

## Review article

# Genetic aspects of pediatric asthma: potential clinical role

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## Introduction

Bronchial asthma is a disease of continuing inflammatory disorder of the airways that causes trouble breathing<sup>1</sup>. It is a major cause of chronic morbidity and mortality throughout the world and there is evidence that its prevalence has increased considerably over the past 20 years especially in children. The prevalence of asthma symptoms in children varies from 1 to more than 30% in different populations and is increasing in most countries<sup>2</sup>.

In Egypt, asthma is the commonest cause of emergency and hospital admission where the prevalence among children aged 3-15 years estimated to be 8.2%, with 10% annual increase in mortality<sup>3</sup>.

The genetics of asthma is important in pediatric asthma. Current clinical Knowledge of genetic aspects of asthma is needed to understand the epidemiology, pathogenesis, natural history and management of children with asthma<sup>4</sup>.

Identifying the genes associated with asthma offers a means of better define of its pathogenesis, with the promise of improving preventive strategies, diagnostic tools and therapies<sup>5</sup>.

## Human genetics and etiology of asthma

The genetic contribution to asthma is large. Twin studies have indicated a considerable genetic component and also have shown that individual environmental factors are important<sup>6</sup>.

There is a growing list of asthma susceptibility genes but limited data as yet on how or to what extent they determine the clinical presentation of asthma<sup>7</sup>. However, several locations have been linked to asthma and atopy<sup>8</sup>.

A major consideration for positional cloning of asthma genes is to determine the specific marker, or phenotype, that will be used to identify asthma. Examples can include immunoglobulin (IgE) levels, doctor-diagnosed asthma, or airway hyper-responsiveness. It is important to consider that although the various asthma markers are correlative, they are not the same, and the phenotype selection can affect the specific genes that are identified. At least 3 "asthma genes" have been identified: DPP10, PHF11, and ADAM3.<sup>9,10</sup>

DPP10 is a dipeptidyl peptidase, with known functions include cleaving the terminal sequences from cytokines and chemokines; PHF11 is a transcription factor; and ADAM33 is a disintegrin and metalloprotease that appears to have a role in cell migration, adhesion, and cell-cell interactions. The identification of these genes has led to intensive research efforts to determine how they modify the risk of asthma. It is hoped that the insights gained from these studies will lead to new therapeutic targets for asthma.<sup>9,10</sup>

Many regions of the genome have been found to have linkage with the phenotypes of asthma and atopy. Over 70 variants in candidate genes have been reported to be associated with these phenotypes. The main regions of these variants have been found on chromosomes 2q, 5q, 6p, 11q, 12q, 16q and 17q. Five potential asthma susceptibility genes or complexes have been identified using a positional approach. These are ADAM33, DPP10, PHF11 and SETDB2, GPRA and SPINK5. It is evident that environmental factors will influence the expression of genes and the ultimate clinical phenotype of asthma and atopy.<sup>11</sup>

## Gene-environmental interactions

It is apparent that investigation of gene-environment interactions will be very important in understanding the genetic basis of asthma and atopy.<sup>12</sup>

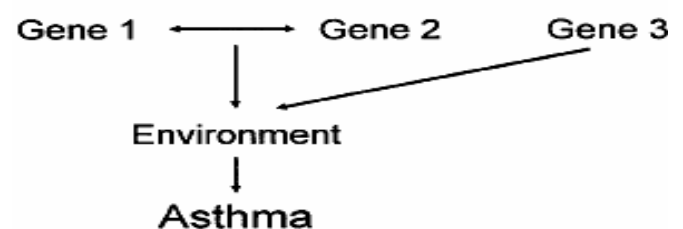


FIGURE 1. Interactions from multiple genes and environmental exposures lead to asthma.

There is evidence that gene-environment interactions play an especially important role in diseases, such as asthma, that have a great deal of variability in their clinical expression. Environmental factors can modify the clinical expression of genetic variability in a variety of patterns. In fact, certain genetic polymorphisms can

either increase, reduce, or have no effect on the clinical expression of asthma<sup>13</sup>.

As an example, a collaborative study with a German group cited that genes may regulate the protective effects of a rural lifestyle on allergies and asthma.<sup>6</sup>

Previous work by this group had revealed a strong relationship between exposure to endotoxin and protection from asthma, strongly suggesting that innate immune responses were responsible for this protection. The research team identified a polymorphism of Toll-like receptor 2 (TLR2), which is a receptor for bacterial products, including endotoxin and peptidoglycan. The study compared asthma and allergic markers, such as serum IgE levels, between farming and non-farming families. A specific polymorphism of TLR2 was associated with protection from asthma among children in farming families, with high exposure to microbial products, but not among families living in relatively "clean" urban and suburban homes.<sup>12</sup>

The influence of environmental factors, including pets, endotoxin, viruses, smoke, and pharmacological agents, on the expression of genes and the ultimate clinical phenotype is being investigated. It appears that they influence the immune development in a genotype and as a result, modulate the development of asthma and atopy. Exposure to dogs in infancy is associated with higher IL10 and IL13 cytokine secretion profiles and reduced allergic sensitization and atopic dermatitis<sup>14</sup>.

