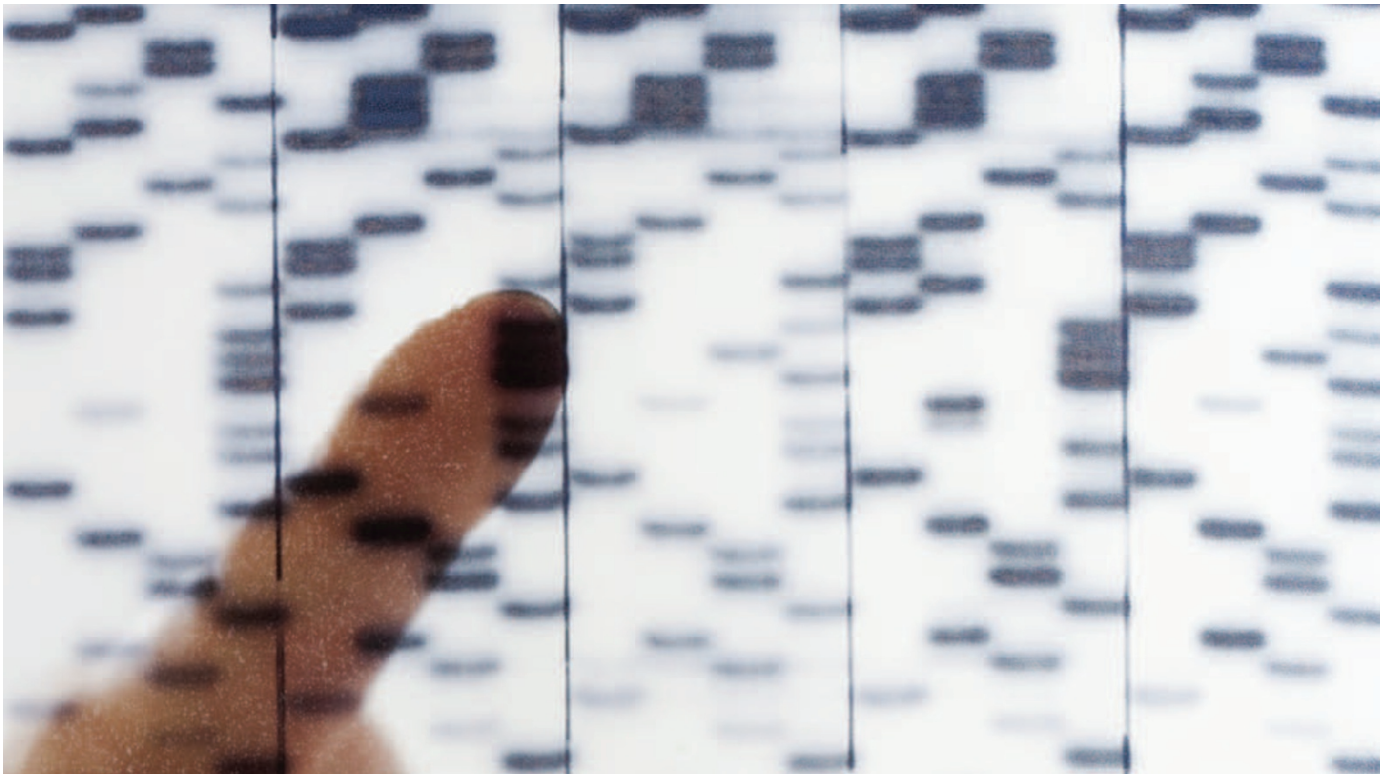

GETTY

GENETICS

Seeking a gene genie

Rare gene variants could be key to unlocking the underlying genetics of allergy, now that whole genome sequencing and other technologies have sharpened the focus of epidemiology.

BY ERICA WESTLY

Go to a doctor with allergy-related symptoms and it's a safe bet you'll be asked about family history. Clearly there is a heritable component to allergies. The genetic elements, however, have proved fiendishly hard to pinpoint. Since a working draft of the the human genome was published in 2001, the focus of research has shifted from trying to link specific genes and allergies, to genome-wide association studies of increasing sensitivity. Evidence of ethnic propensity, and an interplay between environmental factors and genetic predisposition, are starting to acuminate this more subtle search for the heritability factors in allergy and asthma.

