

EDITORIAL



17q21 Variants and Asthma — Questions and Answers

John W. Holloway, Ph.D., and Gerard H. Koppelman, M.D., Ph.D.

It has long been established that many common diseases are the result of interactions between genetic susceptibility and environmental exposure. The identification of genetic variants that underlie susceptibility to diseases and alter the expression or function of proteins (either familiar or novel) can implicate the protein in question in the pathogenesis of the disease. This not only increases the understanding of disease pathophysiology but also can lead to the development of new therapeutic agents. It is this hope that has spurred the search for genetic variants underlying common diseases during the past quarter century.

The advances of the Human Genome Project and the International HapMap Project¹ in cataloging and mapping the extent of human genetic variation and the availability of new genotyping methods have given rise to genomewide association studies. In these studies, array-based technology is used to genotype single-nucleotide polymorphisms (SNPs) across the genome. This approach has led to a surge in the number of genes implicated in common diseases. Most of these genes are of unknown function.²

Asthma is a chronic inflammatory disease of the airways that is associated with increased responsiveness of the airways to environmental stimuli and variable airflow obstruction. Symptoms of asthma include recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. Asthma is a result of the interaction between genes and environment, and several genetic and environmental factors, such as exposure to environmental tobacco smoke in early life, have been identified.³

Last year, a genomewide association study showed that SNPs at chromosome 17q21 were associated with asthma in four groups of patients

of European descent.⁴ Some of these variants were also associated with transcript levels of an adjacent gene, *ORMDL3*, which encodes a protein of unknown function belonging to a family of transmembrane proteins anchored in the endoplasmic reticulum.

The identification of a robust positive association between a genetic variant and a disease lies far upstream (if it has any effect at all) of any effect on clinical practice. Such a discovery poses a series of questions.

First of all, where is the causal variant? The identification of a SNP that is highly associated with the disease phenotype does not necessarily imply causality. The SNP may be in linkage disequilibrium with the true causal SNP and thus act as a proxy marker. The true causal SNP may lie elsewhere in the block of linkage disequilibrium in which the associated SNP lies. This causal SNP may or may not be in or in the vicinity of the same gene implicated by the “discovery” SNP. Second, in which patients is this gene relevant? Does susceptibility relate to all patients who have the disease or to a subgroup of patients that can be classified clinically? Third, at what point in development (or development of disease) does the effect of the variant become critical? In other words, at what point on the continuum between health and overt clinical phenotype does alteration in the expression or function of the gene dispose the patient to disease? Fourth, multiple genes are involved in determining susceptibility to disease. Which interactions between genes or between the gene and the environment exist? And finally, how does the alteration in the expression or function of the gene lead to disease?

Answers to some of these questions are provided by Bouzigon and colleagues⁵ in this issue

of the *Journal*. They describe the results of a replication study of the association between SNPs at chromosome 17q21 and asthma and refine that association in two ways: 17q21 SNPs seem to be specifically associated with the onset of asthma at the age of 4 years or younger and in those who have been exposed to environmental tobacco smoke.

Alongside the internal replication in the initial report⁵ and subsequent related studies,⁶⁻⁹ the study by Bouzigon et al. confirms the role of genetic variation at this locus in predisposing patients to asthma. The novel findings relating to age and the role of early exposure to tobacco smoke will require replication by others before they are carved in stone. However, despite all this, the identity of the genes whose activity or function is modified by the causal variant is still unclear. Although the initial report highlighted the regulation of transcript levels of *ORMDL3* as a potential pathogenic mechanism, the most highly associated SNPs observed by Bouzigon et al. span three genes in addition to *ORMDL3*. These are *ZBP2*, which encodes zona pellucida-binding protein 2; *IKZF3*, which is involved in leukocyte development and regulation of IgE production; and *GSDML* (also called *GSDMB*), which is involved in epithelial barrier function. Furthermore, the authors cite unpublished data suggesting that the markers that are associated with asthma are also associated with changes in the expression of *GSDML*, in addition to that of *ORMDL3*.

