



Impact of genetics in childhood asthma

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Abstract

Objective: To present the most important and recent results of studies on asthma genetics. These data may help general physicians understand the impact of genetics on this complex disorder and how genes and polymorphisms influence asthma and atopy.

Sources: Data were collected from MEDLINE. Genetic association studies were selected from the Genetic Association Database, which is an archive of human genetic association studies of complex diseases and disorders organized by the National Institutes of Health.

Summary of the findings: Considering the data from several important twin studies on asthma genetics, heritability, which measures the contribution of genetic factors to the variance of asthma, may be estimated in 0.48-0.79. A huge number of genetic association studies have been trying to identify asthma susceptibility genes. The most replicated results in the genetic association studies involve the following five regions of the human genome: 5q31-32, 6p21, 11q12-13, 16p11-12, and 20p13. Only recently a new asthma susceptibility gene (ORMDL3) has been identified by a whole genome association study, considered to be a major determinant for childhood asthma.

Conclusions: Genetic contribution to asthma may be estimated ranging from 48 to 79%. Several loci seem to influence asthma susceptibility. Genes located on chromosome 5q (ADRB2, IL13 and IL4) and the recently identified ORMDL3, on chromosome 17, seem to be determinants of childhood asthma. Diagnostics and pharmacogenetics may be the first clinical implication of extensive studies on asthma genetics.

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Introduction

It has been recognized that asthma is of hereditary nature, but that inheritance does not follow the classical Mendelian patterns in this disease. Several family studies have showed evidence of a substantial familial aggregation pattern in asthma.^{1,2} However, the asthma genetics is especially complicated by its polygenic nature and due to the interaction between genetic and environmental factors.³ A better understanding of the genetic mechanisms of both asthma and allergy will enhance our knowledge of their pathophysiology, and represents an important advance for further efforts towards prevention and treatment.

Some aspects of this field of basic research may directly influence our clinical practice. The genetic determination of

allergic responses to environmental stimuli and the role of pharmacogenetics in the management of asthma are highly regarded research topics.⁴ The mapping of complex traits such as asthma is one of the most important areas of research in human genetics.

Although it is known that genetic susceptibility contributes to the risk of asthma, only few linkage or association genetic studies have been performed in non-European populations. Some studies have shown evidence of genetic control that differs between ethnic groups.^{5,6} However, this evidence is scarce and further studies on asthma genetics in non-European populations are necessary and may help to determine worldwide differences in the role of genetic variations in the development of asthma and allergies.

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A classic design to study the impact of genetics on complex traits and to distinguish between genetic and environmental influences is the study of twin pairs, in which the concordance between monozygotic (MZ) and dizygotic (DZ) twins is compared. MZ twins share 100% of their genetic make-up and DZ twins share in average 50% of their genes. These studies allow for calculation of asthma heritability (h^2). In genetics, heritability is the proportion of phenotypic variation in a population that is attributable to genetic variation.⁷ It estimates the relative contribution of genetic and non-genetic factors to the total phenotypic expression in a population.

Twin studies in asthma genetics

If genes influence a particular trait, MZ twins, due to their greater genetic similarity, should share that trait more than DZ twins. An Australian study investigated 3,808 twin pairs,⁸ and the correlations for asthma were greater for MZ twins than for DZ twins (0.48 for MZ, 0.09 for DZ, male; and 0.33 for MZ, 0.12 for DZ, female) implying a significant proportion of the variance accounted by genetics in asthma pathogenesis ($h^2 = 0.60$). Duffy et al.⁹ reanalyzed the 3,808 Australian twin pairs in 1990, and the correlation of self reported asthma was 0.65 in MZ twins and 0.24 in DZ twins. Heritability was estimated in 0.60 for females and 0.75 for males.

Nieminen et al.¹⁰ published a large population-based study of > 13,000 adult Finnish twin pairs. The diagnosis of asthma was performed by linking the twin registries with databases on hospital admissions and utilization of medication. Data were collected from a central office for epidemiology. A total of 4,307 MZ and 9,581 DZ twin pairs aged 18-70 years were included. The heritability estimation was 0.68 for women and 0.48 for men (aged 28-59 years). In this study there was a marked gender difference in heritability and there was a difference in heritability between the various age groups, with heritability decreasing with age, which is in accordance with the clinical and epidemiological evidences.

