

The genetics of atopy

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The study of the genetics of atopy is important to identify the contribution of multiple sets of genes that interact in producing the allergic syndrome in conjunction with prior and proper environmental exposure to protein allergens, chemical sensitizers, viral or bacterial products, or food allergens. If a genetic basis for atopy can be identified, especially in those specifically sensitive to inhalant allergens and with asthma, this would represent a great advantage in identifying those populations at greater risks at different times in their lives to significant syndromes such as anaphylaxis, atopic dermatitis, asthma, and significant food allergy. The predominance of a single gene or even the sole influence of a single gene or single set of genes in atopy is very unlikely. A more credible scenario involves the interaction of multiple sets of genes, each contributing a small percentage to the pathophysiology of the allergic diathesis. Elucidation of these many genes will be critical to develop strategy aimed not only at genetic counseling and screening but also to identify newer mechanisms of immunopathogenesis and to aid in drug discovery in the treatment of allergic disease including food allergy. That genetics plays a major role in atopy is without question, since twin studies have shown a greater prevalence of disease in monozygotic than dizygotic twins. However, the genetics of complex diseases which will be reviewed in my presentation identifies the fact that multiple genes with multiple degrees of heterogeneity make the dissection of the genetic contribution in populations that have a general predisposition to atopy very difficult. The relative risk of atopy, as compared to other relatively restricted diseases of immune dysregulation and/or autoimmunity including SLE, multiple sclerosis, and insulin-dependent diabetes mellitus, will all be compared to allergy and atopy, as will more multigenic diseases that perhaps fit an atopy

mold better, including hypertension and cardiovascular disease.

The development of techniques to sequence the entire human genome is underway, and worldwide attempts to collaborate within the genome project have made genetic analysis of complex disease a more attractive goal in the past 6-7 years (1, 2). There are three or four approaches that one may take to identify the genetics of complex disease, ranging from study of functional candidate genes through a whole-genome screen looking for hot spots linked to markers, followed by more usual methods of gene identification, and finally an area known as transitional cloning or inspirational cloning, in which candidate genes for a particular complex disease can be saturated with markers in a whole-genome screen to enhance clearly the possibility of picking up genetic hot spots for disease. All of these will be examined as a potential for identifying disease linkages to genetic loci in various complex genetic disease models.

The association of asthma and atopy with genetic analysis has elucidated a number of linkages primarily to four major chromosomal locations thus far, although other candidate gene loci and chromosomal placements are sure to emerge as complete genome screening is applied to unique populations. Suffice it to say that there have been linkages in atopy and asthma to chromosome 6 for human lymphocyte antigen and tumor necrosis factor (3), to chromosome 7 for the T-cell receptor α genes (4), to chromosome 11 for presumed polymorphisms in the high-affinity IgE Fc receptor 1β chain (5, 6), and to chromosome 5 where multiple linkages have been associated with primarily interleukin (IL)-4, IL-9, and the β_2 -adrenergic receptor at this point (7-11). In my presentation, we will examine further molecular approaches to the question of the genetics of atopy by examining

in great detail transcriptional dysregulation of the cytokine genes of chromosome 5 in relation to atopic population-based promoter polymorphisms associated with functional outcomes in terms of enhanced gene output and enhanced interleukin activity. For example, we have been able to identify a significant polymorphism in the promoter region of the IL-4 gene associated with enhanced IgE at a population level and a number of other population genetic effects that are associated with the phenotype of the asthmatic syndrome in atopics. We have examined in great detail the transcriptional regulation of IL-4 surrounding this promoter-based polymorphism and have been able to uncover novel mechanisms for nuclear factor of activated T cells (NFAT) function in the promotion of the IL-4 gene. Elucidation of these molecular mechanisms associated with genetic linkages will help clarify the differences between background noises in genome screening and true genetic microheterogeneity in complex diseases such as asthma where molecular variants on a wide number of genes, perhaps as many as 12–20 genes, each with five to six molecular variants, will be required to understand fully the potential contribution of genetics.

The actual contribution of genetic components to asthma remains even more obscure than the relationship of genetics to atopy in general, since the clinical syndrome of asthma has been somewhat difficult to characterize consistently. The firm genetic basis for some of the variants seen in asthma has not yet even begun to be approached. However, identification of candidate genes from general studies of atopy and asthma can be extrapolated to airways hyperresponsiveness, and then new, unique mechanisms that can be uncovered by basic research into airway immunity may further identify other candidate genes unique to the pathogenesis of asthma.