The finding that the association between these SNPs and asthma is specific to that occurring in children who are 4 years of age or younger supports the notion that asthma is not one disease but merely the clinical manifestation of several different disease entities.¹⁰ Although childhood-onset asthma shares some risk factors with adult-onset asthma (for example, a family history of the disease, exposure to environmental tobacco smoke, and atopic sensitization), there are some marked differences. These include sex (more boys than girls are affected in early childhood, and more women than men are affected in adulthood), the timing of symptoms (which tend to be intermittent in childhood and persistent in adulthood), differences in airway obstruction (increased peripheral airway resistance in the absence of central airflow obstruction in childhood, as compared with both peripheral and central airway obstruction in adulthood), and the association with atopy

(which is closer in early-onset disease than in late-onset disease).¹¹

The latter association is not supported in the study by Bouzigon et al., who observed no link between the implicated 17q21 variants and atopic phenotypes. Further work is required to determine whether the 17q21 variants are specifically associated with one or more of these phenotypic characteristics. Moreover, the association with the age of onset should be prospectively tested in longitudinal birth cohorts. One explanation for the observed association between 17q21 variants and early-onset asthma is that in defining an early-onset subgroup, the authors selected a subgroup of patients with asthma with high heritability. It has been suggested that susceptibility to early-onset diseases has a higher genetic contribution than susceptibility to adult-onset diseases, which may have a comparatively greater environmental component.¹²

A wide range of evidence supports a crucial role for early-life events in the pathogenesis of asthma.¹³ The study by Bouzigon et al. provides additional support for this concept through both the restriction of the genetic effect to early-onset asthma and the apparent interaction between 17q21 variants and early-life exposure to environmental tobacco smoke. This interaction further highlights the detrimental effect of such early-life exposure on respiratory health.¹⁴ However, Bouzigon et al. could not differentiate the effects of prenatal and postnatal exposure to tobacco smoke, so the question of timing remains partly unanswered.

The next and as-yet-unanswered questions are how the causal genetic variants alter disease susceptibility and what role the encoded gene products play in the pathogenesis of asthma. Since the identity of the critically affected gene or genes is still a matter of conjecture, the answers are unlikely to be discovered in the near future.

In summary, the evidence for a specific subgroup of patients with asthma starting in early life highlights the fact that asthma may be syndromic rather than a single disease entity. Moreover, Bouzigon et al. have provided additional evidence of a role for early exposure to tobacco smoke in the pathogenesis of the disease. When more is known regarding the mechanism by which genetic variation at this locus alters susceptibility to asthma, ways to translate these findings into clinical practice may become more apparent.

No potential conflict of interest relevant to this article was reported.

This article (10.1056/NEJMe0807576) was published at www.nejm.org on October 15, 2008.

From the Divisions of Infection, Inflammation and Repair and of Human Genetics, School of Medicine, University of Southampton, Southampton, United Kingdom (J.W.H.); and the Department of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (G.H.K.).

1. International HapMap Consortium. A haplotype map of the human genome. *Nature* 2005;437:1299-320.
2. McCarthy MI, Abecasis GR, Cardon LR, et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet* 2008;9:356-69.
3. Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev Immunol* 2008;8:169-82.
4. Moffatt MF, Kabesch M, Liang L, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature* 2007;448:470-3.
5. Bouzigon E, Corda E, Aschard H, et al. Effect of 17q21 variants and smoking exposure in early-onset asthma. *N Engl J Med* 2008;359. DOI: 10.1056/NEJMoa0806604.
6. Sleiman PM, Annaiah K, Imielinski M, et al. ORMDL3 variants associated with asthma susceptibility in North Americans of European ancestry. *J Allergy Clin Immunol* 2008 August 27 (Epub ahead of print).
7. Tavendale R, Macgregor DF, Mukhopadhyay S, Palmer CN. A polymorphism controlling ORMDL3 expression is associated with asthma that is poorly controlled by current medications. *J Allergy Clin Immunol* 2008;121:860-3.
8. Galanter J, Choudhry S, Eng C, et al. ORMDL3 gene is associated with asthma in three ethnically diverse populations. *Am J Respir Crit Care Med* 2008;177:1194-200.
9. Hirota T, Harada M, Sakashita M, et al. Genetic polymorphism regulating ORM1-like 3 (*Saccharomyces cerevisiae*) expression is associated with childhood atopic asthma in a Japanese population. *J Allergy Clin Immunol* 2008;121:769-70.
10. A plea to abandon asthma as a disease concept. *Lancet* 2006;368:705.
11. Gelfand EW. Is asthma in childhood different from asthma in adults? Why do we need special approaches to asthma in children? *Allergy Asthma Proc* 2008;29:99-102.
12. Lander ES, Schork NJ. Genetic dissection of complex traits. *Science* 1994;265:2037-48. [Erratum, *Science* 1994;266:353.]
13. Martinez FD. Toward asthma prevention — does all that really matters happen before we learn to read? *N Engl J Med* 2003;349:1473-5.
14. Strachan DP, Cook DG. Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies. *Thorax* 1998;53:204-12.

Copyright © 2008 Massachusetts Medical Society.