

# Gene-Environment Interactions and Airway Disease in Children

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## ABSTRACT

Asthma is the most common chronic disease of childhood in the United States, affecting nearly 6.5 million children. The prevalence and severity of childhood asthma have continued to increase over the past 2 decades, despite major advances in the recognition and treatment of this condition. Representing a heterogeneous collection of airway diseases, asthma has multiple pathologic processes resulting from the interactions of genetic susceptibility and environmental exposures. Preventing and treating airway disease in children will require new research approaches to understanding these complex interactions. *Pediatrics* 2009;123:S151–S159

**A**STHMA IS THE most common chronic disease of childhood in the United States, affecting nearly 6.5 million children.<sup>1</sup> The prevalence and severity of childhood asthma have continued to increase over the past 2 decades, despite major advances in the recognition and treatment of this condition. Between 1980 and 2002, hospital admissions attributable to asthma increased by 28% for individuals <25 years of age. Asthma-related hospitalizations accounted for ~7% of all hospitalizations for children 0 to 14 years of age in 2002, and asthma was the third leading cause of non-injury-related hospital admissions in that year.<sup>2</sup> Since 1980, the mortality rate for asthma has doubled for persons between 5 and 24 years of age.<sup>3</sup>

Allergic asthma is a syndrome that results when a genetically susceptible individual is exposed to specific allergens that trigger airway inflammation, bronchial hyperresponsiveness (BHR), and airway remodeling. However, individuals can develop asthma without any apparent genetic predisposition, and exposures other than allergens can lead to the development of asthma. Although demographic factors such as age, race, and socioeconomic status, as well as genetic factors, seem to be risk factors for the development and progression of asthma,<sup>4–6</sup> the increasing prevalence and severity of asthma suggest that agents in the general environment play particularly important roles in the pathogenesis of this condition.<sup>7–11</sup> A fundamental, unanswered question in asthma is why only a minority of children who wheeze at an early age develop persistent airway disease that continues throughout their lives. Although genetic factors play an important role in the development of asthma, recurrent airway inflammation, presumably mediated by environmental exposures, may result in persistent airway hyperresponsiveness and the development of chronic airway disease. Because current research approaches to asthma cannot sufficiently describe the relationship and individual relevance of genetic and environmental factors in the development of airway disease in children, a holistic research approach that incorporates new genomic technologies with better exposure data is necessary to elucidate the pathogenesis of asthma.

## ENVIRONMENTAL EXPOSURES AND ASTHMA

A comparison of urban and rural children suggests that the pathogenesis of airway disease is multifactorial and unique exposures may contribute to the development of disease in both settings. In rural communities, children commonly are exposed to organic dusts, agricultural chemicals,<sup>12,13</sup> animal allergens, and grain dust mites that are brought into the home on work clothing.<sup>12</sup> Moreover, for children in rural settings, the farm is their home, playground, and workplace, with children as young as 5 years of age participating in farm chores.<sup>14</sup>

The largest, and perhaps the most clinically relevant, category of agents known to cause asthma in the rural setting are organic dusts. Grain dust, cotton dust, and dusts generated in dairy barns all represent a complex mixture of vegetable particles and fragments; microorganisms and their products; insects and insect fragments; feed additives, including fish meal and antibiotics; avian and rodent proteins; and pesticides. Air pollutants such as ozone also may promote the development of airway disease among rural residents.<sup>15,16</sup>

Chemicals common to the agricultural environment, including pesticides, herbicides, and fertilizers, as well as wood smoke and alternative sources of fuel,<sup>17</sup> may contribute to the exacerbation of airflow obstruction in children with asthma. Organophosphate insecticides may induce bronchospasm in exposed individuals.<sup>18</sup> These pesticides inhibit acetylcholinesterase and may produce a cholinergic response, inducing bronchospasm and bradycardia.

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### Key Words

genetic susceptibility, environmental exposure, bronchial diseases

### Abbreviations

BHR—bronchial hyperresponsiveness

IL—interleukin

TLR4—Toll-like receptor 4

IgE—immunoglobulin E

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Although research is lacking in this area, the exposure-response relationship is reported commonly for agricultural workers and may represent an important point of intervention for childhood asthma.

