Homing in on our sneeze and wheeze genes

When dust, cat dander, or pollen makes your eyes water, it's because these substances set off a complex immune response. The key to this response is a type of antibody called immunoglobulin E (IgE).

These molecules act as the immune system's sentinels; they sound an alarm when they spot foreign substances, called allergens, within the body. In susceptible people, these sentinels can cause the body to overreact. That reaction can snowball: Sneezes, wheezes, coughs, runny noses, rashes, even asthma attacks can result.

Now, two groups have implicated two genes in this overreaction. Their findings help confirm the innate sensitivity of some people to allergens and hint at the complexity of this sensitivity.

Normally, a few IgE scouts float free in the blood, while most take up posts at docking sites, or receptors, at the surfaces of certain immune system cells.

Chromosome 11 contains the gene that codes for one of the amino acid chains that make up an IgE receptor, says William O.C.M. Cookson of John Radcliffe Hospital in Oxford, England. His team has identified three variants of this chain, two of which tend to make people susceptible to asthma and allergies, the researchers report in the June NATURE GENETICS.

Another team has homed in on a section of chromosome 5 as the location of a genetic mutation that causes the body to send extra IgE scouts into the blood. DNA in that section codes for several immune system messengers, or cytokines, known to stimulate the allergic response, says David G. Marsh, an immunogeneticist at John Hopkins University School of Medicine in Baltimore.

He and his colleagues found this section by evaluating parts of chromosome 5 in 170 members of 11 extended Amish families. At least one member of each family had allergies. The researchers focused on comparisons between the 119 brothers and sisters in those families. Using the Amish, who live in similar environments and do not smoke — which tends to elevate IgE — helped eliminate some confounding factors, Marsh says. Also, the team excluded allergic siblings from part of the analysis in order to rule out the effects of exposure to dust or pollen as a cause of high IgE concentrations.

Marsh hopes to pinpoint the gene. He and his colleagues think that mutations in the gene for an immune messenger called interleukin 4 may lead to this variation. This cytokine stimulates the production of white cells that help generate more IgE. However, genes for other cytokines also reside in that part of chromosome 5 and may alter IgE concentrations, albeit in a less direct way, he adds.

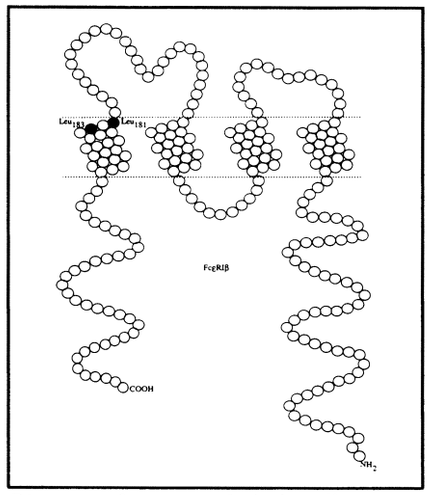
In Oxford, Cookson, Taro Shirakawa from Japan's Osaka University, and their colleagues have not only pinpointed their gene, they have also determined exactly how mutations alter a receptor chain in some allergy-prone people.

They did this by first comparing the DNA of a dozen individuals, half with allergies and half without. In the first six, they found one person whose slightly different DNA resulted in the substitution of a leucine amino acid for an isoleucine at position 181 in the receptor chain. Another's DNA had leucine replacing valine at position 183.

Then the team looked for those substitutions in 163 randomly selected people, finding the switch at position 181 in 25; more than half were allergic. Also, 10 of 60 families with at least one allergic or asthmatic member had this mutation, Cookson reports. In those families, all 13 children who inherited the mutation from their mothers were allergic.

Cookson suspects that this alteration affects the functioning of the receptor. Usually IgE attaches to, but does not activate, the receptor until it snags an allergen. Then these two docked molecules cause the receptor chains to shift and subsequently to signal the cell to release chemicals that make us sneeze and wheeze.

However, "it's a little difficult for me to believe that such a little difference is going to have a big effect," comments Marsh, whose own data can neither confirm nor rule out Cookson's connection between IgE and chromosome 11. "These differences would normally be considered relatively minor."



Shirakawa *et al.*/NATURE GENETICS

Diagram of receptor chain in cell membrane shows locations of amino acid substitutions (black circles).

Indeed, Cookson agrees he has yet to prove these alterations are meaningful. "Just as some people have bigger noses, some people have different receptor shapes," he explains. "The final proof is to demonstrate these are functional changes."

But now that test can be done. "They have come up with something that is experimentally testable," comments Jeffrey V. Ravetch, a molecular biologist at the Memorial Sloan-Kettering Cancer Center in New York City.

"It seems to be a very subtle change, but other people have shown that very subtle changes can have profound effects," he adds. "It's potentially a very important advance." — *E. Pennisi*

Threat from passive smoking is upgraded

Two years ago, epidemiologists reported that among women who had never smoked, those living with husbands who regularly puffed away experienced a 30 percent increased risk of lung cancer. Provocative follow-up data from this same passive-smoking study — the largest to focus on never-smokers — both strengthen and extend the link between lung cancer and the involuntary inhalation of tobacco smoke.

In contrast to the earlier analysis (SN: 1/25/92, p.54), the follow-up of 1,906 women — 653 of whom had had lung cancer — indicates that childhood exposure to smoke does affect one's chance of developing lung cancer. Among the women most exposed to smoke, those who spent their childhood with smokers faced more than three times the cancer risk of those who lived in relatively smokefree environments — and about double the risk of those exposed to smoke-filled air only as adults.

A report of these findings appears in the June 8 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION.

Most passive-smoking studies have focused on exposure to a family member's cigarettes, notes Elizabeth T.H. Fontham of Louisiana State University Medical Center in New Orleans. Her group's findings suggest that the risk posed by breathing smoke-laced air at work or in social settings "is at least as great as that encountered in the home." Specifically, her team correlated adult exposures to smoke at home with a 24 percent average increase in lung cancer risk, exposures at work with a 39 percent increase, and at bars and other social venues with a 50 percent increase in cancer risk.

Overall, women who faced a lifetime exposure of 80 or more "pack-years" of smoke accounted for 80 percent of the above average lung cancer risk in this study. And what constitutes 80 pack-years? Smoking one pack a day for 80 years, four packs a day for 20 years, or some similar combination. — *J. Raloff*