

## Genetics and Asthma

Asthma is an inflammatory disease of the small airways of the lung. It is characterised by intermittent airway narrowing and airflow obstruction that leads to symptoms of wheeze and shortness of breath (1).

The syndrome of asthma is probably due to multiple causes. The asthma of children and young adults is most often associated with allergies (atopic asthma), but the asthma which comes on later in life is less obviously allergic and is more common in women and in smokers. Other variants of asthma may be associated with the presence of severe disease, or brittle disease with sudden intractable episodes of bronchospasm. Asthma also occurs in the industrial setting in response to inhaled proteins such as baker's flour or to particular chemicals, such as paint additives (1).

Atopic asthma is the most common form of the disease, and is predominantly seen in the western world. Asthma affects one child in 7 in some societies, and approximately 15 million individuals world wide (2). However, even within Europe it shows widespread differences in prevalence (2, 3). The reasons for these differences are not known, but almost certainly reflect variable contributions of genetic and environmental factors in different regions.

A rural lifestyle is consistently associated with a low prevalence of asthma. Exposure to farm animals and the drinking of unpasteurised milk is protective in farmers' children (4), and the presence of pets in the house and large family sizes are protective in children reared in an urban environment (3, 5). In Africa a rural environment is also protective against disease (6). These findings suggest that an environment rich in microbial organisms is beneficial in building infants resistance to asthma (the Hygiene Hypothesis) (5).

Although asthma is at present a disease of affluent societies, the increasing westernisation and urbanisation of populations elsewhere in the world are leading to increases in prevalence (2). The possibility exists of an eventual pandemic and thought has to be given to strategies for preventing this. The search for the environmental agents that protect against asthma is extremely important, and probably holds the best chance for successful prevention and control of the disease in the global context.

Asthma is predominantly a disease of the privileged classes and a higher level of education and income is in general associated with a higher prevalence of disease in children. However, some groups, such as impoverished North American individuals of Afro-Caribbean origin living in inner cities are at increased risk of disease (7). This may reflect differences in genetic susceptibility, as well as exposure to particular environmental factors such as cockroach allergens.

Asthma is more common in young boys than in young girls, but late in adolescence the prevalence in young women rises, so that the prevalence of the disease is similar in middle life. Women are more susceptible to adult onset asthma, a variant of the illness which is particularly difficult to treat.

### **Roll of genetics in the development of asthma**

Asthma runs strongly in families and is about half due to genetic susceptibility and about half due to environmental factors (8, 9). 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.

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*, *PHF11*, *DPP10*, *GRPA* and *SPINK5* (10-14). The functions of all of these genes are obscure, but the expression of *DPP10*, *GRPA* and *SPINK5* in terminally differentiating epithelium suggests that they deal with threat or damage from the external environment (15). 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 mucus production, *FcεRI-β* which modifies the allergic trigger on mast cells, and microbial pattern recognition receptors of the innate immune system (15).

These findings all suggest that the airway epithelial barrier and its reaction to the microbial environment contain the most important elements of asthma pathogenesis.

## **The role of genetics in the management and prevention of asthma**

It is to be hoped that genetic findings will lead to a better classification of complex diseases such as asthma, and that novel therapies will result from genetic findings.

Most polymorphisms so far identified do not seem to carry risks that would merit their use for the clinical classification of disease, but combinations of genetic polymorphisms may be much more informative.

It is also to be hoped that genetic findings may help identify the environmental factors that protect against asthma. In this context, associations between asthma and innate immune system receptors for microbial products are particularly exciting.

To become relevant to clinical asthma, potential asthma susceptibility genes now need to be tested in cases and controls with different manifestations of disease and disease severity and in representative population samples with different environmental risk factors. Genotype will then become a predictor of disease that can be understood in the same terms as other epidemiological risk factors, and the size and relevance of effects can be judged objectively.

## **The role of genetics in the treatment of asthma**

Several of the asthma susceptibility genes so far identified potential targets for asthma therapy. However, it will take some years to determine if any of these will be the basis for new treatments.

Polymorphisms may also predict the response to asthma therapy. A positive association between common arginine-16 variants in the  $\beta$ -adrenergic receptor gene and the responsiveness of asthmatic patients to  $\beta$ -adrenergic agonists is particularly interesting (16). It's not known whether these differences in response represent a failure of  $\beta$ -agonists in individuals carrying the arginine-16 genotype, or whether therapy in these individuals will be adequate with an upward adjustment of dose.

A proportion of individuals with severe intractable asthma do not respond to inhaled steroids. It is possible that these individuals also carry mutations in some of the genes that control the anti-

inflammatory response of steroids. The pathways are not completely understood, and it is yet known if genetic testing will be helpful in these circumstances.

Gene therapy is of use in some single gene disorders, but gene therapy can only be administered with arduous clinical protocols, and is not without risk of serious side effects such as leukaemia. It is therefore unlikely that gene therapy will be applied to asthma or to related disorders in the foreseeable future.

### **Future Role of Genetics**

Approximately a third of the genetic predisposition to asthma has currently been uncovered. Existing research programmes carried out in several countries are likely to identify the remaining important genetic effects within the next five years. The stage of genetic knowledge will need to be followed by a number of important studies.

Firstly, all genetic polymorphisms potentially contributing to asthma will need to be examined in representative population samples, and in samples of clinical sub-types of asthma taken from different parts of the world. It is likely that different genes will interact with different environmental variables in different places, with different therapeutic implications.

Second, it is desirable that effective strategies be developed for the prevention of asthma. By identifying the genes which interact with a microbial environment, the reasons for the rise in asthma with progressive urbanisation can be clarified, and effective strategies for prevention can be developed.

Thirdly, the genetic predisposition for asthma probably represents an evolutionary adaptation to dealing with helminth infections. If this is the case, then populations which historically have had a high helminth load may be genetically particularly susceptible to asthma as standards of hygiene improve and as societies develop progressively more urbanised lifestyles. This identifies a significant potential public health problem, and it is desirable that research be carried out on the development of asthma in the transition from rural to urban lifestyles in the developing world.

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