For children living in urban settings in the United States, particularly in inner-city areas where asthma rates are highest, exposure to indoor environmental agents, including allergens and pollutants, can cause asthma or exacerbate asthma symptoms.<sup>19</sup> Among inner-city patients with asthma, sensitivity to indoor allergens is more prevalent than sensitivity to outdoor allergens.<sup>20</sup> Exposure to common indoor allergens, including dust mites, cockroaches, and cat dander, has been shown to exacerbate asthma in sensitized individuals.<sup>20-23</sup> Data from the National Cooperative Inner-City Asthma Study showed that 19% of children with moderate/severe asthma were sensitized to rat allergen in the home and 15% were sensitized to mouse allergen.<sup>24</sup> Data on the relationship between sensitization to rodent allergens and the impact on asthma in children are limited; however, 1 study of inner-city children found that exposure to mouse allergen was associated with wheeze in the first year of life.<sup>25</sup> Another study in a similar population showed that exposure of sensitized, inner-city children to rat allergen was associated with increased asthma morbidity.<sup>26</sup> Children also may be exposed and sensitized to indoor allergens from mold in homes, schools, and day care centers, and several studies demonstrated increases in airway disease and symptoms as a result of such exposure. A prospective longitudinal study of nearly 1000 children showed that *Alternaria alternata* sensitization at age 6 was associated with increased risks of asthma at both 6 and 11 years of age.<sup>27</sup> In a study of >1000 children with mild/moderate asthma, 37% demonstrated positive skin prick test responses to *A alternata*, 24% to a *Penicillium* mixture, and 22% to an *Aspergillus* mixture.<sup>28</sup>

In addition to indoor allergens, children are exposed to a variety of indoor air pollutants that have been shown to cause increased airway reactivity, asthma exacerbations, respiratory illness, and altered host defenses.<sup>10,29-32</sup> The hyperresponsive airways of children with asthma make the children more susceptible to adverse health effects of airborne particles<sup>33</sup> generated from environmental tobacco smoke, frying and smoky cooking, and the use of incense.<sup>34</sup> Postnatal exposure to environmental tobacco smoke has been linked to increased asthma incidence and prevalence rates.<sup>35-37</sup> Although few studies have addressed directly the effects of indoor particles on asthma, 2 studies suggested that chronic exposure to particulate matter may affect lung function and growth in children.<sup>36,38</sup> Other studies associated exposure to indoor air pollutants emitted from appliances such as gas stoves, heaters, and furnaces with exacerbation of asthma symptoms. Studies showed that increases in indoor nitrogen dioxide concentrations resulting from such appliances increased the likelihood and frequency of asthma symptoms and attacks in children with asthma.<sup>39,40</sup> Greater nitrogen dioxide exposure also increased the severity of virus-induced asthma.<sup>41</sup> Other agents in indoor air that have been less well

