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Genetics of asthma and atopy

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Chapter 2 | Defining asthma in genetic studies

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Summary

Genetic studies have been hampered by the lack of a gold standard to diagnose asthma. The complex nature of asthma makes it more difficult to identify asthma genes. Therefore, approaches to define phenotypes, which have been successful in other genetically complex diseases, may be applied to define asthma in genetic studies. These approaches include narrowing of the disease definition and use of intermediate phenotypes of asthma. Future studies are required to apply these approaches in genetic studies of asthma and, most likely, this will facilitate the search for genes for asthma.

Introduction

The definition of asthma has been the subject of ongoing debate, both in clinical¹ and asthma research² fields. Genetic studies of asthma have rekindled this debate.³⁻⁵ There are three reasons to begin discussing the “best” definition of asthma in genetic studies. First, genetic methods, such as linkage studies, are sensitive to the misclassification of individuals. Misclassifying non-affected individuals as individuals with asthma reduces the statistical power of these genetic methods.⁶ Second, replication of linkage results has been proven difficult in genetic studies of asthma. This may be explained by the fact that the definition of asthma and atopy differs between the various studies. As an example, atopy has been defined as a self-report of having an atopic disease (asthma, hay fever and eczema) in genetic studies, or as having (combinations of) elevated serum total IgE levels, positive skin prick tests or elevated serum specific IgE levels. Third, genetic research is hampered by the lack of a gold standard to diagnose asthma.

The aim of this paper is to discuss definitions of asthma. Furthermore, we will discuss applications of different definitions of asthma in research on its genetic background.

The definition of asthma

In previous decades, individuals and expert panels, as reviewed by Wiesch *et al.*,⁶ made different definitions. A recent definition was published by the National Heart, Lung and Blood Institute in 1995: “*asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial responsiveness to a variety of stimuli.*”⁷

Application of this definition does not lead to operational criteria, by which asthma can be diagnosed with 100% specificity and 100% sensitivity. It is therefore not guaranteed that false-positive and false-negative classifications are excluded. This will be briefly illustrated for three elements of the definition: symptoms, variable airway obstruction and bronchial hyperresponsiveness (BHR).

Symptoms consistent with asthma are also reported by patients with other pulmonary diseases. Wheeze and cough is often reported by non-asthmatic children, who have a viral respiratory tract infection. Wheeze is also a major symptom of individuals with chronic obstructive pulmonary disease (COPD). Airway obstruction, which can be detected in the majority of patients with asthma, can be absent in patients with mild and intermittent asthma. Furthermore, the reversibility of airway obstruction is lost in some patients

with asthma in older age.⁸ This irreversible airway obstruction may be the result of airway remodelling in ongoing asthma. This makes the differentiation between asthma and COPD in elderly people sometimes difficult.

BHR is present in the majority of patients with asthma. It can be detected in 6-35 % of the general population. Thus, with approximately 6 % of the population having asthma, BHR is also present in asymptomatic individuals. The population prevalence of asymptomatic BHR varies from 2.2 to 14.3 % in various studies.⁹ In addition, BHR can be detected in approximately two-thirds of smokers with COPD.¹⁰

It is unknown if measures of airway inflammation will bring a solution. Airway inflammation is regarded as the key pathophysiological process in asthma and is partly expressed in BHR. The performance of bronchial biopsies, and/or broncho-alveolar lavage to study airway inflammation is not feasible in large populations that need to be studied in genetic research. Finally, measurements of nitric oxide in expired air, another method to study airway inflammation, are variable in asthma. Elevations in expired nitric oxide levels have been reported for other diseases as well. Thus, genetic studies lack feasible and valid methods to assess airway inflammation.¹¹

A diagnosis of asthma is called an asthma phenotype in genetic studies. The asthma phenotype can be assessed by questionnaires or can be built up by the use of measurements of clinical characteristics associated with asthma, such as BHR or airway obstruction. These characteristics are called intermediate phenotypes of asthma (table 1).

The question, how to define the asthma phenotype, is not easily answered. The goal of current genetic studies is to find genes for asthma: variants in genes that lead to a higher risk of asthma. Thus, a good definition of the asthma phenotype would be the definition that reflects the function of these genes for asthma. However, these genes are not known and no prediction about their function can be made. To overcome this limitation, different approaches can be applied that have been successful in defining a disease phenotype in other genetically complex diseases.¹²

The heterogeneity of asthma

To apply different approaches to define the asthma phenotype, investigators may consider the heterogeneity of asthma and the statistical power of genetic studies.

Heterogeneity

Asthma is a phenotypical heterogeneous disease. This is illustrated by the broad variations in the age at onset; the severity of asthma, from mild asthma to death of asthma; the progression of asthma, from the outgrowing of asthma to persistent asthma; the interrelationship between asthma and atopy and the response to asthma medication.

Asthma is also a genetical heterogeneous disease. It is now well accepted that the development of asthma involves multiple genes that interact with each

other and with the environment.¹³ This is evidenced by the results of family studies, in which the inheritance of asthma could not be explained by a single gene model but rather by oligogenic or polygenic models. In addition, the published data of linkage studies in asthma point to different regions in the human genome, including chromosomes 5, 6, 11, 12 and 14.¹³

Statistical power

Each of these genes for asthma separately may confer only a small increased risk to asthma i.e. it has a low genotype relative risk (GRR). A GRR is the increased chance that an individual with a particular genotype has the disease. A low GRR has consequences for the power of genetic studies. In linkage studies, the power is the probability of correctly identifying a true linkage. The power of the affected sib-pair design and the association design was analyzed in a paper by Risch and Merikangas.¹⁴ Under the assumption of a GRR of 2 and an allele frequency of 0.50, 2498 families are needed to achieve a power of 80 % to detect linkage using the affected sib-pair design. If the GRR is 4, the number of families needed drops to 297.¹⁴ Thus, to identify genes of GRRs of 2 or less, an extremely large number of families is required for the affected sib pair design. Genetic approaches become more feasible if higher GRRs are considered. Thus, approaches that result in a rise of this genotype relative risk are needed. These approaches include narrowing of the disease definition and use of intermediate phenotypes.