Another twin study published in 1997 included 1,480 Swedish twin pairs aged 7-9 years (from the Swedish Twin Registry).¹¹ All twins born in Sweden between 1985 and 1986 were given a detailed asthma questionnaire. The correlation for parental-report of asthma was 0.79 for MZ male twin pairs and 0.64 for MZ female pairs, with correlations of 0.25 and 0.27 for DZ male and female pairs, respectively. The contribution of genetic factors to variance of asthma in this study was about 0.76 for boys and 0.64 for girls.

In a Norwegian study, all twins born between 1967 and 1974 (5,864 children) were identified through the Norwegian National Birth Registry.¹² The prevalence of self-reported asthma was around 5% and there were no significant sex differences. The concordance for asthma was 0.45 for MZ twins and 0.12 for DZ twins. This study showed that genetic effects

explained 75% of the variation in both sexes. The remaining 25% was accounted for by environmental influences.

Another Finnish twin study in 16-year-old twins and their parents presented combined twin-family data on asthma genetics. The heritability of asthma was approximately 79% and the remaining 21% were due to environmental influences.¹³ If only the families with parental asthma were considered, genetic influences explained as much as 87% of the development of asthma in the offspring.

Another large-scale study on 11,688 twin pairs aged 12-41 years was published in 1999 and the heritability was estimated in 0.73 (Danish population sample).¹⁴ A more recent twin study with an estimation of asthma heritability was published in 2001.¹⁵ This last asthma twin study estimated a heritability of 0.68 in a population from the United Kingdom.

All these twin studies have shown the importance of the genetics on asthma variance, with results of heritability estimation ranging from 48-79%. An important finding is that most of these twin studies in different parts of the world (especially in Northern Europe) showed similar and consistent results and stress the fact that especially childhood asthma has a strong genetic background. Table 1 presents the summary of these important population-based twin studies.

Although we can estimate to what extent genetic susceptibility contributes to the risk of asthma, the specific loci that influence the clinical phenotypes are yet far from being clearly identified. A significant number of genetic association studies have been describing asthma susceptibility genes, but these data demonstrate the extreme complexity of the disease, and the identification of these genes and polymorphisms may be still considered a difficult challenge.

Candidate-gene association studies

A widely used approach for the identification of asthma susceptibility genes is the study of polymorphisms in candidate genes. Genetic association studies test whether a specific genetic variant is more common in asthmatics than in non-asthmatics. Controls for association studies should be recruited from a population that shares ethnic or geographic similarities with the cases. The advantages of association studies include their power to detect susceptibility genes and their applicability to the general populations. This approach is powerful if (and only if) the candidate selected for the study is clearly involved in the pathogenesis of the disease.¹⁶

However, because of the multitude of potential candidate genes for a complex trait, the work involved in a comprehensive candidate-gene approach might be overwhelming. In addition, as it is now recognized, results of individual polymorphism studies may be misleading (especially because of linkage disequilibrium), thus the candidate-gene approach has to include multiple variants that are evaluated simultaneously. Considering this, correction for multiple comparisons or replication in different population samples and/or

Table 1 - Revised twin studies with the outcome asthma and the estimated heritability (h^2)

| Study population | N* | Age range | h^2 | References |
|------------------|--------|-----------|-----------|---|
| Australian | 3,808 | 18-88 | 0.60-0.75 | Duffy et al. (1990) ⁹ |
| Finnish | 13,888 | 18-59 | 0.48-0.68 | Nieminen et al. (1991) ¹⁰ |
| Swedish | 1,480 | 7-9 | 0.64-0.76 | Lichtenstein et al. (1997) ¹¹ |
| Norwegian | 5,864 | 18-25 | 0.75 | Harris et al. (1997) ¹² |
| Finnish | 1,713 | 16 | 0.79 | Laitinen et al. (1998) ¹³ |
| Danish | 11,668 | 12-41 | 0.73 | Skadhauge et al. (1999) ¹⁴ |
| English | 4,910 | 4 | 0.68 | Koeppen-Schomerus et al. (2001) ¹⁵ |

* Number of twin pairs included in the twin population study.

