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Allergy by mutation

The search for genetic factors that may predispose people to various allergies takes a promising turn with the publication of some incriminating evidence against the IgE receptor.

FOR many people, common complaints such as hay fever, eczema and food allergies are little more than an irritating nuisance. But at the extreme end of the allergy spectrum, asthma results in thousands of deaths each year. The causes of these conditions, which are given the collective term 'atopy', are thought to involve the familiar conspiracy between environmental and genetic factors. The environmental culprits are fairly well known, including pollens and house dust mites. When these allergens bind to IgE, which is itself held captive on the surface of mast cells by its receptor, it triggers the release of inflammatory substances, such as histamine, which lead to the familiar spring symptoms — sneezing, coughing, wheezing and so on. In atopic individuals, the rise in serum levels of IgE in response to allergen exposure is both prolonged and considerably enhanced.

But what about the genes that might make some individuals particularly susceptible to atopic allergies? A report by Julian Hopkin, William Cookson and colleagues in Oxford, in the June issue of *Nature Genetics*, turns the spotlight onto what in hindsight is a rather attractive candidate gene — that for the high-affinity IgE receptor (FcεRI)[1].

For the past five years, Hopkin and colleagues have been accumulating evidence that a gene on chromosome 11 is associated with up to 60% of atopy cases[2,3]. Prompted by earlier suggestions that the risk of atopy is higher in the children of atopic mothers than affected fathers, they also found that the inheritance of atopy at this locus occurred exclusively through the maternal line[3]. Attempts to replicate these findings have met with mixed results[4], although two other recent studies have supported the Oxford group's conclusions.

Last year, Hopkin and colleagues refined the critical atopy region to the point where they could start testing potential candidate genes[5]. After that encoding CD20 proved negative, they turned to a homologous gene encoding the β-subunit of FcεRI. They first sequenced the gene from six atopic individuals, and in one of them found a mutation in one of the transmembrane domains of the receptor: a substitution of a leucine residue for isoleucine at position 181.

Next, they examined the prevalence of the mutation in two populations. A screen of 163 people selected at random turned up the Ile181Leu variant in 25 (15%), 13 of whom were found to be atopic (as measured by total IgE levels and reaction to grass pollen antigen). Given that earlier studies suggested the transmission was parentally influenced, it may not be surprising to see the disorder in only half of the subjects bearing the putative errant allele. They also looked at 60 nuclear families with atopy, and encountered the same mutation in ten of them. In each case, the mutation was maternally inherited, and all 12 children that had inherited Leu181 had developed marked atopy.

It is possible that the Ile181Leu variant is simply in linkage disequilibrium with another, unidentified mutation at the FcεRI-β locus, but there are reasons to think otherwise. The β-chain of FcεRI is the least well understood subunit of the heterotrimeric IgE receptor; nonetheless, although it does not seem to be required for expression or crosslinking of the molecule, new findings suggest that it has an important and previously unsuspected role in autophosphorylation and signal transduction[6]. Furthermore, a similar mutation in a homologous receptor (the ζ-chain of the IgG Fc receptor, FcγRIII) has been shown to affect receptor assembly[6]. It should be possible, therefore, to examine directly the effect of the Ile181Leu variant on FcεRI-β function.

Good evidence for the existence of genetic heterogeneity in atopy was presented last month by researchers at Johns Hopkins, who performed sib-pair analysis on families in the Amish population and, using a candidate gene approach, mapped a locus on the long arm of chromosome 5 that seems to control total IgE serum levels[7]. Interestingly, this region contains a cluster of several cytokine genes, including that encoding interleukin-4, which plays an important role in T-cell differentiation and IgE production by B lymphocytes. Thus, both candidates identified so far are perfectly plausible, and efforts are continuing to identify other loci involved in atopy. Sorting out the relative contributions of these genes will doubtless be a story for another day.

Since 1989, when the gene for cystic fibrosis (CF) was first identified, more than 400 different mutations have been documented, although the first of them — the deletion of a single phenylalanine residue at position 508 (ΔF508) — is far and away the most common, accounting for 70% of all CF chromosomes. But that figure conceals a stark and surprising variation within Europe: in the north of Europe and Scandinavia, the prevalence of ΔF508 is as high as 90%; but around the Mediterranean, it makes up less than half of the total mutations. So why has ΔF508 assumed such a high overall frequency and graded distribution?

Another study in the June issue of *Nature Genetics*, one coordinated by Xavier Estivill in Barcelona, and involving workers from 13 different European countries, has tackled just this question[8]. The group looked at more than 1,700 CF chromosomes bearing the ΔF508 mutation, and catalogued the haplotype of each chromosome, as composed of three highly polymorphic markers within the CF gene. Of a total of 54 different haplotypes with these three markers, just four accounted for nearly 90% of the chromosomes. By assessing the variability, or 'slippage', at each marker with respect to each other, the team were able to calculate the original haplotype on which ΔF508 was thought to have arisen, and measure the expected time required to account for the variability seen today.

That result turns out to be in excess of 2,500 generations, which (allowing 20 years per generation) yields an origin for ΔF508 of more than 50,000 years ago — considerably older than previous estimates. The authors suggest that the common CF mutation arose in an ancestral European population, and later spread through two distinct populations. The remarkable persistence of ΔF508 supports the notion that CF carriers have a heterozygous advantage, perhaps against cholera or diarrhoea. **Kevin Davies**

Kevin Davies is the editor of Nature Genetics.

Also in June's *Nature Genetics*: different subunits of the glycine receptor mutated in *spastic* and *spasmodic* mouse strains; complete map of the immunoglobulin V_H region on chromosome 14; African origins of oculocutaneous albinism; linkage mapping of Sorsby's fundus dystrophy; and the identification of novel bacterial transcripts by sequence analysis.

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