Are genes important in allergic disease?

Physicians have been aware of the tendency of allergy to run in families as a result of both inherited (familial factors) and environmental exposures for over three hundred and fifty years (by Sennartus in 1650, cited in; also in).

Eighty two years ago the first comprehensive study of the heritability of atopy was undertaken by Robert Cooke and Albert Van der Veer. In their study of 621 atopic probands and 76 non-atopic controls and their families they assessed the frequency of ‘atopic’ symptoms. After initially determining the frequency of sensitisation at approximately 10% in their population, Cooke and Van der Veer went on to show that 48% of their atopic probands had positive family history for atopy, compared to 14% in the control population.

Subsequent to the work of Cooke and Van der Veer, the results of many studies have established that atopy, and atopic diseases such as asthma, rhinitis and eczema, have strong genetic components.

Family studies have shown an increased prevalence of atopy, and phenotypes associated with atopy, among the relatives of atopics compared with non-atopic subjects. Furthermore family studies have suggested that “end organ sensitivity” or which allergic disease an allergic individual will develop is controlled by specific genetic factors, different from those that determine susceptibility to atopy per se.
For example asthma has a high heritability of up to 75%, involving a few genes with moderate effects rather than many genes with small effects. Family studies show that the risk of asthma in children is increased if the parents themselves are asthmatic rather than just atopic, i.e. in addition to a genetic predisposition to atopy, which alters susceptibility to asthma, there are also genetic effects that relate solely to asthma and possibly regulate susceptibility of the conducting airways to both allergic and environmental induced inflammation.

Other allergic diseases such as atopic dermatitis and rhinitis also appear to have unique predisposing factors in addition to any genetic predisposition to atopy.

**Allergic diseases are complex genetic disorders**

Multifactorial or complex genetic diseases are common conditions that affect large numbers of people. They include such wide-ranging conditions as heart disease, obesity, diabetes, bi-polar disorder and allergic disease. Unlike single gene or Mendelian genetic diseases such as cystic fibrosis that are a result of mutations in a single gene, complex genetic diseases result from the interaction of multiple genetic factors that affect disease susceptibility as well as modifying its severity.

However genes alone are not enough to cause complex genetic disease - it is the interaction between an individual’s genetic background and their environmental exposures that determines risk of disease and clinical outcome.

In the same way that people with a genetic susceptibility to obesity won’t manifest this phenotype without exposure to appropriate environmental stimuli (poor diet, lack of exercise), people who inherit genes that increase their risk of developing allergic disease will still not manifest this without experiencing an appropriate environmental stimuli (allergen exposure, pollution, microbial exposure etc).

*Figure 1*
Genetic Factors contribute to many aspects of allergic disease. Atopy is heritable as is which allergic disease (if any will manifest). Genetic factors also play an important role in determining disease severity and response to treatment (Pharmacogenetics). Equally genetic factors do not act in isolation; it is the combination of genes and environmental exposure that determines disease susceptibility.

How can genetic studies of allergic disease aid in the treatment and diagnosis of patients in the future?
The main goal of research into genetic factors behind the development and pathogenesis of allergic disease is to provide a greater understanding of the fundamental mechanisms underlying the disease.

There are four main ways in which genetics can help us understand this:

**Insights into disease pathogenesis:**
identification of genetic variants that alter the expression of a gene or alter the function of its protein product that are associated with increased susceptibility provides evidence of the importance of that gene product (and the biological pathways in which it lies) to the pathogenesis of disease.
This may lead to the identification of novel therapeutic targets and consequent development of specific new drugs both to relieve and prevent symptoms.

**Environmental interaction:**
the study of genetic factors in large longitudinal cohorts with extensive environmental information, will allow the identification of both the environmental factors that in susceptible individuals trigger disease, and the period(s) of life at which this occurs, potentially leading to prevention of disease by environmental modification.

