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Genetics of asthma

Asthma is heterogeneous

Asthma is simply defined as labile airflow obstruction and is a heterogeneous syndrome whose causes include atopy, exposure to industrial toxin such as isocyanates, infection in small calibre airways in childhood, and cigarette smoking. In some older individuals, no external precipitant is identifiable and this has unjustifiably been termed intrinsic rather than idiopathic asthma.

This heterogeneity, the high frequency of asthma (with a life time prevalence of 10%), and its variable severity make the analysis of genetic factors difficult. It is not surprising that it is regarded as a polygenic or multifactorial disorder. Thus the prevalence of diagnosed asthma in the first degree relatives of probands with intrinsic and extrinsic asthma is respectively 4.5 and 11.3%.¹ First degree relatives (parents, siblings, and children) share on average one half of their genes and these prevalence figures do not approach

mendelian predictions for a simple genetic disorder. Attempts to assay the disease phenotype by measurements of bronchial hyper-reactivity (a characteristic underlying abnormality in asthma that can be detected by exercise or methacholine challenge) provide no further evidence of a simple genetic effect.²

Atopy and IgE response

The clearest indication of an important genetic effect on the development of asthma arises in relation to one of its principle causes, atopy.³ Atopy or allergic responsiveness to common but otherwise innocuous antigens, such as house dust mite particles or pollens, is mediated by the prolonged and exuberant production of IgE antibody to these agents.⁴ Clinical symptoms in the nose (rhinitis), bronchus (asthma), and skin (eczema) occur in variable combination and severity

in different atopic individuals in whom allergen interaction with mucosal, mast cell bound IgE triggers a molecular and cellular cascade that results in intense local inflammation.⁵ A strong impression of familial aggregation of atopy is long standing and the observation that most atopic individuals are sensitised to a range of allergens suggests idiosyncrasy. Though accurate immunoassays exist for the detection of total serum IgE and specific IgE to common allergens, the definition of the atopy phenotype remains a contentious issue within the studies on the genetics of atopy.⁶

Genetics of atopy – a centrist view

It is agreed that atopy represents a generalised, rather than allergen specific, phenomenon of exuberant IgE production but whether atopic individuals can be recognised by the demonstration of one, two, or more allergen specific IgE responses as well as by raised total serum IgE (in helminth free environments) is disputed.⁶ In studies, demanding the segregation of these criteria, the summary of genetic observations is as follows.

Total serum IgE concentrations show a continuous skewed distribution and influence by age and smoking that make discrimination between the atopic and non-atopic difficult.⁷ Twin studies, however, comparing similarities or differences between monozygotic and dizygotic twin pairs have consistently suggested a decisive genetic effect with a heritability (that fraction of variation due to genetic factors) of 50–70% for total serum IgE.^{8,9} Family studies have proved difficult to interpret, despite the use of complex path and segregation analysis; there is partial, inconclusive evidence that high concentrations of total serum IgE may be transmitted as an autosomal recessive character.^{10,11}

If discrete elements, though not yet formal epitopes, of specific allergens are identified and IgE response to them tested, then relationships between certain specific responses and different HLA class II genotypes can be demonstrated.¹² It remains to be shown whether HLA class II molecule variation is deterministic in sensitisation to large complex allergens and in the development of clinical disease.

An Oxford view

A group in Oxford has taken a contrary view on the identification of atopy, though accepted that the factors controlling generalised atopic response and specific allergen responses must be different; they have concluded that total serum IgE alone, used at any stage, is an insensitive assay for the atopic state. In their studies, individuals are categorised as atopic if they show IgE response to *any* one or more common allergens, by skin prick test or immunoassay of circulating specific IgE, or if they show a raised total serum IgE.¹³ Striking vertical transmission of this atopy phenotype was noted.¹³ This implied dominant inheritance, though the results of further studies suggest important genetic heterogeneity and the likelihood that one predominant gene effect, transmitted on chromosome 11, is subject to genomic imprinting.

In initial linkage studies (matching the transmission of atopy in seven extended families to restriction fragment length polymorphisms of an anonymous DNA marker D11S97), genetic linkage to chromosome 11q13 was observed with a lod score of 5.6.¹⁴ This observation was replicated, with a lod score of 3.8, in a study of 64 nuclear families recruited via young probands with atopic asthma or rhinitis.¹⁵

Further analysis of genetic linkage data from nearly 1000 individuals by the method of affected sibling pair analysis confirmed genetic linkage of atopy to chromosome 11; sibling pair sharing of 11q alleles was observed for a variety of

definitions of atopy, including high total IgE concentrations used alone.¹⁶ The data also showed that sharing of parental alleles by siblings derived exclusively from the mother¹⁶ and that linkage occurred in approximately 60% of families.¹⁵ The sharing of maternal alleles alone is likely to be due to genomic imprinting of the, as yet, unidentified locus on chromosome 11. It is clear from the data that other loci at other chromosomal locations must confer atopy in a significant number of families.

The Oxford group also show that there is interaction between chromosome 11 linked atopy and other factors, for example house dust mite load in children's beds, in determining the risk of allergen specific sensitisation and of disease, for example to house dust mite and of asthma.¹⁷

A conclusion

What is the status of the Oxford results? Genetic linkage analysis can be confounded by a variety of errors and is essentially a statistical process; any disease linkage observation requires replication. There is one further report of genetic linkage between atopy and chromosome 11 from Japan (with a lod score of 4.8 from four families),¹⁸ but four other studies (from Britain, America, Japan, and the Netherlands) have failed to detect genetic linkage.^{19–22} Small numbers of families tested, varying methodology, and the undoubted genetic heterogeneity of atopy are likely to explain these different results.²³ Further studies are needed that include substantial numbers of families; affected sibling pair analysis, which makes no assumptions about mode of inheritance, may be especially valuable in the meta-analysis.

If the loci (including the 11q13 locus) at which mutations can confer atopy or generalised IgE response can be identified, a major step towards a fundamental and molecular understanding of atopy (the principle cause of asthma) will have been taken. This should surely offer the potential for improved treatments and prevention in the future.

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