functional analysis have been required to define causality in these association studies.^{17,18}

Several candidate genes (> 100 loci) have been proposed and studied in asthma. Several factors contribute to this abundance of candidates. Results from genome screens have provided evidence of linkage to multiple sites in the genome. Therefore, there are many positions including several candidate genes. In addition, immunological pathways associated to the asthmatic response involve a large array of inflammatory mediators such as cytokines and chemokines. However, the best replicated results in the genetic association studies involve the following five regions of the human genome: 5q31-32, 6p21, 11q12-13, 16p11-12, and 20p13 (<http://geneticassociationdb.nih.gov>).¹⁹

Genetic Association Database

The Genetic Association Database (GAD) is an archive of human genetic association studies of complex disorders, organized by the National Institutes of Health (<http://geneticassociationdb.nih.gov>). The objective of this database is to allow the researchers to rapidly identify medically relevant polymorphisms from the large volume of gene variations, in the context of a standardized nomenclature for genes and polymorphisms (rs numbers). The database includes selected published scientific papers. Study data is recorded with the official nomenclature used for the human genome. If a study investigates more than one gene for a particular disorder, there will be more than one record. The submitted records are reviewed before inclusion in the database.¹⁹

Using GAD, we have selected eight genes, located in the five above mentioned regions of the genome, for the current review that have been associated with asthma in more than five population-based genetic association studies. These relevant asthma susceptibility genes are discussed below in detail (Table 2).

Chromosome 5: ADRB2, IL13 and IL4

The beta-2-adrenergic receptor gene (ADRB2) is a member of the G protein-coupled receptor superfamily. This receptor-channel complex contains a G protein, an adenylyl cyclase and the counterbalancing phosphatase. The assembly of the signaling complex provides a mechanism that ensures specific signaling by this G protein-coupled receptor. Different polymorphic loci of this gene have been associated with asthma diagnosis, nocturnal asthma, asthma exacerbations and response to beta-2 agonists in asthma treatment.

Turki found a higher frequency of glycine at position 16 (Gly16, SNP rs1042713), compared to Arg16, in individuals with nocturnal asthma.²⁰ Other evidence has suggested that the presence of Gly16 (amino-acid sequence) of ADRB2 imparts enhanced agonist-promoted downregulation of the type that characterizes this form of asthma.

In a meta-analysis published recently, Contopoulos-Ioannidis et al. confirmed the association between the Gly16 polymorphism and nocturnal asthma, but found no association between this variant and bronchial hyperresponsiveness.²¹ Other studies found association between rs1042713 and different responses to beta-2 agonists (especially albuterol and salmeterol).²²

IL13 encodes an immunoregulatory cytokine produced primarily by activated Th2 cells. This cytokine upregulates major histocompatibility complex class II (MHCII) expression and promotes IgE isotype switching. IL13 inhibits the production of proinflammatory cytokines and chemokines. This cytokine is found to be critical to the pathogenesis of allergen-induced asthma but operates through mechanisms independent of IgE. IL3, IL5, IL4, IRF1 and CSF2 form a cytokine gene cluster on chromosome 5q, with IL13 located particularly close to IL4.

Table 2 - Genes with more than five positive genetic association studies with the outcome asthma (data from National Institutes of Health Genetic Association Database, <http://geneticassociationdb.nih.gov>)¹⁹

