

A genetic approach to atopy

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Atopy, the state of allergic responsiveness to common inhaled antigens, is an essential ingredient of most cases of asthma and rhinitis which are leading causes of chronic morbidity in advanced countries. Since the demonstration of the central role of immunoglobulin E (IgE) in atopy [1, 2] a body of research has focused on the inflammatory events that follow the binding of allergen to mast cell bound IgE, aiming to dissect out the key factors driving this process and which may ultimately become targets for more effective therapeutic interventions [3].

A more fundamental approach has attempted to focus on what factors determine the disposition to mount an IgE response to common inhaled antigens. It has long been a clinical impression that atopy aggregates in families, yet genetic studies that define atopy by the presence of clinical disease or elevated total IgE in serum have not provided a coherent genetic model [4]. Encouraged by the supporting presence of novel molecular genetic techniques, investigations in Oxford have recently re-examined the genetics of atopy [5, 6]. Using the assay of specific IgE responses to an array of common inhaled antigens (in addition to total IgE estimates and symptom assessment) they found that atopic IgE responsiveness (defined by the presence of significant IgE to any one or more common antigens) segregates as an autosomal dominant character. Eighty five percent of family members designated as atopic had some symptoms consistent with allergic respiratory disease, yet only 40% regarded themselves as sufferers from asthma and hay fever. Thus, other factors must interact with the dominantly inherited IgE responsiveness to produce clinical disease.

The idea that atopic IgE responsiveness is determined by a single gene locus was further tested by the Oxford Group, by molecular genetic linkage analysis [6]. In this, they used deoxyribonucleic acid (DNA) extracted from the white blood cells of their family members to trace the transmission of polymorphic DNA markers from different chromosomal sites within the families, contrasting these with the transmission of atopic IgE responsiveness. It is one of the fundamental laws of genetics (Mendel's Second Law) that different gene loci are independently assorted at the time of meiosis and the

formation of gametes, except when gene loci are very closely aligned on any particular chromosome. This exception to the law, the cotransmission of alleles at proximate gene loci, is termed linkage and was used by the Oxford investigators first to test whether the putative single gene for IgE responsiveness could be consistently cotransmitted with one genetic region and, allied to this, to determine what region this was. Their data has shown that atopic IgE responsiveness was significantly cotransmitted with a variable genetic marker on the long arm of chromosome 11. The most recent estimates from the laboratory provide a statistic favouring linkage at this site exceeding $10^6:1$ and suggest that this gene locus underlies atopy in the majority of British families. Thus, the strength of the linkage fully supports the concept of single gene control and assigns the gene to chromosome 11q.

The nature of the gene and its mutant product are of special interest, not least because there is a reasonable probability that such information may provide a real opportunity for planning novel treatment and prevention for atopic diseases. The nature of such therapeutic interventions are now merely speculative but the chance that the genetic pathology lies at the level of cell communication or interaction within the immune system makes pharmacological inhibition or replacement by recombinant product (which ever may become appropriate) attractive possibilities.

The quest for the atopy gene is a formidable undertaking but the success of American and Canadian groups in capitalizing on gene localization by linkage, and then defining the gene loci and mutant products underlying cystic fibrosis [7] and Duchenne muscular dystrophy [8] provides great encouragement.

References

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