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Gene-environment interactions in asthma

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Activity Objectives

1. To relate examples of clinical manifestations of asthma that reflect interaction between genetic factors and environmental influences.

2. To describe the utility of linkage studies, genome wide association studies, and candidate gene approaches for understanding the genetics of asthma.

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Asthma is a complex disease, and its incidence is determined by an intricate interplay of genetic and environmental factors. The identification of novel genes for asthma suggests that many genes with small effects rather than few genes with strong effects contribute to the development of asthma. These genetic effects may in part differ with respect to a subject's environmental exposures, although some genes may also exert their effect independently of the environment. Whereas the geneticist uses highly advanced, rapid, comprehensive technologies to assess even subtle changes in the human genome, the researcher interested in environmental exposures is often confronted with crude information obtained from questionnaires or interviews. There is thus substantial need to develop better tools for individual exposure assessment in all relevant environmental fields. Despite these limitations, a number of important gene-environment interactions have been identified. These interactions point to the biology of environmental exposures as the involved genetic variation is suggestive of certain underlying mechanisms. Furthermore, the identification of subjects who are particularly susceptible to environmental hazards through genetic analyses helps to estimate better the strength of effect of environmental exposures. Finally, the analysis of gene-environment interactions may result in a reconciliation of seemingly contradictory findings from studies not taking environmental exposures into account. (J Allergy Clin Immunol 2009;123: 3-11.)

Key words: *Asthma, genes, environment, interactions*

Asthma is not well understood. As with many other ill-defined diseases in which numerous extrinsic influences and a number of intrinsic factors contribute to the new onset of the condition, the term *complex disease* is used. Such terminology implies complicated relations between genetic and environmental components contributing to a number of mechanisms resulting in the clinical manifestation of the disease. Before we discuss the various intrinsic and extrinsic factors involved in the development of asthma, we consider some key features of the disease because these still significantly limit our scientific approach and our understanding of the mechanisms underlying asthma.

ASTHMA IS A DISEASE OF THE AIRWAYS IN THE LUNG

The cardinal symptom of asthma is reversible wheeze over time or by medication, hinting at a variable airway abnormality as an underlying phenomenon. In acute episodes, the airway obstruction is audible through a stethoscope, or in more severe attacks, by the patient and physician without an auxiliary tool. The airway obstruction is furthermore indirectly visible on outputs of various measures of lung function testing. Beyond these instruments, we have very few means of imaging the affected organ either during symptomatic or asymptomatic periods. Furthermore, these tools record just a snapshot, whereas a hallmark of airway obstruction

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Abbreviations used
ADBR2: α2-Adrenergic receptor
AHR: Airway hyperresponsiveness
aOR: Adjusted odds ratio
ETS: Environmental tobacco smoke
GST: Glutathione S transferase
MIT: Mean interaction test
NOD: Nucleotide-binding oligomerization domain
NPSR1: Neuropeptide S receptor 1
PST: Predivided sample test
SNP: Single nucleotide polymorphism
TLR: Toll-like receptor

in patients with asthma is variability over time.[1] However, with the exception of peak flow variability, we do not have means of assessing, investigating, and analyzing normal or aberrant variability of airway size and tone before the new onset of disease. These limitations are particularly pronounced at young age. Yet much of childhood asthma begins in the first 4 years of life.[2,3]

Because of these inherent difficulties, researchers have turned toward more accessible tissues, in particular blood, and have investigated associated immune responses by measuring total and specific IgE, eosinophilia, and markers of activated eosinophils, or systemic and local inflammatory immune responses. Thereby, more is known about the determinants of atopy than of asthma. However, not all asthma is atopic, and the strength of association between asthma and atopy is likely to depend on environmental factors. In the International Study of Asthma and Allergies in Childhood phase II study, socioeconomic status as assessed by the gross national income of the included study centers around the world was the best predictor of the strength of association between asthma and atopy.[4]