The potential rewards are huge. For a start, allergic diseases are heterogeneous in terms of symptom profile and symptom severity. Deciphering the underlying genetics would help researchers make connections between the various allergy types and subtypes, which could aid both diagnosis and treatment. Clinicians are also interested in using genetics to clarify the relationship between allergy and asthma; epidemiological reports indicate that about 80% of childhood asthma patients also suffer from allergic rhinitis, or hay fever, but there are still many questions about how, why and when this association develops (see 'Breathing new life into research', page S20).

NO SINGLE CULPRIT

When geneticists started studying allergy 40 years ago they followed the functional candidate gene approach, using symptom profiles to identify genes likely to be of interest. Most of the early gene associations in this field involved the immune system. A particular favourite for investigation was the human leukocyte antigen (*HLA*) gene family, on chromosome 6, which encodes proteins that help the body recognize allergens and other invaders. The problem was that few of these gene associations reached statistical significance. By 2010, nearly 1,000 studies had been published proposing various candidate genes for allergic disease, but there was still no clear answer.

Some intriguing candidates have emerged, however, particularly in the past few years. One contribution came when researchers at the University of Dundee in the UK linked a skin disorder called ichthyosis vulgaris to a relatively rare mutation in *FLG*, the gene for filaggrin, a key epidermal protein. Subsequent studies tied *FLG* mutations to several allergic conditions, including eczema, asthma and, most recently, peanut allergy. This genetic data, combined with biochemical evidence, led researchers to the hypothesis that allergen susceptibility may be because of an impaired epithelium rather than further downstream in the immune system.

Genome-wide association studies are one of the strongest methods for finding new candidate genes because they use larger sample sizes and they allow researchers to scan for thousands of variants at once. "One of the benefits is that you do genome-wide association studies without a hypothesis," explains Michael Kabesch, an asthma genetics researcher at Hannover Medical School in Germany. "So you can find connections you hadn't thought about before." For example, in 2007, a European genome-wide association study linked a mutation

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on chromosome 17 to asthma but found no link to atopy, which was unexpected given the high incidence of overlap between the two conditions. This finding, which has since been replicated by groups in the United States, Japan and elsewhere, suggests that asthma is not necessarily as tied to allergen exposure as previously believed and may involve novel pathways. Even more surprisingly, there seemed to be an association with the digestive disorder Crohn's disease, a link that Kabesch is investigating further.

ALLERGEN-SPECIFIC PROFILES

The evidence is equivocal when it comes to determining correspondence between genetic profile and specific allergies. One school of thought suggests that although genes control a person's susceptibility to develop allergies, the actual allergens to which the person reacts are determined by the environment. This theory is supported by anecdotal reports of patients trading one allergy for another, say pollen for mould, after moving to a new climate. On the other hand, there is evidence connecting particular mutations to specific allergens: a 2003 study, for instance, found a link between a specific *HLA* variant and sensitivity to rat allergens.

"There is a lot of conflicting evidence," says Rana Tawil Misiak, a clinician who studies allergy at the Henry Ford Health System in Detroit, Michigan, and the lead author of a recent review of allergen specificity[1]. Misiak says that the best prospect of clarification lies in studies that are large enough to include genetic variants that have been associated with different allergies. Indeed, some researchers, including Misiak, have proposed that allergy may only be associated with rare genetic variants, such as the *FLG* mutation, which would explain the absence of positive data from genome-wide association studies that look for links with common gene variants.