**Targeting of therapy:**
Identification of genetic risk factors may allow the sub-classification of asthmatics into groups who while phenotypically similar, have different underlying disease pathology. This may aid in the selection of appropriate therapeutic strategies for patients.
Genetic variants in the targets of therapeutics (for example the β2-adrenergic receptor (β2AR)) or the enzymes that metabolise drugs (such as cytochrome P450 enzymes), may influence response to therapy or risk of side effects. Thus identification of individuals with altered response to current drug therapies will allow optimisation of current therapeutic measures.

**Predicting risk:**
The identification of genetic markers of disease susceptibility may allow early identification of susceptible children, allowing them to be targeted at early age for both preventative therapy and environmental intervention such as avoidance of allergen exposure.
Genetic screening in early life may thus potentially become a practical and cost effective option in preventing allergy and allergic disease.

**Examples of genetic insights into allergic disease:**

*Insights into disease pathogenesis:*
as well as studies reporting association between genetic variants in genes whose products are already known to be involved in the pathogenesis of allergic disease (‘candidate genes’), a number of novel genes have been identified in which genetic variation increases susceptibility to allergic disease. These include genes such as ADAM33, DPP10, PHF11, GPRA and HLA-G.

Perhaps a good example of how identification of such genes can give insight into the pathogenesis of allergic disease has been the identification of genes involved in epithelial barrier function in the pathogenesis of atopic dermatitis. Ichthyosis Vulgaris (IV) is a single-gene disorder with a phenotype including palmar hyperlinearity, keratosis pilaris, and a fine scale that is most prominent over the lower abdomen, arms, and legs. Interestingly, IV patients often have atopic dermatitis.

Noting the presence of atopic dermatitis in the families utilised to identify filaggrin as the susceptibility gene for IV, Palmer et al. established that atopic dermatitis was prevalent (44% of cases) in individuals with mild IV, all of whom were heterozygous for a filaggrin null-allele.

This, together with a linkage analysis for atopic dermatitis within the IV pedigrees strongly suggested that filaggrin was a predisposing factor for atopic dermatitis. To investigate this further, Palmer et al. examined the frequency of filaggrin null-alleles in three independent cohorts which confirmed the association between filagin polymorphisms and atopic dermatitis, with the combined frequency of the two common null-alleles (R501X and 2282del4) being 9.6% with an odds ratio of 3.3 (95% CI 2.0-5.6) for atopic dermatitis in the largest cohort. This has been subsequently independently confirmed in several other populations.

Filaggrins are complex polypeptides that play an important role in the formation of stratum corneum during epidermal
differentiation and thus are crucial to epidermal barrier function. This fact, together with lack of association of filaggrin with asthma in the absence of atopic dermatitis, suggests that in these subjects asthma is secondary to atopic dermatitis.

Possibly occurring due to increased allergic sensitisation as a result of allergen penetrating a defective epidermal barrier. More recently, polymorphism in another gene involved in epithelial barrier function, the epidermal collagen gene COL29A1 has also been identified as an susceptibility factor for atopic dermatitis.

**Environmental interaction:**
The major organs that are the site of allergic disease (respiratory tract, gut, skin, eye) are continuously exposed to the external environment. The development of allergic disease depends on the interaction between inherited susceptibility (genomics) and response to exposures (environment). A number of studies have demonstrated that environmental exposure modifies the risk conferred by particular genetic variants for developing allergic disease and vice versa.

For example, recent genetic association studies have again observed reduced risk of asthma and atopy with early life farm environment and house dust endotoxin exposure, and increased risk with exposure to environmental tobacco smoke, especially during the antenatal period. These associations are modified by the presence of polymorphisms in the CD14 gene, a receptor for endotoxin. One area where the study of gene environment interactions is likely to be of benefit is the determination of ‘safe” exposure levels of known environmental triggers of allergic disease such as air pollution.

Although overall effects are seen in the population as a whole, there is clearly inter-individual variability in the adverse health effects of air pollutants.
Certain groups within the population are more vulnerable, including the young and the elderly. Even in healthy adults who have undergone controlled exposure to an air pollutant, there is much variability in the measured effects. Identifying the factors that influence this variability would help to recognise at-risk groups who would benefit the most from preventive strategies.

Furthermore, identification of at-risk groups, the degree of their sensitivity to exposure and their frequency in the population, will aid in the cost-benefit analysis of ‘safe’ exposure levels in the public health setting.