| Position | Gene | Number of positive studies | Polymorphisms | References (first author and year) |
|----------|----------|----------------------------|--|--|
| 5q31-32 | ADRB2 | 11 | rs1042713 | Holloway JW (2000), Wang Z (2001), Ohe M (1995), Turki J (1995), Barr RG (2001), Dai LM (2004), Gao JM (2002), Gao G (2000), Xu X (2002), Summerhill E (2000), Fu J (2002) |
| | IL13 | 13 | rs1800925 rs20541 | van der Pouw Kraan TC (1999), Arima K (2002), Xi D (2004), Heinzmann A (2000), Kim HB (2006), Hosseini-Farahabadi S (2007), Hunninghake GM (2007), Kabisch M (2006), Battle NC (2007), Leung TF (2001), Howard TD (2001), Tsunemi Y (2002), Noguchi E (2001) |
| | IL4 | 11 | rs2243250 | Zhu S (2000), Chouchane L (1999), Burchard EG (1999), Rosenwasser LJ (1995), Noguchi E (2001), Kabisch M (2003), Gervaziev YV (2006), Hosseini-Farahabadi S (2007), Kabisch M (2006), Kabisch M (2003), Suzuki I (2000) |
| 6p21.3 | HLA-DQB1 | 10 | rs12722107 rs1049086 rs1049107 rs1130386 rs1049133 | Gao J (2003), Guo X (2001), Torio A (2003), Kim SH (2005), Schubert MS (2004), Lara-Marquez ML (1999), Lin YC (2002), Cho SH (2000), Kim YK (2002) |
| | TNF | 6 | rs1800629 | Witte JS (2002), Albuquerque R (1998), Winterton DL (2001), Noguchi E (2002), Hong SJ (2006), Kim SH (2006) |
| 11q12-13 | SCGB1A1 | 6 | rs3741240 | Choi M (2000), Sharma S (2004), Gui Q (2003), Sengler C (2003), Laing IA (1998), Candelaria PV (2005) |
| 16p11-12 | IL4R | 9 | rs1805015 | A-M Hytonen CEA (2004), Ober C (2000), Mitsuyasu H (1999), Cui T (2003), Risma KA (2002), Mitsuyasu H (1998), Zhang AM (2006), Loza MJ (2007), Battle NC (2007) |
| 20p13 | ADAM33 | 9 | SNP * | Werner M (2004), Howard TD (2003), Lee JH (2004), Jongepier H (2004), Noguchi E (2006), Kedda MA (2006), Hirota T (2006), Qiu YM (2007), Sakagami T (2006) |

SNP = single nucleotide polymorphisms; TNF = tumor necrosis factor.

* More than 15 ADAM33 polymorphisms have been associated with asthma or asthma-related phenotypes.

Howard et al. reported that the promoter variant (C-1112T, rs1800925) of the IL13 gene contributes significantly to bronchial hyperresponsiveness and asthma susceptibility but not to total serum IgE levels.²³ Heinzmann²⁴ determined that a R130Q variant of IL13 (rs20541) is associated with asthma in case-control populations from Britain and Japan (odds ratio, OR = 2.31, 95%CI 1.33-4.00); the variant

also predicted asthma and higher serum IL13 levels in a Japanese pediatric population.

The protein encoded by the IL4 gene is a Th2 cytokine produced by activated T cells that influence allergic immune response. The IL4 receptor also binds to IL13, which may contribute to many overlapping functions of IL4 and IL13. IL4,

IL13 and IL5 are found to be regulated coordinately by several regulatory elements on chromosome 5.

Kabesch²⁵ have demonstrated a possible involvement of SNP in the IL4 gene in the development of asthma and the regulation of total serum IgE. In addition, this group has shown in 2006²⁶ that especially the combined analyses of genetic alterations in the IL-4/IL-13 pathway reveal its significance to the development of atopy and childhood asthma. Additionally, other genes harbored in the locus, as CD14 and IRF1, may also contribute to asthma and allergy.

Chromosome 6: HLA-DQB1 and TNF

HLA-DQB1 belongs to the human leukocyte antigen (HLA) beta chains. This molecule is a heterodimer consisting of an alpha (DQA) and a beta chain (DQB), both anchored in the membrane. It plays a central role in the immune system by presenting peptides derived from extracellular proteins. Within the DQ molecule both the alpha and the beta chains contain polymorphisms, leading to four different molecules. Several studies²⁷⁻²⁹ have shown association between HLA-DQB1 variations and asthma or aspirin-induced asthma (Table 2).

The tumor necrosis factor (TNF) gene encodes a multifunctional proinflammatory cytokine that belongs to the TNF superfamily. This cytokine is mainly secreted by macrophages and is involved in the regulation of a wide spectrum of biological processes including cell proliferation, differentiation and apoptosis.

Witte³⁰ evaluated the relation between the G-308A (rs1800629) promoter polymorphism of the TNF gene and risk of asthma in 236 cases and 275 non-asthmatic controls. This study indicated that having one or two copies of the -308A allele increased risk of asthma (OR = 1.58), the magnitude of which was increased when restricting the cases to those with acute asthma (OR = 1.86, $p = 0.04$) or further restricting the subjects to those with a family history of asthma and those of European American ancestry (OR = 3.16, $p = 0.04$).