The trouble is that genome-wide analyses simply haven't been sensitive enough to detect rare variants. That is changing, however, as whole genome sequencing technologies become more affordable. Genome-wide association studies normally just scan for single DNA mutations (single nucleotide polymorphisms, or SNPs), but incorporating whole genome sequencing would allow researchers to analyse a larger set of genetic variations. The multi-institute 1000 Genomes Project, the largest whole genome-sequencing effort to date, has already sequenced the genomes of more than 2,000 people and identified millions of previously unknown gene variants. It's still unclear whether any will relate to asthma and allergies, but Carole Ober, a geneticist at the University of Chicago, Illinois, who specializes in asthma and allergy, is optimistic. "My guess is that there are at least a few important rare variants that haven't yet been discovered," she says.

Expanding the population genetics studies to include subjects of non-European ancestry should also help identify new candidates. Epidemiological evidence suggests there is a connection between ethnicity and risk of developing allergy and asthma. According to the Centers for Disease Control and Prevention, children of Puerto Rican descent have the highest risk for developing asthma of any group in the United States, with prevalence rates as high as one in six; 125% higher than Caucasians and 80% higher than African Americans. Another study in 2009 found that eczema is significantly more prevalent in African and Latin American countries than in Asian nations, such as China and India. Yet non-European ethnic groups have been severely under-represented in the population genetics studies of allergy-related disease.

CORBIS

What role does ethnicity play in allergy risk?

This is starting to change. In 2010, researchers from Johns Hopkins University in Baltimore, Maryland, published the first genome-wide analysis of asthma and allergy to focus exclusively on people of African American and African Caribbean descent[2]. The chromosome 17 mutation associated with asthma in Asian and European populations did not prove significant in this study, but the researchers did find an association between four other genes, including one on a different part of chromosome 17.

Ethnicity could also play a role in a person's reaction to an allergen. Researchers are using ethnicity-specific gene chips with single DNA mutations to study asthma and allergy genetics in Latin American and African American populations. "We're finding that the same variant can confer either risk or protection depending on ancestry," says Esteban González Burchard, an asthma genetics researcher at the University of California, San Francisco. When it comes to developing allergies and asthma, "it shows that ancestry matters," he adds. For example, a variant of the *DENND1B* gene has been associated with asthma in children of European ancestry, but it appears to offer a protective effect in African American children. Geneticists refer to this as the 'flip-flop phenomenon'.

The epigenetics approach, which seeks to understand how a phenotype may result from the interaction of genes and environmental factors, has been paired with ethnicity-based perspectives through research by Burchard's group. In a recent study they showed a correlation between a mutation in *CD14*, an immune system gene, and asthma severity in Mexican children who had been exposed to tobacco smoke.

Providing more evidence of the relevance of epigenetics in understanding allergy, recent European studies suggest that microbes found on pets and farm animals can cause alterations in *CD14* and in genes that control the Toll-like receptors, which are also involved with the immune response and confer a protective effect against asthma and allergies. In order to translate these findings into treatments or preventive strategies, however, researchers need to figure out when and how these epigenetic interactions occur.

LOOKING BEYOND BLOOD

Methodological issues may explain why it is so difficult to replicate findings like this in large-scale studies. "The tricky part when you start to get into epigenetics is you have to be looking at DNA from the appropriate cell type, and we don't always know what that's going to be," says Ober. "It's a challenging area because we're really in the dark about where to look. You may need to have a specific lung or immune cell type to see the relevant genetic modification."

Collecting the tissue samples for this is a lot harder than obtaining blood, the traditional biologic material used for genetic studies. As a result, these studies are in their infancy, and the sample sizes will be quite small compared to genome-wide association studies, which typically include thousands of subjects. "Many people are willing to give blood for science, but bronchoscopy (the procedure used for taking lung tissue) is much more invasive," says Kabesch. Fortunately, advances in stem cell technology might offer a non-invasive alternative.

What's more, epigenetics allergy studies might do more than help scientists understand the development of allergies. Their findings could also inform research into other disorders that involve gene-environment interactions such as autism and schizophrenia, which is a rich incentive indeed. ■

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1. Misiak, R. T. *et al. Curr. Allergy Asthma Rep.* **10**, 336–339 (2010).
2. Mathias, R. A. *et al. J. Allergy Clin. Immunol.* **125**, 336–346 (2010).