THE GENETIC IMPLICATIONS OF BRONCHIAL ASTHMA

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ABSTRACT

It has been recognized that bronchial 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. Genetic and environmental factors play a significant role in asthma, and interest in the genetics of asthma has grown over the last 2 decades because of the significant increase in prevalence in many countries. However, the asthma genetics is especially complicated by its polygenic nature besides the interaction between genetic and environmental factors. The genetic determination of allergic responses to environmental stimuli and the role of pharmacogenetics in the management of asthma are highly regarded research topics and the current review highlights the same. A proper understanding of the genetic aspects underlying the pathophysiology and expression of bronchial asthma are likely to unveil new, personalized therapeutic strategies in future.

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INTRODUCTION

Bronchial asthma or simple ‘asthma’ is the most common chronic childhood disease in developed nations. It is characterized by increased responsiveness of the tracheobronchial tree to a multiplicity of stimuli, increased infiltration of various inflammatory cells especially eosinophils into the airway, epithelial damage, airway smooth-muscle hypertrophy, variable airway obstruction usually associated with inflammation in the conducting airways and mucous hypersecretion in the bronchiolar walls of the lungs. It is manifested physiologically by widespread narrowing of the air passages and clinically by paroxysms of dyspnoea, cough, wheezing and tightness, provoked by one or more triggers such as physical exertion and airway irritants (cold, dry air, smoke, etc.). In unusual circumstances, acute episodes can cause death [1].

PROBLEM LOAD

Worldwide, asthma cases are increasing at a rate of 50% every decade, and according to the World Health Organization, by the year 2020, asthma, along with chronic obstructive pulmonary disease (COPD) will become the third leading cause of death. An estimated 300 million people in the world currently have asthma and there may be an additional 100 million persons with asthma by 2025 [2]. It has been reported that India has approximately 15-20 million asthmatics and 10-15% of Indian children between the ages of 5 and 11 years show symptoms of asthma. In a study in Mumbai, the prevalence of asthma in adults was 3.5 and 17% when broad definitions including asymptomatic bronchial hyper-responsiveness were used. In rural children in Delhi, parental smoking, paracetamol intake, current exposure to cat, exposure to traffic pollution were found to be significantly associated with current wheezing [3] whereas in children aged 4-15 years in Chandigarh, a prevalence of 7% was observed. India accounts for a third of the world’s asthma patients [1].

RISK FACTORS

Several risk factors have been identified in the pathophysiology of asthma, including sensitization and exposure to cockroaches, house dust mites, and the mold Alternaria tenuis, among other aeroallergens. Viral respiratory infections, primarily those caused by respiratory syncytial virus, are a significant risk factor for the development of childhood wheezing in the first decade of life [7]. A population based, 6-year prospective cohort study of 1984 children 1 to 7 years of age found that 7.2% of children developed asthma during the study period, resulting in an incidence rate of 125 cases per 10,000 person-years. Maternal history of asthma influences the relation between day care related exposures and childhood asthma. In children without a maternal history of asthma, day care attendance in early life was associated with a decreased risk for asthma and recurrent wheezing at the age of 6 years, and with a decreased risk for any wheezing after the age of 4 years. Among children with a maternal history of asthma, day care in early life had no protective effect on asthma or recurrent wheezing at the age of 6 years. Instead, it was associated with an increased risk for wheezing in the first 6 years of life, suggesting a greater contribution of genetics [4].

Asthma and COPD are common respiratory diseases that are caused by the interaction of genetic susceptibility with environmental factors. Environmental influences are important in both diseases, and although there are differences in genetic susceptibilities, there are also similarities [5]. The Dutch hypothesis, formulated in the 1960s, holds that the various forms of airway obstruction are different expressions of a single disease entity. It suggests that genetic factors (such as airway hyperresponsiveness and atopy), endogenous factors (such as age and sex), and exogenous factors (such as allergens, infections, and smoking) all play a role in the pathogenesis of chronic nonspecific lung disease (Fig. 1) [6]. An expert working group of the National Heart, Lung, and Blood Institute identified the genetics, gene–environment interactions, and pharmacogenetics as one of six of the top priority areas for research in asthma [7].
Fig. 1. Risk factors for chronic non-specific lung disease (Dutch hypothesis).