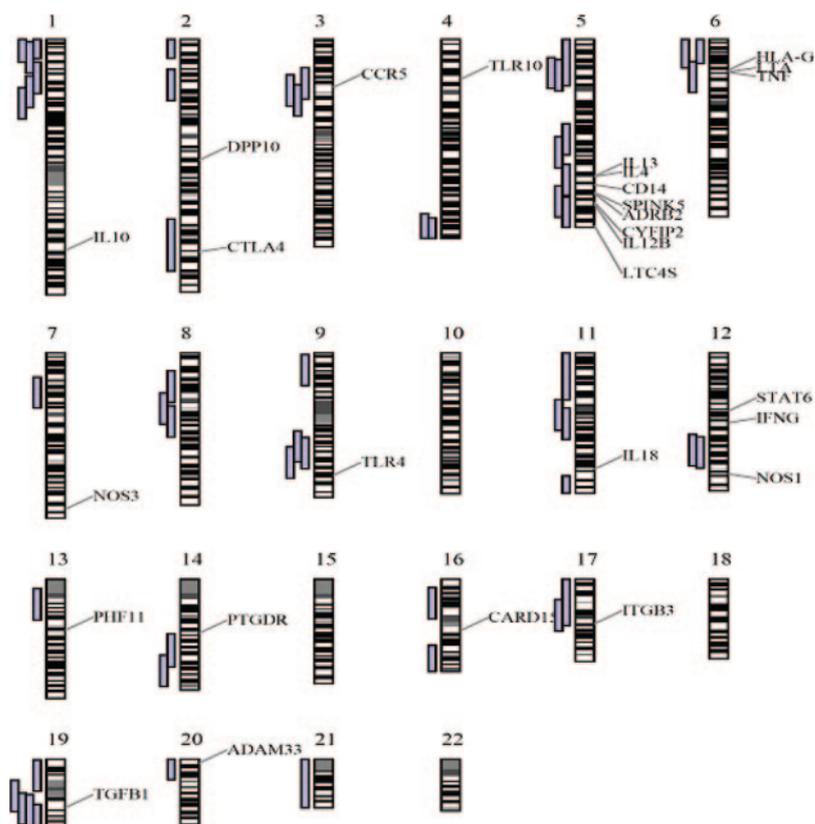
studied but offer compelling interest for asthma research include carbon monoxide, pesticides, volatile organic compounds, plasticizers, and compounds in fragrance and personal hygiene products.<sup>42</sup>

### GENETIC BASIS FOR ASTHMA

Multiple studies have shown that the likelihood of developing asthma is inherited. However, those genetic studies have shown that asthma does not follow classical patterns of Mendelian inheritance; instead, asthma is inherited as a complex trait and results from the interaction of multiple genes. Problems with accurate phenotyping have hampered identification of the genes responsible for the development of asthma. Recent attempts to decipher the genetic basis of this complex trait have relied on specific intermediate phenotypes such as BHR, serum immunoglobulin E (IgE) levels, and atopy. These traits are thought to identify subsets of patients with distinct types of asthma or a predisposition to develop asthma and have been used to facilitate the identification of the many genes involved in this complex disease. Although a large number of studies have identified possible genetic loci and chromosomal mutations that may be involved in the development of asthma or these related phenotypes, additional research is needed to clarify the interactions between these genes and the multiple environmental exposures that lead to the asthmatic phenotype.

Family and twin studies have shown that there is a major genetic component to the development of asthma. Familial aggregation was probably first recognized by Sennertus in 1650.<sup>43</sup> Subsequent familial aggregation studies have examined the prevalence of a disease among the relatives of affected individuals versus control groups to determine the risk attributable to inheritance. In 1952, Schwartz<sup>44</sup> showed that relatives of probands with asthma had increased risk of developing asthma. He found the prevalence of asthma to be 6.6% among the relatives of subjects with asthma, compared with 1% among control subjects. In a study of ~80 children with asthma and control subjects in a general pediatric practice in London, England, the prevalence of asthma in first-degree relatives was 13% for the subjects with asthma, compared with 4% for the control subjects. The greater prevalence of asthma in relatives of probands with asthma was present for both atopic and nonatopic asthma.<sup>45</sup>

Because the definitions of asthma and the populations studied have varied, estimates of the relative risk attributable to a family history of asthma cover a wide range. Most studies have demonstrated that there is a major inherited component to both asthma and its intermediate phenotypes. Familial clustering has been demonstrated for BHR, eosinophil levels, atopy, and serum IgE levels. Although each of these subtypes has been shown to aggregate among families, they seem to segregate independently,<sup>46</sup> which suggests that these intermediate phenotypes represent distinct pathophysiologic processes.<sup>47-50</sup> The familial inheritance of asthma and these intermediate phenotypes has led to attempts



**FIGURE 1**

Chromosomal map of human linkage to associated genes for asthma. The 95% confidence intervals of human quantitative trait loci are shown as blue bars to the left of their respective chromosomes, with the peaks indicated by black lines. The specific genes associated with asthma are identified to the right of each chromosome.

to identify the specific genes involved in this complex disease.