The purpose of this discussion will be to examine the potential role of food allergens in the generation of the overall food-allergic syndrome. While the overall genetics of atopy may be similar for asthma, atopic dermatitis and other skin diseases, and, presumably, food allergy, there may still be unique genes that combine with the general atopy genes to give the overall syndrome of significant food allergy. An examination of those issues will also be studied and discussed in the presentation. Tables 1–3 examine candidate genes that are present in linkages suggested by the whole-genome screens (12, 13) that identify candidate genes that reflect CD4⁺ TH2 T-cell activation and candidate genes that reflect hyperreactivity and inflammation in Tables 1 and 2, and in Table 3 multiple spots at the genetic control of IL-4 in the cascade may be potential candidate genes for the genetics of atopy

Table 1. Candidate genes that reflect CD4⁺ TH-2 activation

Recognition genes	MHC, TCR
Signaling genes	STAT, STAT-5, STAT-6
Cytokine genes	5q32, 33, INF, TNF, TGF- β
Cytokine receptors	IL-4R α , IL-2R β
Transcription factors	NFAT, c-maf, EGR

Table 2. Candidate genes that reflect hyperreactivity and inflammation

β 2AR
GCR
iNOS
LTC-4 synthase

as well on the basis of the effect of IL-4 in generating allergic and atopic responses.

IL-4 is a critical cytokine in the expression of atopy and allergic diseases. Through its receptor, a unique IL-4 receptor α chain and the common lymphoid receptor γ chain, it signals target cells and tissues to mount a response. IL-4, through its receptor, triggers B cells to produce IgE. IL-4 induces the endothelium to express adhesion molecules that specifically attract eosinophils. Finally, IL-4 signals T cells to become CD4⁺ TH2 cells which further produce IL-4 and mediate allergic disease (14).

Genetic regulation of this IL-4 cascade may be an important “choke point” or regulator in the genetic predisposition to allergy. We have already published work demonstrating gain of function polymorphisms in the IL-4 gene associated with

Table 3. Genetic control of IL-4 cascade

Allergen
↓
NFAT
↓
IL-4
↓
IL-4R
↓
STAT-6
↓
↑ Biologic activity
(IgE, allergic inflammation, asthma)

greater IL-4 output (15, 16), the higher output form of the IL-4 gene promoter being associated with asthma, skin test positivity, and total IgE. Recent reports extend the genetic regulation of the IL-4 cascade to the IL-4 receptor α chain (17). This report identifies a nucleotide exchange in the IL-4 receptor α chain that is associated with greater IL-4 signaling and function in a variety of *in vitro* assays. Basically, the genetic exchange within the cytoplasmic domain of the receptor alters the ability of the receptor to bind to tyrosine kinases intracellularly and leads to greater IL-4 activity. This is true in atopic patients and those with the hyper-IgE syndromes. Studies that have now implicated the IL-4 gene and the IL-4 receptor gene in asthma must now also examine other candidates in the IL-4 signaling pathway including JAK kinases and the STAT-6 transcription factor. Furthermore, transcription factors that induce IL-4 gene activation and, presumably, function in the selection of CD4⁺ TH2 cells must also be considered. Both the IL-4 gene and the IL-4 receptor α gene have been shown to be linked to atopy and asthma in previously published studies (7, 18, 19).

The relationship of these studies to the overall study of the genetics of asthma and atopy needs to be commented upon. In a complex syndrome such as atopy or asthma, the predominance of a single gene or even the overriding influence of a small number of oligogenes is unlikely. A more credible scenario would involve the interaction of multiple sets of genes, or polygenes, each contributing a small amount to the pathophysiologic condition of asthma. Such mechanisms are highlighted in the above studies on IL-4.

To date, three types of studies of the genetics of asthma and atopy have been done. The first involves utilizing candidate genes to generate linkage or association studies in families or populations of patients with disease to establish those particular candidate genes as potentially being involved in disease (3–5, 8, 9, 20). A second approach has involved utilizing DNA microsatellite markers to scan the entire genome and to look for linkages associated with asthma in families. Two such studies have been reported in the past year and have turned up multiple linkages within the genome, each of which may be associated with attractive candidate genes (12, 13). Although the overall point of doing positional cloning is to identify new, heretofore undiscovered genes that might be associated with disease, these studies have uncovered at least 14 or 15 separate linkages, some of which may be false positives. Nonetheless, multiple genes are probably involved in the asthmatic syndrome, each of which may be contributing a small percentage of the total genetic influence of the

disease. Yet, each makes an important contribution, along with environmental exposure, to the development of the syndrome. The third form of studies undertaken has identified structure and function associations with polymorphisms or mutations in the DNA and/or protein structure of candidate genes and/or their promoters/enhancers. Examples of these include the IL-4 gene studies cited above; other examples include the alternate forms of the β chain of the high-affinity receptor (Fc ϵ RI) and structural variants in the β -adrenergic receptor (6, 10, 11).

These studies of genetic variation in IL-4 function will provide a means of assessing potential genetic mechanisms in complex disease associated with atopy. However, these changes are too subtle to be considered as targets for gene therapy. Hence, their value will be as markers for susceptibility and as models for newer treatments for allergic disease and asthma.

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