Vercelli further discussed the conflicting results reported regarding CD14 polymorphisms, atopy, and exposure to endotoxin. She suggested that there would be no association between genotypes and atopy with low levels of endotoxin exposure, but that the 159T allele would be protective among children with moderate exposure.<sup>15</sup>

Colilla et al.<sup>16</sup> reported evidences of a gene-environmental interaction in a linkage study of asthma and smoking exposure. Also, virus exposure appears to be related to the development of asthma in children.<sup>17</sup>

In addition, Hull et al.<sup>18</sup> suggested that variants in IL8 or IL13 may be involved in the development of bronchitis or asthma.

Drug exposure interactions with genes such as the  $\beta$ -2 agonists and leukotriens inhibitors appear to influence the clinical phenotype of asthma.<sup>19,20,21</sup>

### **Genome wide linkage analysis for asthma and atopy and related phenotypes**

A review in December 2002 reported that there were 12 genome screens for asthma and atopy

related traits studied and the authors noted at least 18 regions of the genome having linkage.<sup>22</sup>

The replicated regions reported for the asthma phenotype have been on 1p, 2q, 4q, 5q, 6p, 12q, 13q, 14q, 19q, and 21q; For total serum IgE sites on 2q, 3q, 5q, 6p, 7q, and 12q; Atopy on chromosomes 3q, 4q, 6p, 11q, and 17q and blood eosinophils counts on 15q.<sup>21</sup>

### **Candidate genes for asthma and atopy and related phenotypes**

Genome-wide linkage analysis (positional) or biological factors influencing the asthma phenotypes (functional) is the basis used for the selection of candidate genes studied for this association. The investigations of the most common candidate gene variants by chromosomal regions will be reviewed<sup>11</sup>.

#### **• Chromosome 2q Region:**

The chromosome 2q region identified in genome screens to be linked with the asthma phenotype contains the IL1 receptor antagonist (IL1RN) and the cytotoxic T lymphocyte antigen-4 (CTLA4) genes. Confirmation of variants in IL1RN being associated with asthma and allergy has been reported<sup>23-24</sup>.

Van Oosterhout et al.<sup>25</sup> noted that CTLA4 is expressed only in activated T cells and is a powerful negative regulator of T cell activation. While Yang et al.<sup>26</sup> reported that a polymorphism in CTLA4 is associated with elevated serum levels of total IgE and allergic rhinitis in females.

Single nucleotide polymorphisms (SNPs) in CTLA4 have been reported to be associated with asthma, serum IgE, asthma severity, and airway responsiveness<sup>19</sup>. Moreover, Bourgain et al.<sup>27</sup> recently reported a P-selectin as an atopy susceptibility locus.

#### **• Chromosome 5q and 16q Regions**

It has been well demonstrated that activation of the IL4 receptor gene (IL4RA) stimulates the production of total serum IgE. IL4 receptor gene is located on chromosome 5q31 and IL4RA on chromosome 16p12, both of which are found on genomic regions linked to the asthma phenotype.<sup>19</sup>

Recently, Beghe et al.<sup>28</sup> noted that a polymorphism in the IL4 and IL4RA chain genes confers susceptibility to asthma and atopy in a Caucasian population.

Other genes on chromosome 5, including those for IL13 (IL13), monocyte differentiation antigen CD14 (CD14), serine protease inhibitor kazal type 5 (SPINK5), and leukotrien C4 synthase.<sup>19</sup>

- *Chromosome 6p21 Region*

Human leukocyte antigen (HLA) DRB1 (HLA-DRB1), TNF  $\alpha$ , and lymphotoxin-  $\alpha$  (LTA) have been reported to be associated with asthma phenotypes. For years, it has been known that HLA class II molecules are involved in controlling the immune response to allergens.<sup>29</sup>

Functional SNPs or haplotypes in HLA-DRB1 have been reported in association with allergic specific IgE responses<sup>11</sup>.

Recently, Moffatt et al.<sup>30</sup> noted a relationship of atopy, respiratory function, and HLA-DR in aboriginal Australians. Also, a functional variant of TNFA-308 is associated with asthma. Moreover, The observation of a functional variant in the promoter of TNFA was associated with asthma and high serum IgE levels.<sup>31,32</sup>

- *Chromosome 11q13 Region*

The gene for the beta chain of the high affinity receptor for IgE on chromosome 11q13, a genome region linked to atopy, has been reported. SNPs or haplotypes in FCER1B have been associated with asthma and their associated phenotypes<sup>19,29</sup>. No recent studies have been conducted on this area.