The inheritance of asthma demonstrated in the studies of familial aggregation was confirmed in twin studies. The study of monozygotic and dizygotic twins allows researchers to separate the effects of shared environmental factors from the effects of genetic factors in the development of asthma. A 1971 study of Swedish twin pairs found that the concordance of asthma was 19% among genetically identical individuals (monozygotic twins), compared with 4% among dizygotic twins.<sup>51</sup> The importance of genetic factors and the lack of evidence supporting the influence of a shared environment was shown in a study of Norwegian twin pairs, in which 75% of the variation in susceptibility was attributable to genetic influences.<sup>52</sup> Comparable results were found for several other twin populations; the estimates of heritability ranged from 35% to 80%.<sup>53–56</sup> In each study, the concordance among monozygotic twins was <100%, which demonstrates a role for environmental triggers as well.

Segregation analyses have attempted to discern the mode of inheritance of asthma and its related phenotypes. The inheritance of asthma does not fit classical Mendelian inheritance of a single gene locus; >1 gene seems to be involved, and the studies have supported either an oligogenic or polygenic model of inheritance.<sup>46,57,58</sup> The Tucson Children's Respiratory Study, a large longitudinal study investigating the risk factors for asthma, found that the correlation of forced expiratory volume in 1 second values among families with and

without asthma had a strong familial component and followed a polygenic mode of inheritance.<sup>57</sup> The study also found a maternal influence to the inheritance of forced expiratory volume in 1 second values among families with asthma.<sup>57</sup> Subsequent analyses of the inheritance of the intermediate phenotypes of asthma were performed. The Tucson Children's Respiratory Study also examined the mode of inheritance of eosinophil levels and found that eosinophilia seemed to fit best a polygenic mode of inheritance and there was no maternal effect.<sup>46</sup> These and other studies show that future research will need to focus on the identification of multiple genes that combine to form the predisposition to develop asthma.

One method of identifying genes associated with asthma is linkage analysis, in which randomly spaced markers throughout the human genome are typed for individuals with and without the affected phenotype. Families are then studied to determine which marker segregates with the affected phenotype. When a marker and the phenotype segregate together, genetic linkage is said to exist. The determination of linkage is based on the statistical probability that cosegregation is unlikely to happen by chance. Linkage studies have identified several areas of chromosomes that segregate with the asthma phenotype and may carry some of the major genes involved in the development of asthma.

Studies have identified markers and candidate genes on nearly every chromosome that demonstrate linkage or association with asthma or its intermediate phenotypes (Fig 1). Some of the most reproducible linkages

and plausible chromosomal regions are described below. The chromosome 5q31-33 region contains multiple genes that may influence susceptibility to the development of asthma, including several cytokines (interleukin 3 [IL-3], IL-4, IL-5, IL-6, IL-9, IL-12, and IL-13) and growth factors (tumor growth factor  $\beta$ 1 and fibroblast growth factor 1). The  $\beta_2$ -adrenergic receptor has been linked to asthma and its related phenotypes in several studies of different populations, including families from China, Australia, England, Japan, and the United States.<sup>58-63</sup> A study of children from the Netherlands demonstrated that elevated serum IgE levels were coinherited with BHR and these traits were linked to an area on chromosome 5q.<sup>64</sup>

Marker D11S97 on chromosome 11q13 was first linked to atopy in 1989,<sup>65</sup> and this association subsequently was demonstrated multiple times.<sup>58,62,65-68</sup> Chromosome 11q13 contains candidate genes such as the high-affinity IgE receptor and Clara cell secretory protein. Other areas of linkage include chromosome 6p21-22, which contains some of the genes for the major histocompatibility complex along with the tumor necrosis factor  $\alpha$  gene.<sup>69,70</sup> Chromosome 12q14-24 contains the genes for interferon  $\gamma$ , insulin-like growth factor 1, glutathione-S-transferase, nitric oxide synthase 1, leukotriene A<sub>4</sub> hydrolase, and mast cell growth factor.<sup>71-75</sup> Finally, chromosome 14q11-13 contains the genes for the subunits of the T-cell receptor.<sup>76</sup>

