

Genetics of Asthma—Personalizing Healthcare

a report by

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Asthma, a chronic inflammatory lung disease characterized by symptoms of cough, wheeze, shortness of breath and chest tightness, is a major public health problem for which global pharmacotherapeutic costs exceed US\$5 billion per year. The clinical picture is derived from many pathophysiologic changes in the lungs, including airway hyperresponsiveness, reversible obstruction, excess mucus production, and inflammatory cell infiltration. Although patients suffering from asthma share similar clinical symptoms, the disease itself is heterogenous in terms of phenotypes and natural history. This heterogeneity, along with the variety of possible environmental exposures, contributes to the difficulty in both studying and treating asthma and other complex polygenic diseases.

The pathogenesis of asthma is dependent on multilayered gene by environment interactions over time. The interactions between the dimensions are bidirectional and the relevant genes may vary dependent on the environmental exposures present in a given population. Likewise, the relevant environmental exposures will be dependent on the genetic context. The final dimension of time further complicates the situation since certain genetic and environmental influences may only be relevant in specific age groups or segments of the population. Although the interdependence of all of these variables makes it very difficult to conduct studies to elucidate any given effect, investigators have identified over 100 potential asthma susceptibility genes using positional cloning and the candidate gene approach. Seventy-nine of these genes have been reported in at least two independent study samples and the 10 most commonly associated genes have been reported in more than 10 studies. Genetic variations in these genes from naturally occurring single nucleotide polymorphisms (SNPs) may lead to altered disease susceptibility among individuals depending on their environmental exposures. Similarly, SNPs may also determine a patient's response to pharmaceuticals. Thus, investigations into molecular genetics may be a powerful tool to guide medical therapy and assist in identifying patients who could benefit from prevention strategies. This potential for "predictive, personalized, and preemptive" care, as stated by Dr Zerhouni of the National Institutes of Health (NIH), underlies the concept of personalized medicine.

Personalized medicine is a treatment paradigm where one size does not fit all. It is based on combining well-characterized disease subphenotypes with genetic and genomic data, as well as pharmacotherapeutic knowledge, to develop individually tailored prevention and treatment strategies for patients. The first step in developing a personalized asthma regimen requires correctly diagnosing and properly defining disease phenotypes. The importance of clinical phenotyping was highlighted in a recent analysis of four double-blind, placebo-controlled trials in moderate asthmatics by Peters-Golden and colleagues. The investigators identified an inverse correlation between body mass index (BMI) and treatment response to both placebo and inhaled corticosteroids (ICS), but not a leukotriene antagonist, suggesting that elevated BMI may worsen baseline asthma control as well as response to ICS. While this study focused on BMI, similar effects will likely be observed for other asthma subphenotypes.

Another step in developing personalized asthma care is based in genomics. Early genetic studies focused on individual genes or chromosomal regions associated with asthma. More recently, advances such as microarray technology have been utilized to gather large quantities of genomic information and identify whole gene profiles associated with disease states. An additional advantage of microarray analysis is its potential to identify novel genes not generally associated with the specific disease process. Recently, Guajardo and colleagues utilized microarray analysis of nasal respiratory epithelium to examine the genetic portrait of childhood asthma and found that distinct sets of genes were activated during stable versus acute asthma. This study established that exacerbated asthma status can be readily distinguished based on the occurrence of strong gene expression signatures. Stable asthma patients also exhibited differential gene expression but with more variability, suggesting clinical and/or mechanistic heterogeneity among these patients. The identification of genetic signatures that reflect clinical asthma attack status in readily sampled patient tissues provides an opportunity for molecular subclassification and, potentially, the clinical treatment of asthma patients.