- *Chromosome 12q Region*

SNPs and haplotypes for the signal transducer and activator of transcription 6 gene (STAT6) and the nitric oxide synthase 1 gene (NOS1) have been well described to be associated with asthma and atopy.<sup>19</sup>

STAT6 has been reported by Nagarkatti et al.<sup>33</sup> to be involved in the initiation of signals from Th2 cells, particularly through IL4 and IL13 receptors in an Indian population. They and others have reported that variants of STAT6 are associated with asthma, allergic diseases and total serum IgE.<sup>19,34,35,36</sup>

Studies have been reported that SNPs in NOS1 are associated with asthma, eosinophil counts and total serum IgE levels<sup>19</sup>. Also, it was confirmed that SNPs in NOS1 are associated with IgE-mediated allergy in a Central European population.<sup>37</sup>

- *Chromosome 17q Region*

The predominant eosinophil chemo-attractant on chromosome 17q is the gene for eotaxin (SCYA11), which is involved in allergic inflammation. SNPs in its promoter region have been found in many studies to be associated with asthma, eosinophil count, and lung function.<sup>19</sup> Shin's group<sup>38</sup> confirmed its association with asthma and serum total IgE.

In addition, many other asthma and atopy susceptibility genes have been suggested in the literature. These have included those for colony-stimulating factor 2 (CSF2), IL12B (IL12B), and glutathione-S-transferase P1 (GSTP1), all of which are located on chromosome 5q. A polymorphism of

the GMM-CSF gene and the development of atopic disease have been reported.<sup>39</sup>

Moreover, Khoo et al.<sup>40</sup> reported an association of the IL12B promoter polymorphism with reduced pulmonary functions in girls. In addition, Lyon et al.<sup>41</sup> reported that an IL10 gene polymorphism was associated with an asthma phenotype in children.

### **Pharmacogenetic and pharmacogenomic approach to asthma treatment**

Pharmacogenomics is the study of the relationship between patterns of genetic variability, or polymorphism, in sets of genes and individual variability in the response of pharmacotherapy. An estimated 70% to 80% of variability in the individual responses to therapy may have genetic basis.<sup>42</sup>

Although genes coding for some key treatment targets contain little polymorphic variation, like the muscarinic M2 and M3 receptors, other genes whose products are important targets of asthma treatment contain extensive genetic variation. The best example of the later are the beta (2)-adrenoceptors and 5-lipoxygenase (ALOX5) genes.<sup>43</sup> Polymorphism of the beta (2)-adrenoceptors may influence airway responses to regular inhaled beta-agonist treatment.<sup>44,45</sup>

Treatment with anti-leukotriene drugs results in clinical improvement in many though, not all patients of asthma. Polymorphism of two genes in the leukotriene pathway; the gene and the synthase gene, have been demonstrated to have pharmacogenetic associations with asthma. Polymorphisms of the (ALOX5) promoter genes and the leukotriene C4 synthase gene have been associated with variation in responses to leukotriene modifier therapy.<sup>46,47</sup>

Children with asthma having a genetic variant that impairs their ability to express ALOX5 have more severe disease than those bearing genotypes that have more efficient baseline expression of ALOX5<sup>46</sup>.

Corticosteroids are the most potent anti-inflammatory agents used to treat chronic inflammatory diseases, such as asthma. About 5% of asthma patients do not respond well or at all to corticosteroids therapy. Although this phenomenon is uncommon, it poses a difficult therapeutic problem.<sup>48</sup>

Asthma treatment with inhaled corticosteroids demonstrates significant person-to-person variability. Genetic variation could contribute to these variable responses. One gene, corticotrophin-releasing hormone receptor 1, demonstrated multiple nucleotide polymorphisms association.<sup>49</sup>

### The future of asthma genetic studies

Asthma genetics researches are still in early stages and face some technical problems. Such studies require the identification of standardized definitions of asthma phenotypes, intermediate biologic measures associated with the risk of asthma, well-defined populations in unbiased studies with sufficient power to detect small effects, and the methods to concurrently measure both environmental and genetic risk factors<sup>4</sup>.

Such association studies and biologically informative pharmacogenomic trials over the next decade should allow us to minimize drug side effects and also maximize drug efficacy<sup>4,2</sup>.

Pharmacogenomic assays will be readily available in clinical laboratories by 2010. By widening the number of potential drug targets and better identifying those children, a specific drug is likely to benefit and another is likely to harm<sup>4</sup>.

### Conclusion

In view of the complexity of asthma and atopy, it is not clear how many genes and environmental factors are involved. The genome screens suggest that there may be many genes with moderate effects. Most likely, many of these genes that influence immunity will prove to be polymorphic. As a result, almost any immune response gene may be found to have an effect on any immune-mediated disease. To determine the clinical relevance of these polymorphisms, they should be tested in case-control studies involving patients with different manifestations and severity of the disease.<sup>11</sup>

The study of genetic variation with the mapping and sequencing of the human genome will have major implications in our understanding of variability in pathogenetic pathways and response to treatment. It is now important to define the biological consequences of the small variations in genetic sequences known as single nucleotide polymorphisms. This is becoming a major driving force for understanding the basis for genetic variation and disease states such as asthma. This concept of pharmacogenetics and pharmacogenomics in relation to identification of genetic variance in response to drug therapy will have a major clinical impact in the near future.<sup>4,50</sup>

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