be conquered only one step at a time. The study by Thwaites et al. is a stride in the right direction.

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Making Sense of Asthma Genes
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There are two causes of asthma — the environment and genetic variants. Each cause accounts for about 50 percent of the risk of the disease. The power of the public databases and the methods of genotyping used in genetics mean that the discovery of genes and the genetic variation underlying the various forms of asthma is increasing quickly.

Genetics concerns polymorphism (variation) in genes. The most obvious effects of polymorphisms appear when they alter protein coding sequences and cause mutations. However, most of the polymorphisms that cause common diseases alter gene function through more subtle mechanisms. Such mechanisms may affect upstream sequences for the promotion and initiation of gene transcription and intronic sequences, which regulate both the timing and cellular or tissue expression of the gene and the factors that regulate splicing.

The sheer volume of the genetic information available is causing problems. With the completion of the Human Genome Project, all 30,000 human genes may now be studied. Several hundred of them could be plausible candidates for a role in an inflammatory disorder. Common single-nucleotide polymorphisms and other polymorphisms appear in the human genome in every 500 to 1000 base pairs. A typical gene may therefore contain 20 to 40 polymorphisms, only a small proportion of which will have any effect on the function of the gene. To avoid a deluge of suggestive but inconclusive information, journals should apply stringent criteria for the publication of studies of candidate genes. In this issue of the Journal, Oguma et al. describe an exemplary investigation of the prostaglandin D2 receptor gene (PTGDR) as a candidate for a role in the susceptibility to asthma in young adults.1

Prostanoid DP mediates the chemotaxis of T cells that follows the degranulation of mast cells. Its gene was identified as a candidate asthma gene in a mouse model of asthma. The mouse, which was deficient in functional Ptgdr, was unable to mount an airway inflammatory response to allergen.2 Oguma et al. first observed an association between PTGDR polymorphisms and asthma in case–control studies of white patients recruited in the United States. The authors took pains to replicate this finding in a second population with a different ancestry — black Americans. They showed that the implicated polymorphisms affect the binding of regulatory factors to the PTGDR gene promoter and that these polymorphisms alter the level of transcription of the gene. The conclusion that variation in the expression of the receptor influences susceptibility to asthma suggests that the receptor is a therapeutic target. PTGDR antagonists are now being studied in early-phase trials for rhinitis, although not yet for asthma. PTGDR joins a growing list of asthma-susceptibility genes (Fig. 1). Although the identification of all asthma genes is not nearly complete, genetic findings are already changing the prevailing view of the pathogenesis of asthma.

Positional cloning is a process of systematic
identification of disease-associated genes that begins by locating genetic regions that are coinherited with the disease. It requires no assumptions about the probable disease pathogenesis. Five asthma genes or gene complexes have now been identified with the use of positional cloning. ADAM33 is expressed in bronchial and other muscle tissues; its most likely functions are in myogenesis, and it is thought to influence bronchial hyperresponsiveness in the presence of airway inflammation. The complex of PHF11 and SETDB2 encodes nuclear transcription factors with multiple splice variants in T and B cells. DPP10 encodes a peptidase that may nibble off the two terminal peptides of chemokines. GPRA encodes a G-protein–coupled receptor that is up-regulated in epithelial cells in inflamed airways. SPINK5 encodes a multidomain serine protease inhibitor that probably has activity against multiple substrates. The functions of all these genes are obscure, but the expression of DPP10, GPRA, and SPINK5 in terminally differentiating epithelium suggests that they deal with threats posed by or damage from the environment.

Many of the candidate genes identified may exert effects within the cells that make up the mucosa (Fig. 1). The polymorphisms in the gene for interleukin-13 may influence the production of mucus as well as the levels of serum IgE. Findings with polymorphisms in FceRI-β, which modifies the activity of the high-affinity receptor for IgE, and the key mast-cell signaling factor prostanoid DP synthase both have confirmed that the mast cell is a target for asthma therapy. Exposure to microbes (as opposed to infection) in childhood protects against asthma. Microbial pattern-recognition receptors of the innate immune system are expressed on dendritic and other cells, and polymorphisms in CD14, TLR-2, and TIM-1 have all been shown to influence asthma susceptibility. Other recognized effects are mediated by tumor necrosis factor α, which is a potent proinflammatory cytokine released by many cells, including airway epithelial cells, and transforming growth factor β, which is an important regulator of epithelial inflammation.

Clinicians who need to come to grips with this complexity may reasonably ask just how many genes for asthma there will be when all have been counted. The results of several screenings of the genome suggest that there may be 10 genes with moderate effect. However, owing to the relentless evolutionary pressure of infection, many genes that influence immunity will prove to be polymorphic.

In this case, almost any immune-response gene, if prodded hard enough, may be found to have an effect on almost any immune-mediated disease.

To become relevant to the clinical diagnosis and classification of asthma, all these polymorphisms need to be tested in case-control studies that involve patients with different manifestations of the disease and disease of differing severity and in samples drawn from representative populations. In this way, the genotype becomes a predictor of disease that can be understood in the same terms as
other epidemiologic risk factors, and the size and relevance of the effects can be judged objectively. Most polymorphisms identified so far do not appear to carry risks that would merit their use in a clinical setting, but combinations of genetic polymorphisms may be much more informative.

The extent to which polymorphisms will predict the response to therapy is not yet known, but a positive association between common variants in the β-adrenergic-receptor gene and the responsiveness of patients with asthma to β-adrenergic agonists is encouraging. In addition, the proteins encoded by a minority of the newly identified asthma genes may become novel targets for therapy with small molecules or other therapies. PTGDR is one such example.


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