to the intensity of immune responses to specific allergens. Associations have been found between polymorphic markers within T-cell receptor loci on chromosomes 7q and 14q and the tendency toward allergic immune responses to dust mite and cat allergens.⁵⁴

In addition to promoters and coding regions of cytokine genes, several studies have demonstrated a linkage of asthma or atopic diseases with chemokine genes. The Collaborative Study on the Genetics of Asthma demonstrated evidence for linkage of asthma with the C-C chemokine cluster, mapped to chromosome 17p11, in a black population.⁵⁵ Two promoter polymorphisms have been identified in the *CCL5* (RANTES) gene located in this gene cluster. The polymorphism at position -403 was a G-to-A base pair exchange that created a new transcription factor (GATA 3) binding site, resulting in increased promoter activity. This polymorphism was associated with atopic dermatitis in both white and black descendant populations, and in a different study this polymorphism was linked with both asthma and atopy.^{56,57} Another group studying a Japanese population showed association of a polymorphism at position -28 of the *CCL5* gene with susceptibility to late-onset asthma, whereas no association with asthma was observed with the -403 polymorphism.⁵⁸

Recently, two groups have identified a G-to-A base pair exchange at position +67 within the coding region of the *CCL11* (eotaxin) gene that results in an amino acid

change from an alanine to threonine. Nakamura et al. showed that cells expressing the A variant of the *CCL11* gene secreted less eotaxin than did cells with the G variant.⁵⁹ Patients with asthma with the A variant had decreased eosinophil counts and higher levels of lung function. Miyamasu et al⁶⁰ found no associations of this polymorphism with susceptibility to asthma, suggesting that this base exchange may influence the severity of asthma rather than being a causative agent.

An A-to-G polymorphism at position -2518 in the distal promoter region of the *CCL2* (monocyte chemoattractant protein 1) gene influences the level of *CCL2* expression in response to IL-1 β .⁶¹ As with the *CCL11* polymorphisms, the *CCL2* polymorphism correlates with asthma severity. Asthmatic patients homozygous for the G allele displayed increased blood eosinophil levels and increased asthma severity.⁶²

PHARMACOGENETICS

Pharmacogenetics, which is defined as the study of variation in drug response in different individuals as a result of genetic differences, is one of the potential uses of an understanding of the genetics of complex diseases. Genetic variations in drug target genes can be used to predict clinical responsiveness to treatment. Polymorphisms have been reported in the promoters of the 5-lipoxygenase gene (*5LO*) and leukotriene C₄ synthase gene (*LTC4S*), which are involved in cysteinyl leukotriene production. Abnormalities in the transcriptional regulation of these genes may be important in producing the aspirin-sensitive phenotype and may identify individuals who will be more responsive to leukotriene modifiers. Base exchanges in the *5LO* promoter alter the number of binding sites for the stimulator protein 1 transcription factor and influence promoter strength. Their role in aspirin sensitivity remains speculative; however, these alternative genotypes influence responsiveness to the 5-lipoxygenase inhibitor zileuton.⁶³ Similarly, mutations with the *LTC4S* gene, coded for in the cytokine gene cluster complex on 5q, link with aspirin-sensitive asthma.⁶⁴

Similar findings have been related to the response of airways to β -agonists. Four structural genetic variations within the β_2 -adrenergic receptor gene, which is also coded within the 5q31 complex,⁶⁵ have been identified. Although none of these amino acid substitutions have been linked to the presence of asthma, they have been associated with asthma severity. The presence of glycine at amino acid residue 16 is associated with the presence of corticosteroid-dependence, nocturnal symptoms, and loss of bronchodilator responsiveness with long-term administration of albuterol. In contrast, the presence of glutamine at amino acid residue 27 is associated with less severe bronchial hyperreactivity. Finally, a component of the steroid responsiveness and steroid resistance observed in asthmatic populations is due to variations in the glucocorticoid receptor (another gene coded within the 5q31 complex). These pharmacogenetic variants may be of great value in trying to craft and develop individualized forms of treatment for asthma.

In the future, it will be possible in the clinical setting to analyze the patient's genetic repertoire. From this information, the physician will gain insight into the genes involved in producing that subject's allergic or asthmatic phenotype and predict responses to pharmacologic agents. The end result will be the ability to tailor a specific treatment regime to each patient.

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