By using genome-wide association approaches with assays that test up to 1 million single-nucleotide polymorphisms, investigators have been able to identify common genetic variations that contribute to complex diseases, such as age-related macular degeneration, type 2 diabetes mellitus, and prostate cancer. The first genome-wide association study in asthma was published recently; it identified multiple single-nucleotide polymorphisms on chromosome 17q21 that were strongly associated with childhood asthma.<sup>77</sup> The investigators went on to validate these associations in other populations and demonstrated that the single-nucleotide polymorphisms were strongly associated with the transcriptional regulation of *ORMDL3*, a gene that encodes transmembrane proteins anchored in the endoplasmic reticulum. These findings suggest that *ORMDL3* represents an important susceptibility gene in childhood asthma, and they also illustrate the potential of genome-wide association studies to identify common genetic variants that contribute to the development of asthma.

Multiple genes thought to be important in the pathophysiologic development of asthma have been sequenced specifically, to determine whether genetic polymorphisms in these candidate genes influence inheritance patterns (Fig 1). Candidate gene analysis involves sequencing the genes of interest in both affected and unaffected individuals, to identify polymorphisms or mutations that are associated with the different phenotypes. Candidate genes also have been identified on the basis of results of previous linkage analysis studies. Most of the candidate gene studies have focused on various cytokines, growth factors, and receptors that are thought

to play a role in the development of asthma and therefore may influence its inheritance.

The large number of candidate genes identified through linkage analysis and the conflicting results reflect the difficulty of classifying subsets of individuals with asthma, as well as the complex genetic nature of this syndrome. Many of the studies could not be replicated or lacked sufficient statistical power to prove linkage between specific chromosomal regions.<sup>78</sup> Despite the difficulty of conducting linkage studies of asthma because of the complex inheritance patterns, these studies successfully identified multiple regions and genes that warrant additional study.

## GENE-ENVIRONMENT INTERACTIONS

The difficulties encountered in previous candidate gene studies may reflect inaccurate phenotyping of asthma. Given the importance of environmental exposures in the development of this heterogeneous disease, several studies have used such exposures to limit the genetic study to specific environment-gene-asthma phenotype combinations. Instead of examining intermediate phenotypes such as atopy, serum IgE levels, and BHR, studies of specific gene-environment interactions have defined the pathophysiologic phenotype more narrowly and have begun to identify a series of key genes that may be involved in the development of asthma.

Perhaps the most well-studied example of gene-environment interactions for asthma is the relationship between exposure to endotoxin and the development and exacerbation of asthma. Endotoxin is a lipopolysaccharide molecule associated with the cell membrane of many Gram-negative bacteria. Several lines of evidence indicate that endotoxin is 1 of the primary agents in organic dust that causes airway inflammation and airflow obstruction. Naive, healthy, study subjects challenged with dust from animal confinement buildings developed airflow obstruction and increased concentrations of neutrophils and IL-6, all of which were most strongly associated with the concentration of endotoxin, not dust, in the bioaerosol.<sup>79</sup>

Endotoxin exposure may have a variety of influences on the development of airway inflammation and asthma that are dependent on the timing and extent of exposure. Exposure to endotoxin during the first year of life has been shown to be protective with respect to the development of airway hyperreactivity and allergic sensitization<sup>80</sup>; however, this protective effect remains controversial.<sup>81</sup> In contrast, endotoxin exposures later in life can lead to the development of asthma and airway inflammation. In a study of 49 patients with asthma and house dust mite sensitization, the severity of asthma was related not to the concentration of house dust mite allergens but rather to the concentration of endotoxin. Specifically, endotoxin concentrations were correlated significantly with spirometry results, the need for steroids and  $\beta$ -adrenergic receptor agonists, and clinical symptom scores.<sup>82</sup>

Because endotoxin influences the development of airway inflammation and airway hyperresponsiveness, researchers have studied it in an attempt to identify