A central component of personalized medicine is

pharmacogenetics, which is based on the potential for individually tailored drug therapy that maximizes therapeutic efficacy and minimizes adverse effects. This field of study developed from observations in the 1950s that inherited inter-individual variability exists in the responses to pharmacologic treatment. The basic principles of pharmacogenetics were described in 1957 from independent observations of familial adverse events to primaquine, succinylcholine, and isoniazid. Initially, pharmacogenetic research was based on phenotype to genotype flow of information. Studies of adverse drug reactions yielded information on altered proteins involved in pharmacokinetic (drug absorption, distribution, metabolism and excretion) and pharmacodynamic (effects on drug targets) pathways with subsequent identification of the responsible genetic variants. This flow has become bidirectional since the Human Genome Project was completed and mapping of SNPs began. While pharmacogenetics has traditionally focused on the effects of a single gene on drug response, advanced genotyping abilities will eventually lead to true pharmacogenomic studies, which will encompass the effect of entire sets of genes on this response.

Although pharmacogenetics has yet to enter into the common clinical treatment paradigm of asthma (and most other diseases), progress is being made. Currently, asthma medications are broadly divided into two categories, anti-inflammatory ‘controller’ medications (ICS and leukotriene modifiers) and ‘rescue’ medications (short-acting bronchodilators). Studies have confirmed what clinicians have observed in practice, that response to these medications can vary significantly among individuals. For example, the Montelukast/Beclomethasone Study Group reported that both medications significantly improved clinical outcomes and FEV₁ in patients with chronic asthma. However, the inter-subject response to both medications varied from a greater than 30% decrease to more than 50% increase in FEV₁, with nearly 22% of patients treated with beclomethasone and 34% with montelukast demonstrating a decline in lung function. While this study did not stratify by genetics, others have evaluated the effects of SNPs in mechanistic pathways of the three most commonly used classes of asthma drugs: (β₂-agonists, ICS, and leukotriene modifiers).

The pharmacogenetics of the (β₂-adrenergic receptor ((β₂AR) has been the most extensively studied of the three. This receptor is highly polymorphic and non-synonymous SNPs encoding for either Arg or Gly at position have been linked to altered responses to short acting (β₂-agonists both retrospectively and in a prospective clinical trial. Israel and colleagues found that homozygosity for Gly16 was associated with improved lung function with regular albuterol use compared to Arg/Arg individuals who experienced adverse effects to

such therapy. A recent study also found similar results with salmeterol therapy. For ICS, improved therapeutic responses have been associated with polymorphisms in corticotropin releasing factor receptor type 1 (CRHR1) in three study populations and the functional relevance of this pathway in asthma was supported by studies with CRH gene targeted mice. In leukotriene biology, SNPs in the 5-lipoxygenase (ALOX5) promoter and the leukotriene C₄ (LTC₄) synthase gene have also been associated with differential responses to leukotriene modifiers. All of these reports have focused on the effects of individual polymorphisms or a limited number of SNPs in a single gene. As genotyping and microarray technology improves and expense decreases, broader pharmacogenomic studies will be required to examine the effects of SNPs in combination. This is relevant because the functional significance of a given SNP might only be evident in a specific setting of additional SNPs in the same or different genes. Small functional changes in gene products that act along a common pathway will likely have a significant effect on an individual’s therapeutic responses.

The challenge now lies in the implementation and application of personalized medicine to routine clinical practice. Despite significant advances, however, much remains to be accomplished. The goal is to provide a lifelong, individually tailored healthcare approach to the detection, prevention and treatment of disease based on knowledge of an individual’s precise genetic, biologic, environmental, and clinical profile. In order to achieve this goal, information in each of these areas needs to be collected and incorporated into clinical and epidemiological studies, and clinical pharmaceutical trials. Patients need to be classified based on their integrated pattern of these variables. Additionally, exposures in the macro- and micro-environment must be evaluated since they can affect the natural history of the disease and response to treatment. Physicians and health care providers will require education at each level so that these concepts and methods can be incorporated into clinical practice, both in terms of procurement of samples and the testing, as well as in the interpretation of the tests. Finally, it will be critical to partner with communities and families as we move into this new era of medicine so that we can inform each other and share in the decision making process as the concept of personalized medicine continues to materialize. In the approaching age of personalized medicine, the accurate prediction of asthma susceptibility, personalization of treatment regimens, and even the possible prevention of disease will become the standard of care. ■

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