TYPES

Nowadays, asthma is considered as an inflammatory disease in the conducting airways of the lungs and eosinophilia with variable airway obstruction, which may lead to tissue destruction and loss of lung function [8-11]. Different clinical forms of asthma exist such as allergic (extrinsic) asthma, asthma without evidence of atopy (intrinsic), early and late-onset asthma, occupational and exercise-induced asthma. Most genetic studies have concentrated on asthma associated with atopy. Atopy is defined in a number of different ways: by elevated total serum IgE levels and/or positive skin tests to one or more allergens. The binding of IgE with both high-affinity and low-affinity receptors provides a signal for mast cell activation and eosinophils recruitment. An inflammatory process involving the release of inflammatory mediators (prostaglandins, leukotrienes and proteolytic enzymes) may lead to tissue destruction, epithelial disruption, smooth muscle and microvascular proliferation, which eventually lead to an an bronchoconstrictor response and bronchial hyperresponsiveness of the airways to chemical stimuli [10].

GENETIC ASPECTS

Asthma runs strongly in families and is about half due to genetic susceptibility and about half due to environmental factors. The strong familial clustering of asthma has encouraged an increasing volume of research into the genetic predisposition to disease. Although identification of all asthma genes is incomplete, genetic findings are already changing the prevailing view of asthma pathogenesis [12].

Studies of family history, twins, familial aggregation and segregation studies in asthma have convincingly shown that the disease has a strong genetic component. A heterogeneous condition of asthma may predominate in different geographic locations, and is strongly influenced by environmental factors that may differ among populations and at different ages. However, it is likely that the risk of developing asthma is greatest when both genetic and environmental risk factors are present simultaneously. The inheritance of asthma and allergy does not follow the classical Mendelian patterns of inheritance [1]. Segregation analysis can provide insight into the genetics of a trait, e.g. The number of genes involved and the genetic model: dominant or recessive, polygenic, and those with environmental effects. Using this type of analysis, the heritability, mode of inheritance, penetrance and frequency of a trait are being estimated and also indicated the involvement of major genes [13]. Ober et al [14] conducted a genome-wide screen in the Hutterites, a religious isolate of European ancestry, to identify genes that influence asthma and asthma-associated phenotypes. A primary sample of 361 individuals and a replication sample of 292 individuals were evaluated by a genome-wide screen using 292 autosomal and three X-Y pseudautosomal markers. Using the semi-parametric likelihood ratio, χ2 test and the transmission-disequilibrium test, 12 markers in 10 regions were identified that showed possible linkage to asthma or an associated phenotype. They showed markers in four regions (5q23-31, 12q15-24.1, 19q13 and 21q21). More than 100 loci on 22 autosomes, X and Y chromosomes have been linked to asthma. Gene is located on chromosome 16 and represents an ideal candidate gene for atopy susceptibility because of its pivotal role in IL-4 signaling and its key role in allergic inflammation by promoting IgE production and Th2 cell development [1].

Asthma and the associated clinical disorders atopy, rhinitis and eczema are strongly familial and are due to genetic and environmental influences. Similar to conditions such as hypertension, atherosclerosis and diabetes mellitus, it is a complex genetic disorder in which the mode of inheritance cannot be classified as autosomal, recessive or sex-linked. Another important aspect that
often distinguishes complex genetic disorders from single gene disorders is their prevalence. Asthma is more common in the population (4–8%) than, for example, cystic fibrosis which occurs once in every 2,000 live Caucasians births [15]. The genetic complexity of asthma may include that a number of genes are involved in its pathogenesis (polygenic inheritance), that different combinations of genes act in different families (genetic heterogeneity) and that the same gene or sets of genes influences multiple traits (pleiotropy) for example, asthma and eczema. Furthermore, environmental influences could be of importance for the expression of asthma. Studies on the genetics of asthma are complicated by the fact that there are difficulties in standardizing the diagnosis of asthma [16].