Genetic factors are likely to be important in defining those particularly at-risk from low exposure levels.

The processes involved in the response to air pollutants - oxidative stress and inflammation - are known to be under genetic regulation. For example, there is evidence that antioxidant glutathione S-transferase (GST) polymorphisms are associated with childhood lung function growth, and may modify the effects of prenatal and passive smoke exposure on risk of childhood asthma as well as those of traffic pollution such as ozone.

**Targeting therapies:**
Genetic variability can not influence susceptibility to allergic disease, but may also modify its severity or influence the effectiveness of therapy. The science of using genetics to predict the effectiveness of therapy for an individual or the risk of adverse drug reactions is termed pharmacogenetics. There is now considerable research activity focussed on trying to understand the individual variability in response to pharmacological treatments for allergic disease.
Perhaps the most well studied example is that of genetic variation in the 2-adrenergic receptor (β2AR) and response to inhaled beta agonists. Clinical have shown that β2AR polymorphisms may influence the response to bronchodilator treatment. 
This led Israel et al. to undertake the retrospective analysis of a clinical trial assessing the effectiveness of regular versus as-needed salbutemol use in controlling asthma symptoms in children.

In this study, during the 16-week treatment period there was a small but significant decline in morning peak expiratory flow (PEF) in patients homozygous for the Arg16 polymorphism of the β2AR that use salbutemol regularly. The effect was magnified during the 4-week run out period when all patients returned to salbutemol as needed.

These observations led to a large-scale randomised study, in which individuals with known β2AR were randomised to regular salbutamol or placebo in a crossover design. Interestingly, it was shown that individuals homozygous for the Arg16 form of the receptor failed to maintain responses to salbutamol. In addition, there were clinically relevant differences in relief bronchodilator usage and symptom scores between the groups.

The effects of β2AR polymorphism on response are also evident with long-acting β-agonists. Asthmatics homozygous for the Arg16 polymorphism have been shown to have a significantly lower morning PEF when treated with salmeterol combined with or without continued inhaled corticosteroid (ICS) use.

While these studies, and others, have shown that polymorphism in the β2AR is likely to influence responses to both short and long acting inhaled β2-agonists, currently it is not possible to alter treatment for patients on the basis of genotype. Further large-scale prospective randomised trials are required in order to establish the potential benefits of altering therapy and the
effectiveness of alternative treatments in patients carrying the Arg16 genotype.

**Predicting risk:**
Will it be possible in the future to make accurate prediction of risk for asthma based on an individual’s genetic make-up?
In some respects in clinical practice this is done by taking into account family history, however it is hard to be certain whether testing of a series of genetic variants to accurately predict risk and target preventative therapy will be possible for asthma.

This uncertainty reflects the complex interactions between different genetic and environmental factors required both to initiate disease but also modify its severity.
What is certain is that we are not at this stage yet for allergic disease but the use of genetic information in clinical decision making or ‘genomic medicine’ is becoming more and more prevalent and we do not know what the future holds.

One issue that will need considerable thought before this becomes a reality in clinical practice are the numerous ethical issues that are raised by the potential wide-spread use of genetic testing in clinical practice.

**Summary**
The varying, and sometimes conflicting, results of studies to identify allergic disease susceptibility genes reflect the genetic and environmental heterogeneity seen in these disorders and illustrate the difficulty of identifying susceptibility genes for complex genetic diseases.

However, despite all of the difficulties and complexities in identification of genes for allergic disease, the discovery of the importance of genes such as filaggrin in atopic dermatitis shows that genetic approaches can lead to identification of new biological pathways involved in the pathogenesis of allergic disease, the development of new
and better targeting of current therapeutic approaches and the identification of at risk individuals.

The application of genetics to explain variability in patient response to current therapies such as inhaled β-agonists and anti-leukotrienes is likely to lead to changes in clinical practice in the near future. In short, the application of genetics to the study of allergic disease has proved highly successful and greatly aided our understanding of these common conditions and is likely to play an increasingly important role in clinical practice in the future.

References


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