Commentary

Interleukin-4 receptor α gene variants and allergic disease

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Abstract

The interleukin-4 (IL-4) signalling cascade has been identified as a pathway potentially important in the development of asthma. Genetic variants within this signalling pathway might contribute to the risk of developing asthma in a given individual. A number of polymorphisms have been described within the IL-4 receptor α (IL-4Rα) gene. In addition polymorphism occurs in the promoter for the IL-4 gene itself. This commentary accompanies a paper by C Ober *et al* describing the contribution of IL-4Rα polymorphism to susceptibility to asthma and atopy in the Hutterite population and other outbred populations collected during the collaborative studies on the genetics of asthma (CSGA) programme.

Keywords: asthma atopy, genetics, interleukin-4, interleukin-13

Several genome-wide screens have now been performed in different populations, looking for susceptibility genes for asthma and allergic disease. In general, the results of these genome screens have been somewhat disappointing in that, although chromosomal regions showing linkage have been identified, the strength of linkage at any given site has been inconsistent. These data suggest that a number of genes of moderate effect rather than a small number of genes with marked effects contribute to the genetic basis of allergic disease.

To try to dissect out the important candidate genes that contribute to the risk of developing asthma or its important sub-phenotypes, several groups have concentrated on strong candidate genes that map to known susceptibility loci for asthma and atopy. Several such candidates have been identified (Table 1), including the gene for interleukin-4 receptor α (IL-4Rα), which is situated on chromosome 16p and is known to contain a number of polymorphisms. The recent paper from Carole Ober and colleagues [1] provides important information on the potential relevance of IL-4Rα gene variants in determining the risk of developing atopic disease.

The IL-4Rα subunit forms part of the signalling complex for IL-4 itself but also serves as the α chain of the IL-13 receptor. Both IL-4 and IL-13 themselves have been implicated as potential candidate genes in the development of asthma, both being present in the TH2 cytokine locus on chromosome 5q23–31 [2]. Both IL-4 and IL-13 have overlapping functions, including mediating isotype switching to IgE synthesis.

CSGA = collaborative studies on the genetics of asthma; IL = interleukin; IL-4Rα = IL-4 receptor α; SNP = single nucleotide polymorphism.

Table 1

Chromosomal candidate regions in asthma and atopy

Chromosome	Candidate genes
5q23–31	Interleukin-4, interleukin-5, interleukin-9, interleukin-13
5q31–33	β_2 adrenoceptor
6p	HLA complex including tumour necrosis factor-α
11q13	FcεR1β
12q	Interferon-α
	NO synthase
	Mast cell growth factor
14q	T cell receptor
16	Interleukin-4 receptor α

Several previous studies have suggested association and/or linkage between IL-4Rα gene variants and allergic disease, although not all studies have been positive. Mitsuyasu *et al* [3] reported the Ile50 allele of the IL-4Rα to be associated with atopic asthma, whereas Kruse *et al* [4] reported an association between the Pro478 and Arg551 alleles and low IgE levels. Hershey *et al* [5] reported an association between the Arg551 allele and IgE levels and atopic dermatitis. Functional evidence for the importance of these polymorphisms has been obtained with assays of signal transduction *in vitro* [3,5,6]. Several other amino acid polymorphisms have been reported within this gene, although good functional evidence supporting their importance has not yet been obtained [7].

Ober's study provides important additional information on the potential role of the IL-4Rα in allergic disease [1]. In this study, all known SNPs (single nucleotide polymorphisms) within the IL-4Rα locus were genotyped in the South Dakota Hutterite population (in whom a chromosome 16 susceptibility locus has already been identified), and also in ethnically diverse outbred populations collected as part of the CSGA [8]. The major findings of this study were that all the population samples studied showed evidence of association to markers of atopy or asthma *per se* for different alleles within this locus, but the haplotypes with the best evidence for association differed between the populations. These data suggest that the true disease susceptibility allele (if one exists) remains to be identified, or alternatively that different haplotypes in different populations might confer risk. In favour of the first explanation, a careful haplotype analysis (ie an examination of combinations of polymorphisms rather than the polymorphisms in isolation) suggested that the true susceptibility locus might depend on additional variation outside the coding region of the IL-4Rα gene itself.

An important finding from this study that has wider implications in the study of asthma genetics is the finding that different haplotypes showed the strongest evidence for association in different ethnic groups. When a candidate gene contains a number of polymorphisms these are usually in tight linkage disequilibrium because of the relatively small genetic distances between the polymorphisms. Hence it can be difficult in a single population to dissect out the important polymorphism, in other words that which actually confers susceptibility to a given disease at a given locus. The IL-4Rα subunit gene is not unique in having a large number of polymorphisms within its coding region. Several other candidate genes, which might be important in allergic disease, also demonstrate quite marked polymorphic variation; the best example is perhaps the β_2 adrenoceptor locus on chromosome 5q31–33, which contains at least 17 SNPs within a region of approx. 3 kilobases containing the gene and important 5′ and 3′ flanking regions [9,10]. Another important observation in Ober's study is that even in an inbred population such as the Hutterites, with relatively few founders and recent origins [11], potentially important association would have been missed by the use of evenly spaced SNPs across the genome at the density currently being proposed for use by the SNP consortium. It might be that the use of multiple SNPs in strong candidate genes for association-based studies is the best way forward for determining the effect of variants that have small or moderate effects on disease risk, as has previously been suggested [12,13].

Another possibility worthy of further study is that combinations of variants in a number of components of a signalling pathway might overall provide an important risk factor for disease susceptibility. For IL-4 it would be reasonable to believe that polymorphisms that increase the level of expression of IL-4 itself might interact with polymorphisms altering the binding of IL-4 to the receptor and/or signalling of the receptor. Additional polymorphisms in the downstream signalling pathways could also contribute to the overall response to produce 'high' and 'low' IL-4 responsive phenotypes. Some evidence that IL-4 promoter polymorphisms might contribute to levels of IL-4 expression in allergic disease has already been described [14] and it will be interesting to look for interactions between these polymorphisms and polymorphisms of the IL-4Rα subunit.

In summary, the paper by Ober *et al* suggests that a locus near the IL-4Rα gene determines a susceptibility gene for the development of asthma and atopy both in the Hutterite population and in other outbred populations. However, despite a number of clinical studies and functional studies on signalling of the receptor *in vitro*, the most important polymorphisms at this locus still remain to be determined, and additional studies concentrating on different components of the relevant signalling cascade need to be performed.

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