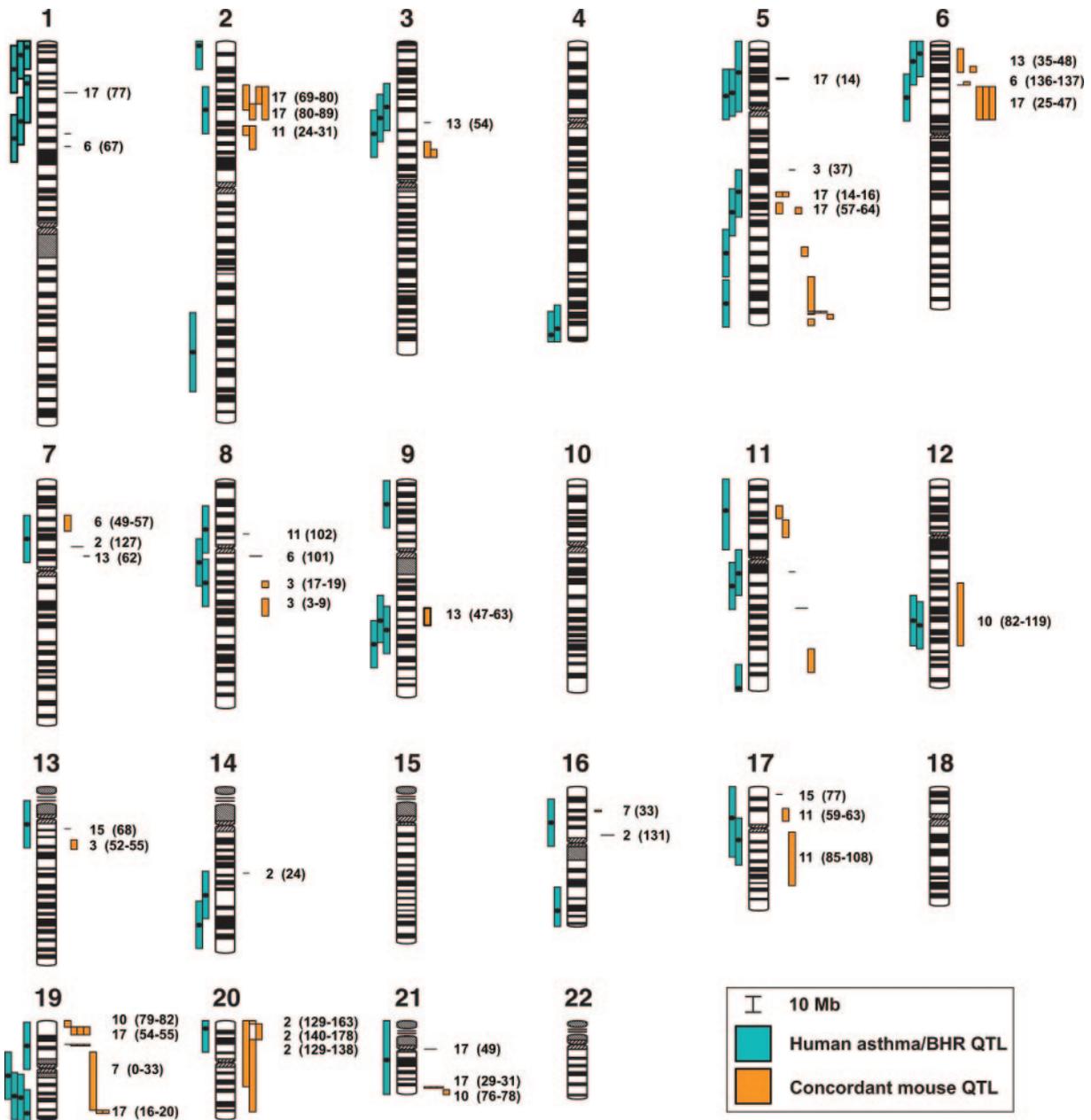


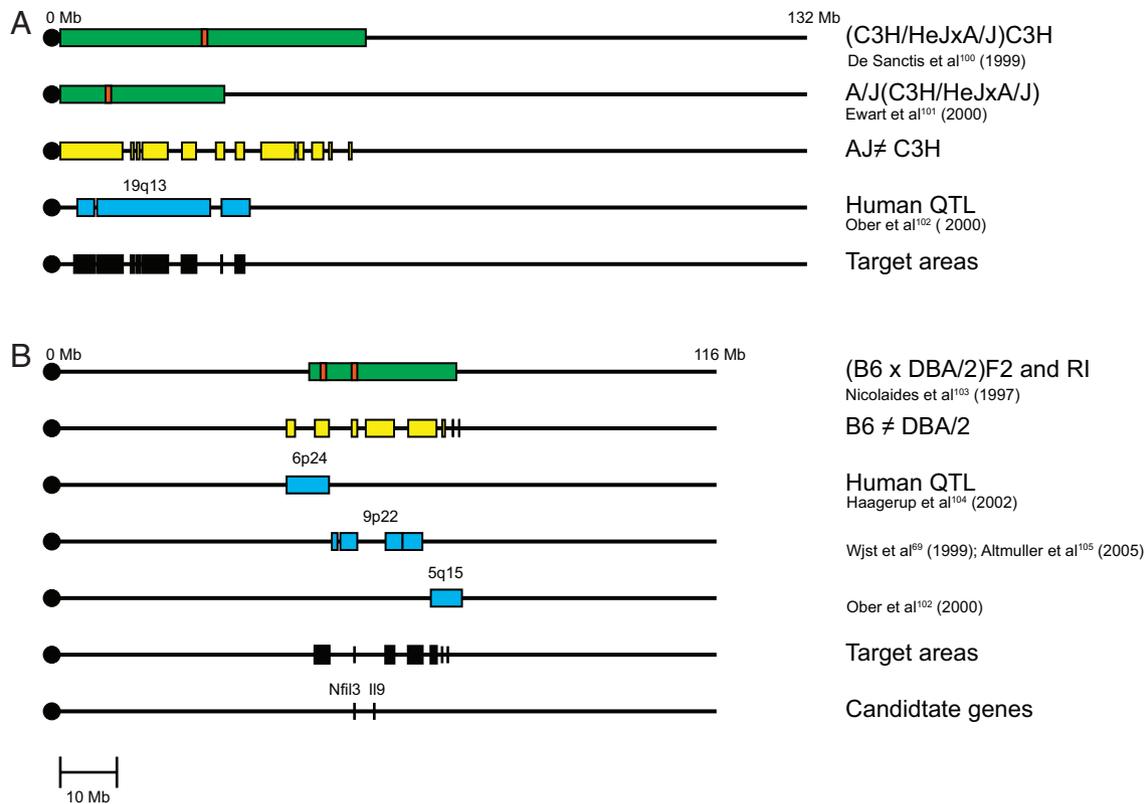
FIGURE 2

Chromosomal map of human quantitative trait loci (QTL) for asthma and BHR and mouse concordant regions. The 95% confidence intervals of the human quantitative trait loci are shown as blue bars to left of their respective chromosomes, with the peaks indicated by black lines. Mouse asthma quantitative trait loci that are concordant with human quantitative trait loci are shown in orange to the right of each chromosome, with the mouse chromosome and the position given in parentheses. Chromosomes are drawn to scale on the basis of the length of each chromosome from the Human Genome Browser ([www.ensembl.org/Homo\\_sapiens](http://www.ensembl.org/Homo_sapiens)). Because many human studies did not report the confidence intervals or the names of the markers that flank the intervals, determining accurate confidence intervals is difficult. This map shows conservative confidence intervals that were generated by including a region of 15 million base pairs both upstream and downstream of the peak.

possible genetic determinants for the development of asthma. Previous exposure-response studies showed that inhaled grain dust and endotoxin produced similar physiologic and biological effects in humans<sup>83-85</sup> and mice<sup>85-88</sup> and genetic or acquired hyporesponsiveness to endotoxin substantially reduced the biological response to grain dust in mice.<sup>86</sup> Researchers identified strains of mice that are hyporesponsive to endotoxin exposure and are defective in endotoxin Toll-like receptor 4 (TLR4).<sup>89</sup>

Similarly, TLR4 mutations have been associated with hyporesponsiveness to inhaled endotoxin in humans.<sup>90</sup>