Approaches to define an asthma phenotype

Narrowing the disease definition

The first approach is to narrow the disease definition. Four approaches to narrow the disease definition of genetically complex diseases were reviewed by Lander and Schork.¹²

1. The use of age at onset. In genetic studies of breast and prostate cancer, the selective inclusion of families with early onset of disease identified a subset of the population and in this subset significant linkage results were found.^{15,16} In asthma, there is some evidence that the heritability of asthma, i.e. the proportion of the phenotypical variance that is due to genetic factors, decreases with age.¹⁷ Thus, in genetic studies, it may be rewarding to include patients with asthma with an early age at onset.
2. The use of differences in the clinical phenotype. This strategy was successful in the identification of a gene for colon cancer in patients with extreme polyposis.¹²
3. The selective inclusion of individuals with a family history of the disease.
4. The use of a "severe" phenotype. In the case of asthma, patients with ongoing, severe, asthma may be especially interesting for genetic studies. However, the evidence that the severity of asthma is due to genetic factors is scanty.¹⁸

These approaches have not been explored in full detail in genetic studies of asthma, yet they may improve the prospects.

Table 1 Possible definitions of asthma and atopy in genetic studies

Asthma

- questionnaire
 - symptoms (wheeze, dyspnea, cough, nocturnal symptoms)*
 - self-reported (doctor diagnosed) asthma*
 - use of medication for asthma*
- video questionnaire
- doctor's diagnosis

Intermediate phenotypes of asthma

- bronchial hyperresponsiveness
 - direct (methacholine, histamine)*
 - indirect (AMP, cold air challenge)*
- reversibility on β_2 -agonist
- variability of peak expiratory flow measurements
- lung function measurements (e.g. FEV₁, VC)
- total number of eosinophils in peripheral blood

Combination of questionnaires and intermediate phenotypes

- asthma score
- asthma algorithm

Atopy

- questionnaire
 - symptoms of atopic asthma, rhinitis and dermatitis*
 - self reported (doctor's diagnosed) atopic asthma, rhinitis or dermatitis*
 - use of medication for atopy*
- doctor's diagnosis

Intermediate phenotypes of atopy

- serum total IgE
- serum allergen specific IgE
- allergy skin tests

Intermediate phenotypes

A second approach is to study intermediate phenotypes of asthma and atopy. Examples of intermediate phenotypes of asthma are BHR, peak flow variability and reversibility to a β_2 -agonist (table 1). As asthma is likely to be the end-stage of the action of multiple genetic and environmental factors, intermediate phenotypes may be due to the action of a limited number of genes. As an example, atopy may be due to multiple genes, including genes for the regulation and production of levels of total IgE, genes for the specificity of IgE and tissue specific expressed genes for end-organ responsiveness. When total IgE is studied separately, it may be easier to identify genes important in total IgE regulation. This can be illustrated by a study of 92 Dutch families, ascertained through a proband with asthma. In this study, a two locus segregation analysis of serum total IgE was performed. The first locus alone explained 50.6 % of the variance in total IgE, the second 19.0 % Taken together, these two loci account for 78.0% of the variability in serum total IgE levels.¹⁹ This result also confers with the insight that even more than two genes are relevant in the regulation of high or low serum IgE levels. A drawback of the separate study of intermediate phenotypes is that genes of pleiotropic effects could be missed. These are genes that have effects on multiple phenotypes.

From intermediate phenotypes of asthma to asthma

Two different approaches have been used to combine reported symptoms and intermediate phenotypes to assess the complex asthma diagnosis: an asthma score and an asthma algorithm.

An *asthma score* is a quantitative score, in which asthma symptoms and intermediate phenotypes (BHR, FEV₁) are combined.²⁰ The asthma score is calculated as the first principal component of the results from questionnaires, the bronchial provocation test and FEV₁. This quantitative score is then used as a phenotype in genetic studies. Wilkinson *et al.* reported linkage of this phenotype to chromosome 12q.²⁰

An *asthma algorithm* is a flow chart, which combines results from questionnaires and intermediate phenotypes. An example is an algorithm that was developed to classify family members of probands with asthma. This algorithm included BHR, pulmonary symptoms, smoking history, and (reversibility of) airway obstruction. Individuals were classified as having asthma, probable asthma, unclassifiable airway disease, COPD or unaffected. 265 First degree offspring of 92 patients with asthma were classified. 49 Individuals (18%) had definite asthma and 22 individuals (8%) had probable asthma. This study illustrated the familial clustering of asthma.²¹

The use of an asthma score or algorithm provides a reproducible way to diagnose asthma in participants of genetic studies. It should facilitate comparison of studies and pooling of data. This could improve the understanding of the genetics of asthma.

Conclusion

Genetic studies of asthma have been hampered by the lack of a gold standard. Asthma is a heterogeneous disease with variable age at onset, variable clinical expression and variable progression during a lifetime. The development of asthma involves multiple genetic factors that interact with each other and with environmental factors. This complex nature of asthma makes it more difficult to identify genes for asthma. Therefore, it may be advantageous to apply different approaches that have been successful in other genetically complex diseases to the field of asthma. These approaches include narrowing of the disease definition and use of intermediate phenotypes of asthma. Furthermore, scores or algorithms to define asthma may be used to make comparison and pooling of data a possibility. Future studies are required to study these approaches and, most likely, this will facilitate the search for genes for asthma.

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