Instead, Aoki et al.³¹ did not find a significant association between this TNF G-308A polymorphism (rs1800629) and childhood atopic asthma in two independent Japanese populations; however, meta-analysis of a total of 2,477 asthma patients and 3,217 control individuals showed that the G-308A polymorphism was significantly associated with asthma. The combined OR was 1.46 for fixed or random effects ($p < 0.001$).

Chromosome 11: SCGB1A1 (or UGB; CC16; CCSP)

Clara cell secretory protein (CC16) is a protein primarily expressed in the respiratory tract by nonciliated bronchiolar secretory cells³² and the immunomodulatory activity of CC16 has been well documented. Mice deficient in CC16 expression exhibit a higher susceptibility to lung injury and an excessive inflammatory response.

The CC16 gene was screened for mutations and a polymorphism (A38G, rs3741240) was identified and associated with an increased risk of physician-diagnosed asthma in a population of Australian children.³³ In a study with adults, a moderate risk of asthma was found to be associated with the CC16 38A allele.³⁴ Laing et al. have shown that the 38A sequence was associated with reduced plasma CC16 levels and individuals with lower plasma CC16 levels were more likely to have asthma.³⁴ However, studies with larger population samples are required to confirm this association.

Chromosome 16: IL4R

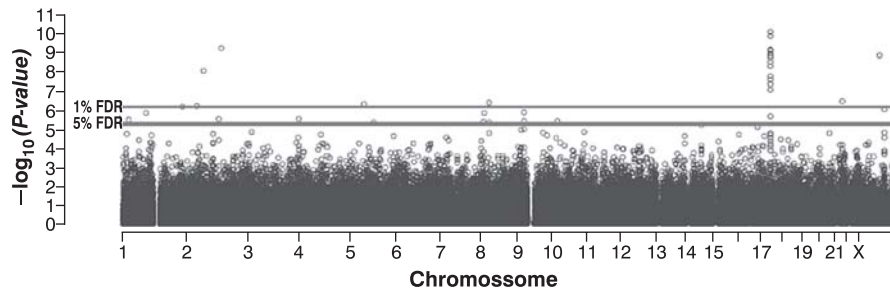
This gene encodes the IL4 receptor, a transmembrane protein that can bind IL 4 and IL13 to regulate IgE production. Binding of IL13 or IL4 to the IL4 receptor (IL4R) induces the initial response for Th2 lymphocyte polarization. Both IL13 and IL4 are produced by Th2 cells and are capable of inducing isotype class-switching of B cells to produce IgE after allergen exposure.

Allelic variations in this gene have been associated with atopy, a condition that can manifest itself as allergic rhinitis, asthma, or eczema. Howard et al. investigated 5 IL4RA single-nucleotide polymorphisms in a population of Dutch families ascertained through a proband with asthma.³⁵ The authors observed significant associations of atopy and asthma-related phenotypes with several IL4RA polymorphisms, especially S503P (rs1805015). A significant gene-gene interaction between S503P in IL4RA and the C-1112T promoter variation in IL13, previously shown to be associated with bronchial hyperresponsiveness, was detected. Individuals with the risk genotype for both genes were at almost five times greater risk for the development of asthma compared to individuals with no-risk genotypes. These data suggest that variations in IL4RA contribute to elevated total serum IgE levels, and interaction between IL4RA and IL13 markedly increases a subject susceptibility to asthma.

Chromosome 20: ADAM33

This gene encodes a member of the disintegrin and metalloprotease domain (ADAM) family. Members of this family are membrane-anchored proteins and have been implicated in a variety of biological processes including muscle development and neurogenesis. This protein is a transmembrane protein implicated in asthma and bronchial hyperresponsiveness. Alternative splicing of this gene results in two transcript variants encoding different isoforms. This was the first published asthma candidate gene detected by positional cloning.

