Asthma Genetics

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Summary

Asthma is an increasingly common condition that affects people worldwide. Although it has long been appreciated that the disease appears to cluster within families, it is only in the last decade that the genetic factors involved have begun to be explored in detail. This article discusses the methods used to investigate the genetics of asthma and reviews the current understanding of this area.

Introduction

Asthma is a common condition affecting both children and adults. Estimates suggest that there are approximately 155 million individuals with the condition worldwide, with a prevalence of more than 20% in some countries including the United States, the United Kingdom and Australia [20, 34]. In fact asthma is the most common chronic disease of childhood. Epidemiologic studies conducted over the last decade indicate a wide variation in the incidence of the disease between countries and there also appears to be a rising prevalence rate in most developed countries [69]. It has been estimated that the cost of treating asthma in the USA alone is $6 billion per annum [64].

Asthma is characterised by variable airflow obstruction and bronchial hyperresponsiveness (BHR), caused by acute and chronic airway inflammation. Atopy is an associated disorder, involving the production of excessive amounts of immunoglobulin E (IgE) antibody against common environmental allergens. It has been known for many years that both asthma and the other atopic diseases (rhinitis, eczema) have a familial tendency.

Evidence for heritability in asthma phenotype

Familial clustering of asthma has long been appreciated and was recognized by Salter in his treatise of 1860 [57]. This clustering could be the result of environmental influences, genetic influences, or both. It is likely that genetic and environmental factors interact in a complex fashion to produce both disease susceptibility and expression.

Two types of study have helped to differentiate these genetic and environmental factors. Firstly, there are twin studies, which compare monozygotic twins (with identical genotypes) and dizygotic twins (share an average half their genes), as well as twins reared apart in different environments. Diseases with a significant genetic component will show higher rates of concordance in monozygotic than in dizygotic twins. Secondly, segregation analysis attempts to determine the mode of inheritance of a disease phenotype by studying its segregation (transmission) within families.

Numerous studies have used these methods to show conclusively that the familial concordance of asthma [17, 19, 21, 37, 52, 61, 68] and serum IgE [7, 46] is at least partly due to shared genes. Although debate continues, many authors conclude that genetic influences are more important than...
environmental influences. Estimates of the contribution that genetic factors make to asthma susceptibility range from 35% to 70%, depending on the population under consideration and the design of the study. There is also evidence to suggest that the specific end-organ involved in allergic diseases, i.e., airways, nose, skin, is also inherited in a familial fashion [19, 31].

Segregation analysis has not identified a consistent Mendelian pattern of inheritance, as is seen for example in cystic fibrosis. This is suggestive of a complex genetic disorder (i.e., the disease involves the interaction of multiple genetic and environmental influences). This does not mean that the genes involved are not inherited in a Mendelian fashion, rather that multiple independently segregating genes are required to express the disease phenotype, in the same way as diabetes, atherosclerosis and hypertension. This is known as polygenic inheritance.

The importance of phenotypic definition
Studies of the genetic basis of disease can be carried out using complex phenotypes or intermediate phenotypes. Each approach has its own advantages and disadvantages. Complex phenotypes (e.g., affection status – does the patient have asthma or not?) have the advantage of identifying all genes that contribute to the disease; however, the contribution of each gene to the overall phenotype is small, reducing the power of studies. On the other hand, intermediate phenotypes (e.g., BHR, IgE levels, eosinophil counts, or skin prick test responses) are easier to measure objectively and involve fewer genetic influences and so the power to identify an important gene is higher; however, genetic influences on intermediate phenotypes may not always influence the complex phenotype being considered.

Whilst most current definitions of asthma highlight the role of airway inflammation in the pathophysiology, this is less useful in population studies, since non-invasive measures of inflammation are either not readily available or are not well validated. Reliance on history or prior diagnosis alone appears to underestimate the prevalence of asthma/allergy. Therefore, investigators tend to use several intermediate phenotypes associated with asthma, such as BHR, skin test responses, eosinophil counts, or total serum IgE, since these can be measured objectively and relatively easily. In addition, quantitative scores, where all information gathered on an individual is used to derive the score, may be useful [40].

Thus, genetic analysis of a complex disease such as asthma requires careful and accurate phenotyping. Many existing studies use multiple different definitions of the same phenotype, making reviews of the genetics of asthma and atopy more difficult.

Finally, when considering phenotypic definitions, it is useful to note that at present there is no agreement amongst consensus panels on the way in which asthma severity should be characterised. In addition, the literature gives plenty of examples of confusion in differentiating between asthma control and asthma severity.

Approaches to genetic studies
In order to identify specific loci in the human genome that might confer the genetic susceptibility to asthma, researchers have used two main approaches, which in practice are often combined. One approach is known as the “candidate gene approach”, where polymorphisms within a gene of known function that influences asthma or atopy are identified, and the frequency of the polymorphism within cases and controls is ascertained. Another method is known as a “genome scan” or “positional cloning”. Genome scans use a panel of microsatellite DNA markers that label the entire human genome at known positions, typically 5–10 cM apart. Linkage studies are conducted within families or inbred populations, correlating the inheritance of genetic material, identified by the markers, with the phenotype of interest. The closer a microsatellite marker is to a disease-related gene, the less chance that they will be separated during meiosis. Linkage can then be measured by the lod score (log of the odds ratio of the probability of linkage to the probability of no linkage) and a lod score of greater than 3.6 is considered significant. Thus, genome scans identify candidate susceptibility loci, within which susceptibility genes might reside. However, it is not currently possible to narrow the focus to less than 1 cM (1 million base pairs), corresponding to up to 400 genes, and so whilst studies have identified candidate susceptibility loci within chromosome regions 5q, 6p, 11q, 12q, and 13q, no genome scan has yet identified a candidate susceptibility gene for asthma or atopy [9].

Evidence for linkage to specific chromosomal regions and genes
The table outlines the wide spectrum of candidate loci and genes linked to asthma and atopic phenotypes. Some of these are discussed in more detail below.

Chromosome 5q
There are several genes on chromosome 5q31–33 that may be important in the development or progression of the inflammation associated with asthma and atopy, including the cytokines IL-3, IL-4, IL-5, IL-9, IL-12 (β-chain), IL-13 and GM-CSF.