ASTHMA MIGHT BE NOT ONE DISEASE BUT MANY

Although we cannot rule out with certainty that 1 or a few unidentified causes underlie the development of asthma at all ages and varying clinical manifestations, there is evidence to suggest that many pathways open out into 1 rather uniform clinical presentation. From other areas of medicine, this is a well known fact. For example, anemic patients often present with pallor and fatigue as the only symptoms, yet a large variety of differential diagnoses is guiding the work-up of such a patient. In asthma, a number of distinct wheezing phenotypes in children and adults have been proposed on the basis of epidemiologic observations of the natural course, the age of onset, the presence or absence of features such as atopy and airway eosinophilia, and others.[2,5,6] The claim of distinct disease entities rather than of 1 illness is underpinned by the identification of individual predictors and determinants of the wheezing phenotypes and also by the need for different treatment approaches.[7,8]

Given the hereditary nature of asthma, difficulties in defining the disease and its phenotypes may be overcome by studying the genetics of asthma. According to this reasoning, the identification of 1 or several asthma genes may unravel the underlying disease process and by reverse genetics define the illness. Yet asthma cases must *a priori* be selected for inclusion in all types of genetic studies, thus rendering the notion of reverse genetics a somewhat circular argument.

GENETICS OF ASTHMA

With the introduction of new powerful genetic tools, the heritable component of asthma has gained increasing attention over the last few years. With these extraordinary technological advances, the identification of alterations in the sequence of the base pairs of our DNA may help us understand better the underlying biology of asthma and lead to the discovery of so far unknown processes in the airways resulting in the development of the disease. This expectation calls for open approaches to the genetics of asthma such as linkage studies and genome-wide association studies more than to candidate gene approaches. However, findings from a number of candidate gene approaches have also been informative. A brief summary of some important findings follows, but it is not exhaustive.

Linkage studies

Genome-wide linkage studies rely on families with individuals affected by asthma.[9] Evenly spaced genetic markers covering all chromosomes are typed in family members, and a search is made for genetic regions containing a higher than expected number of shared alleles among affected individuals within a family. The identification of such a region signals that somewhere within this genomic interval, a disease-predisposing allele is to be found. The genes within this region are further examined by positional cloning—that is, by typing denser and denser collections of genetic variants, until the underlying disease-associated gene(s) are found. A number of asthma susceptibility genes have thus been identified: a disintegrin and metalloproteinase 33, plant homeodomain finger protein 11 locus, dipeptidyl peptidases 10, neuropeptide S receptor 1 (NPSR1), histocompatibility locus A-G, cytoplasmic fragile X mental retardation protein interacting protein 2, IL-1 receptor-associated kinase-M, and collagen XXIX.[9]

However, as with most genetic studies, replication has been inconsistent. A recent study reported that of 5 asthma susceptibility genes previously identified by positional cloning (a disintegrin and metalloproteinase 33, dipeptidyl peptidases 10, NPSR1, histocompatibility locus A-G, and the plant homeodomain finger protein 11 locus), single nucleotide polymorphism (SNP)–level replication was found only for NPSR1 in 2 ethnically different populations (European-American and Hispanic children, respectively).[10] In the NPSR1 gene, 3 SNPs were associated with childhood asthma in both populations, although the opposite alleles were associated in either study. These results highlight the challenges of replicating genetic associations, even for genes identified by linkage analysis.

Genome-wide association studies

The main strength of genome-wide association studies is expected to lie in their ability to discover truly novel disease candidate genes, especially those associated with moderate risks.[9] In a recent genome-wide association study for asthma, more than 317,000 SNPs were characterized in DNA from 994 patients with childhood asthma and 1243 subjects without asthma by using family and case-control panels. Multiple markers on chromosome 17q21.1 were found to be strongly associated with childhood asthma.[11] The association was independently replicated in 2320 subjects from a cohort of German children and in 3301 subjects from the British 1958 birth cohort.[11] Analysis of the relationships between markers in the 17q21 locus and transcript levels in