The asthma phenotype is that the clinical expression of asthma may vary over time even within an individual, especially at older age. Thus lack of a gold standard to diagnose asthma, variable clinical expression, variable age at onset and variable progression during lifetime are providing some difficulties in the studies on the genetics of asthma [17, 18]. In the last 15 years, molecular genetics has been developed extensively, and has been used to identify which genes may cause asthma. Since the existence of different phenotypes of asthma, and the intricate immunological network which is involved in the pathogenesis of asthma, it is hypothesized that different genes are responsible for this disease. Different approaches have been used to detect genes which are involved in asthma. Genetic linkage is the analysis of the inheritance of genetic markers within pedigrees to establish linkage between a marker and the disease. Linkage analysis requires a genetic model to be specified, and the mode of inheritance, allele frequencies and penetrance to be known. In the last fifteen years, many genetic studies have identified chromosomal regions that may contain genes that contribute to asthma or associated phenotypes. Linkage for high levels of total IgE has been found on chromosome 5q, chromosome 11q, and chromosome 12q. Bronchial hyperresponsiveness, another phenotype of asthma, has shown linkage to chromosome 5q, while other chromosomal regions (6p21.3, 12q14.3–24.1 and 14q11.2–13) are involved in the immunological network associated with asthma.

Until now, four genome-wide screens have significantly contributed to our understanding of the genes associated with asthma and associated phenotypes. A study from the Swedish Twin Registry involved 1480 Swedish twin pairs aged 7–9 years [16]. This questionnaire-based study examined the importance of genetic and shared environmental influences in atopic diseases. All parents of twins born in Sweden between April 1985 and December 1986 were mailed a detailed questionnaire on asthma and allergies. The correlation for parental-report of asthma was 0.79 for monozygotic male twin pairs and 0.64 for monozygotic female pairs, with correlations of 0.25 and 0.27 for dzygotic male and female pairs respectively. The contribution of genetic factors to variance of asthma was about 0.76 for boys and 0.64 for girls. Genetic modeling showed no evidence of shared environment in both sexes. The genetic correlation between asthma and allergy was 0.90, indicating that there are sets of genes common for these traits. In families with parental asthma, genetic influences explained as much as 87% of the development of asthma in the offspring. The cumulative incidence was fourfold in twins with parental asthma when compared with the incidence of asthma in twins without parental asthma (14.7 % versus 3.3 %). A large-scale study on 11 688 twin pairs aged 12–41 years was published by Skadhauge et al [19]. The same results were found as in the twin studies described above. The heritability was 0.73 and the model incorporating additive genetic effects with non-shared environment was the best fitting model. These studies have shown the importance of genetic influences in the variance of asthma, but environmental influences are important since they contribute at least 25 % of the total variance of asthma [16].

The Collaborative Study on the Genetics of Asthma concluded that the chromosomal regions most associated with asthma differ between ethnic groups, although several genes are relevant to asthma regardless of ethnicity. Asthma has been associated with genes such as ADAM33, IL4, IL17A, and IL17F [20]. Asthma can be designated as a complex genetic disease because there are multiple genetic effects that interact with the environment to modify both the susceptibility to and severity of the disease [21]. Childhood asthma candidate gene PPP1R12B was identified in the first genome-wide association study (GWAS) in Russians of west Siberia [22].

Positional cloning is a process of systematic disease gene identification that begins by finding genetic regions co-inherited with disease. It requires no assumptions about likely disease pathogenesis. Five asthma genes or gene complexes have now been identified by positional cloning, including ADAM33, phll, dpplo, GRPA and SPINK5. The functions of all of these genes are obscure, but the expression of dpplo, GRPA and SPINK5 in terminally differentiating epithelium suggests that they deal with threat or damage from the external environment. Many of the genes identified by candidate gene studies may also exert their effects within the cells that make up the mucosa. These include il13 which modifies mucous production, FcRI-I-p which modifies the allergic trigger on mast cells, and microbial pattern recognition receptors of the innate immune system [12].