Van Eerdevegh³⁶ performed a genome-wide scan on 460 Caucasian families and identified a locus on chromosome 20p13 that was linked to asthma and bronchial hyperresponsiveness. A survey of 135 polymorphisms in 23 genes identified the ADAM33 gene as being significantly associated with asthma using case-control, transmission disequilibrium, and



FDR = false discovery rate.

Figure 1 - Genome-wide association of 317,447 SNP and asthma in 994 asthmatic children and 1,243 non-asthmatic children (figure from Moffat et al.³⁸). Position in the genome is divided by chromosome. Strength of association is shown on the y axis. The result for each individual marker is depicted as a black circle. The genome-wide thresholds for 1 and 5% FDR are shown as horizontal red lines. Numerous markers on chromosome 17q21 show association with asthma

haplotype analyses ($p = 0.04-0.000003$). However, these results were not replicated by several other ADAM33 association studies. Studies in Icelandic and UK populations revealed no association when taken in isolation.

Recently, a meta-analysis showed that the rs511898 and rs574174 variants (located on ADAM33 gene) were significantly associated with asthma.³⁷ The additional risk imparted by these variations would account for 50,000 excess asthma cases in the UK alone.

Genome-wide association studies

With the completion of the Human Genome Project in 2003 and the International HapMap Project in 2005, researchers have now a set of advanced research tools that may allow identifying genetic contributions to common diseases more easily. These tools include computerized databases containing the reference human genome sequence and a map of human genetic variation. A genome-wide association study (GWA) is an approach that involves scanning markers across complete sets of human polymorphisms.

Recently, the first asthma GWA study³⁸ characterized more than 317,000 SNP in the DNA from 994 patients with childhood-onset asthma and 1,243 non-asthmatics, using both family and case-referent panels. The authors showed multiple markers on chromosome 17q21 to be strongly and consistently associated with childhood asthma with a combined p value $< 10^{-12}$. An independent replication study showed that the 17q21 locus has a significant association with the diagnosis of childhood asthma in 2,320 subjects from a cohort of German children ($p = 0.0003$) and in 3,301 subjects from the UK's 1958 Birth Cohort ($p = 0.0005$). This study³⁸ has evaluated the relationship between markers of the 17q21 locus and transcript levels of genes. The SNP (rs7216389) associated with childhood asthma was consistently and strongly associated ($p = 10^{-22}$) with transcript levels of

ORMDL3, a member of a gene family that encodes transmembrane proteins anchored in the endoplasmic reticulum. Moffat et al.³⁸ concluded that genetic variants regulating ORMDL3 expression are determinants of susceptibility to childhood asthma. In the subset of individuals for whom expression data were available, the T allele of SNP rs7216389 was the marker most strongly associated with disease in the combined GWA (Figure 1).

Conclusions and future perspectives

Several different loci seem to influence asthma susceptibility. Genes located on chromosome 5q (ADRB2, IL13 and IL4) and the recently identified ORMDL3, on chromosome 17, seem to be major determinants for childhood asthma.

However, there are only a few studies of asthma genetics in Latin America and not many in underdeveloped areas of the world where asthma is highly prevalent. A recent study from the ISAAC-Phase II group³⁹ has shown that asthma in non-affluent communities is significantly less associated with allergy in comparison with more socially developed areas.

It is not clear whether the results from genetic studies in European populations can be easily transferred to populations of different ethnicities. Epidemiological genetic studies in Latin America, Asia and Africa are needed to determine the impact of genes and environment in these regions, which may differ dramatically from the findings in population samples from Europe and the USA.

Improvements in diagnostics and pharmacogenetics may be the first clinical implications of these extensive studies on asthma genetics. In a randomized, placebo-controlled study involving 78 patients with mild asthma, 37 with the R/R genotype and 41 with the G/G genotype (rs1042713), Israel²² found that there were significant genotype-related differences in response to albuterol compared with placebo. Patients with the R/R genotype improved when beta-agonist

therapy was withdrawn and replaced with ipratropium bromide, whereas those with the G/G genotype did better with regular beta-agonist therapy than when it was withdrawn. Genotype at amino acid 16 of ADRB2 significantly affects the response to albuterol. Furthermore, bronchodilator treatments avoiding albuterol may be appropriate for patients with the R/R genotype.²² This is only an example of how genetics may influence our clinical practice in the near future.

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