CD14 and TLR4 are components of the lipopolysaccharide receptor complex, whose gene is encoded on chromosome 5q, near areas identified in previous linkage studies. Polymorphisms in CD14 that influence the propensity to develop asthma and allergy have been described. A cytosine to thymine transition at base pair -159 in the promoter region has been associated with



**FIGURE 3**

Fine detailed maps of mouse chromosomes 7 (A) and 13 (B). These maps were generated with 3 sets of data, leading to target areas that satisfy the best conditions for containing candidate genes of interest. Each map shows the mouse chromosome with 95% confidence intervals of the quantitative trait loci (QTL), shown as green horizontal bars; within these intervals, the peaks are shown in red. The regions that should be considered further are those that are not homologous by descent between the strains of mice that generated the quantitative trait loci. For example, for chromosome 7, the regions that are of further interest are the regions that differ between C3H and A/J (indicated by yellow bars in A). Taking into account the regions that contain concordant human quantitative trait loci (shown as blue bars), the black bars indicate optimal target areas.

serum IgE levels and atopy.<sup>91,92</sup> Also, elevated levels of CD14 have been found in the airways of individuals with asthma.<sup>89,93–96</sup> Both TLR4 and CD14 polymorphisms seem to be involved in the development of asthma from occupational or household exposures.

#### NEW APPROACHES: COMPARATIVE GENOMIC AND EPIGENETIC ANALYSES

Asthma seems to be a heterogeneous clinical syndrome that can result from many distinct pathologic processes. Therefore, the development of asthma depends on complex relationships of genes and the environment over time. New research approaches can expand the body of knowledge beyond linkage studies and the identification of candidate genes to incorporate more-accurate biomarkers of environmental exposures, more-precise genotyping of disease susceptibility loci, and clarification of pathophysiologic phenotypes of asthma. One such approach involves the use of comparative genomic analyses between mice and humans. Quantitative trait loci have been found for asthma and airway hyperresponsiveness in mouse and human genes, and studies showed that many of these loci map to homologous locations in the 2 species (Figs 2 and 3).<sup>97–105</sup> Because findings of homologous regions support the concept that a gene affecting a specific phenotype maps to that spe-

cific region, comparing concordances across species can narrow the field of quantitative trait locus regions of interest and focus efforts on the most promising potential candidate genes. These candidate genes can then be tested with greater statistical confidence in humans, in case-control association studies.

Clarifying the role of genetic factors in asthma is only one part of the equation, however. Because the development and prevalence of asthma and airway disease are not related to inheritance of a specific gene but have been shown to be affected by exposure to environmental factors, understanding how environmental exposures affect gene expression is critical to understanding these diseases. Genomic imprinting through differential methylation results in preferential silencing of maternal or paternal alleles. Histone modification through methylation, acetylation, or phosphorylation also can affect gene transcription.<sup>98</sup> Study of epigenetic modifications of the genome offers a ripe area for new understanding of immune-mediated diseases such as asthma. Although there is a wide range in the rates of concordance of asthma in studies of monozygotic twins, rates are always <100%. One study of monozygotic twins showed that one third of twin pairs harbored epigenetic differences in DNA methylation and histone modification and these markers were more distinct in monozygotic twins who

were older, had different lifestyles, and had spent less of their lives together, which indicates a role for environmental factors in the development of a certain phenotype.<sup>99</sup>

## CONCLUSIONS

Although evidence shows that there is a large genetic component to the development of airway disease in children, inheritance alone does not account for the incidence and prevalence of this disease. Clearly, susceptibility to the development of asthma depends on the interaction of multiple genes, coupled with environmental exposures. Understanding the precise role of environmental exposures in the development of asthma is absolutely critical to reducing the burden of this disease in children. For a better understanding at a basic biological level of how such exposures affect individuals who are genetically susceptible, we must develop much more precise and personalized measures of exposure, as well as early indicators of disease, and we must take advantage of new research approaches incorporating genomic and epigenetic analyses to identify susceptible populations. In addition to this basic research, reducing the burden of asthma in children will require novel clinical approaches to diagnosis and treatment, integrated with public health and regulatory activities aimed at preventing exposures across populations to protect the most-susceptible children.

## ACKNOWLEDGMENTS

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