Studies in both humans and animals have demonstrated a genetic predisposition to bronchial hyperresponsiveness, such as greater concordance for this trait among monozygotic twins than among dzygotic twins. Bronchial hyperresponsiveness to carbachol appears to be inherited as an autosomal dominant trait, but the bimodal distribution of bronchial responsiveness to methacholine is not controlled by a single gene. Bronchial hyperresponsiveness is accompanied by bronchial inflammation and an allergic diathesis in patients with asthma. Even in children with no history or symptoms of atopy or asthma, bronchial hyperresponsiveness is strongly associated with elevated serum ige levels. This chromosomal region is rich in candidate genes, many of which regulate ige production either directly or indirectly and affect the activation and proliferation of cells involved in inflammatory processes associated with bronchial hyperresponsiveness, allergy, and asthma. Although population studies clearly show a very strong association between atopy and bronchial hyperresponsiveness, they cannot identify patterns of inheritance or the number of genes involved, the magnitude of their effects, or in most cases, their location. However, linkage analysis can facilitate the dissection of the genetics of complex diseases such as asthma. Chromosome 5q31-q33 was originally examined because it is especially rich in genes that are implicated in bronchial inflammation associated with asthma. Granulocyte–macrophage colony-stimulating factor, fibroblast growth factor acidic, other colony stimulating factors and receptors, the lymphocyte-specific glucocorticoid receptor 1, and the b2-adrenergic receptor map to this area. A cluster of cytokines, interleukin-3, 4, 5, 9, and 13, are also tightly linked and map to this region. These cytokines have overlapping effect on the growth and proliferation of B cells and other cells associated with allergic inflammation. Interleukin-9
enhances interleukin-4-dependent synthesis of immunoglobulin, and interleukin-13 regulates the expression of CD23, an ige surface-antigen-binding factor [23].

HLA super-locus is a genomic region in the chromosomal position 6p21. Since no gene can be considered as an asthma gene, able to reflect the complex etiology and the heterogeneity of the disease, the terms 'phenotype' and more recently 'endotype' have been used. The most common HLA haplotypes in the different asthma phenotypes are HLA-DRB1 in allergic asthma, HLA-DQB1 in occupational asthma and HLA-DPB1 in aspirin-sensitive asthma. However, it is difficult to study the role of class II genes in vivo because of the heterogeneity of human population, the complexity of MHC, and the strong linkage disequilibrium among different class II genes [24]. Another research group aimed to determine the frequency of the selected HLA classes I and II allelic groups in asthmatic and control groups. HLA typing was performed using polymerase chain reaction-sequence-specific typing (PCR-SSP) method. The allele frequency was estimated by direct counting. Frequency of each HLA allelic group was compared between asthmatic group and control group using χ² test. P-value was corrected by multiplying with the number of the allelic groups studied. Odds ratio (OR) and its corresponding 95% confidence interval (CI) for each allelic group were calculated. There was a significantly higher frequency of HLA-DRB1*03 in asthmatics than in controls (11.43% vs 3.64%, OR = 3.78, 95% CI = 1.61-8.85, P = 0.0025, Pc corr < 0.05). Analysis of HLA alleles in low and high total serum immunoglobulin E (ige) level in asthmatics revealed no significant association. HLA-DRB1*03 may be implicated in the susceptibility to asthma in the pediatric population[25]. Results from a GWAS on asthma performed in 3855 subjects using a panel of 455089 single nucleotide polymorphisms (snps). The GWAS resulted in the prioritization of 33 variants for immediate follow-up in a multi-staged replication effort. Of these, a common polymorphism (rs9272346) localizing to within 1 Kb of HLA-DQA1 (chromosome 6p21.3) was associated with asthma in adults (P-value = 2.2E-08) with consistent evidence in the more heterogeneous group of adults and children (P-value = 1.0E-04). Moreover, some genes identified in prior asthma GWAS were nominally associated with asthma in our populations. Overall, the findings further replicate the HLA-DQ region in the pathogenesis of asthma. HLA-DQA1 is the fourth member of the HLA family found to be associated with asthma, in addition to the previously identified HLA-DRA, HLA-DQB1 and HLA-DQA2 [26].

THERAPEUTIC IMPLICATIONS

Certain principles of treatment are common to chronic non-specific obstructive lung diseases because of some shared patho-physiological features [27-28]. Once an individual has been diagnosed with asthma, a physician will develop an asthma action plan to help the patient to monitor the condition. Although the worldwide market for asthma medication is currently worth US$5.5 billion a year to the pharmaceutical industry, [1] there is no cure for asthma and only the symptoms can be controlled. Current asthma management is aimed at reducing airways inflammation by using daily “controller” anti-inflammatory medications, minimizing proinflammatory environmental exposures, and controlling co-morbid conditions that can worsen asthma. Less inflammation typically leads to better asthma control, including less need for “quick-reliever” asthma medication (i.e., beta-agonist bronchodilators) and fewer exacerbations [29].

In pharmacogenetic studies, response to asthma therapy has been frequently assessed using quantitative methods, such as change in FEV1 (forced expiratory volume in 1 s), PC20 (provocative concentration of methacholine causing a 20% drop in FEV1, which reflects the degree of airway hyperresponsiveness), and bronchodilator response (change in FEV1 shortly after administration of a short-acting b2-agonist (SABA)). These measures of lung function are reproducible and their quantitative nature allows for increased statistical power in genetic analyses. Peak expiratory flow rate (PEFR) has also been used as a response phenotype, although it correlates poorly with symptoms and may lack reproducibility. Although qualitative measures, such as asthma exacerbations or presence/absence of symptoms, do not fully correlate with measures of lung function, they may nonetheless be useful pharmacogenetic outcome measures. In general, the change in lung function associated with asthma treatment administration follows a near-normal distribution, demonstrating substantial inter-individual variability, with a significant proportion of both non-responders and high responders to therapy. This wide variability in inter-individual response, combined with high intra-individual repeatability, suggests a genetic basis to the heterogeneity in asthma treatment response [30].

Pharmacogenomics is the study of the relationship between patterns of genetic variability, or polymorphisms, in sets of genes and individual variability in the response to pharmacotherapy. An estimated 70% to 80% of variability in individual responses to therapy may have a genetic basis. Mechanisms that may have heritable variations that can alter therapeutic and toxic responses to drugs include absorption, distribution, metabolism, excretion, interaction with biologic pathways, and unintended targets. 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 examples of the latter are the beta(2)-adrenoceptor and 5-lipooxygenase (ALOX5) genes. Genetic variability in both of these genes may account in part for inter-individual variability in treatment response. Polymorphisms of the beta(2)-adrenergic receptor may influence airways responses to regular inhaled beta-agonist treatment. Albuterol (R)- and (S)-enantiomers may have distinct effects on airway relaxation and regulation of inflammation, suggesting that mono-isomeric therapy may have therapeutic advantage. In one study, levalbuterol decreased the need for asthma hospitalization; however, the length of stay was similar in racemic albuterol and levalbuterol groups. Treatment with anti-leukotriene drugs results in clinical improvement in many, though not all, patients with asthma. Polymorphisms 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 gene and the leukotriene C4 synthase gene have been associated with changes in the function of these genes, leading to association studies of the polymorphisms’ effects on responses to leukotriene modifier therapy [7].
THE WAY AHEAD

Genetic aspects are known to influence disease processes as well as their treatment [31]. Asthma genetics research is still in the early stages and faces some technical problems (Table 1). Genetics studies of asthma provide a greater understanding of disease pathogenesis. The identification of novel genes and associated pathways delineates new pharmacologic targets for developing therapeutics. Asthma genetic research may improve diagnostics that could identify susceptible individuals allowing early life screening and targeting of preventive therapies to at-risk individuals. The bottom line is that asthma pharmacogenetics can subclassify disease on the basis of drug-metabolizing polymorphisms and genetic modifiers, permitting targeting of specific therapies. Such data also may determine the likelihood of an individual’s responding to a particular therapy and permit the development of comprehensive individualized treatment plans.

Table 1. Technical hurdles in asthma genetics research.

- Require identification of standardized definition of asthma phenotypes
- Require intermediate biologic measures associated with the risk for asthma
- Require well defined population in unbiased studies
- Require sufficient power to detect small effects
- Require methods to concurrently measure both environmental and genetic risk factors

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