Uncovering asthma's genetic origins

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Researchers are combing through mountains of data to understand a disease that afflicts growing numbers of children and adults. Credit: Yale University

The statistics about asthma are staggering. According to a recent Global Burden of Disease Study, more than 334 million people worldwide may suffer from this common chronic disease. In the United States, the Centers for Disease Control and Prevention reports that asthma afflicts an estimated 25 million people, about 8 percent of the population. It hits children even harder— about 10 percent of them have this respiratory

malady that hinders breathing. Asthma accounts for a quarter of all emergency room visits and more than 500,000 hospitalizations in the United States each year. It kills about 3,500 Americans annually—most of these deaths are preventable with proper treatment—and contributes to another 7,000 deaths.

And the financial tab is steep. Medical care, absences from work and school and premature deaths cost the United States an estimated $56 billion every year. Worse, all of these numbers are rising, alarmingly so among certain populations. In just a decade, for instance, the asthma rate among black children rose more than 50 percent, and the disease now affects 17 percent of this group. Asthma is increasingly damaging to economies and public health, and researchers and policymakers have noticed. In recent years the United Nations has spotlighted the disease several times, citing it as a growing threat to global health and economic development. The Global Asthma Network, formed to improve asthma care internationally, has published two reports about the disease, most recently in 2014. In 2013 the World Health Organization (WHO) called for a global action plan and international monitoring of asthma and other noncommunicable diseases.

Genetic Sleuthing

To fight asthma effectively, its causes must first be identified. Scientists have established that the disease stems from some combination of genetic inheritance and environmental factors such as air pollution, chemical substances and indoor and outdoor allergens (smoke and pollen, for example). But much about asthma remains unknown. "The fundamental causes of asthma," according to the WHO's most recent fact sheet, "are not completely understood." Science is still many years away from solving the mystery of the biological causes of this disease. "Asthma is what we in the field of genetic epidemiology classify as a complex trait," said Andrew T. DeWan, M.P.H., Ph.D., associate

professor in the Department of Chronic Disease Epidemiology. "Genetic characteristics inherited from your parents make about a 50 percent contribution to the risk of developing asthma, but there is also a large component that is not inherited—all sorts of environmental influences."

So far, researchers have postulated associations between asthma and more than 400 genes, a huge pool of possibilities. But that's just the start of this disease's complexity. To discover asthma's foundations, researchers must identify not only the causative genes but also the specific mutations within them that point to the disease. Further, the genes that may affect risk for asthma seem to connect or interact in myriad combinations, and these are not necessarily consistent: the combinations that lead to asthma seem to vary from individual to individual and group to group. All of these possible genetic combinations may be further influenced, or not, by how they respond singly or collectively to factors in each individual's environment. A cluster of genetic characteristics that leads to asthma in one person might have little or no effect on someone else, possibly because of other genetic factors or because of differences in the individuals' environments. To muddy things further, a study published recently in the *Journal of the American Medical Association* found that a third of 600 adults diagnosed with asthma didn't actually have the disease, which casts some doubt on statistics about asthma.

DeWan works to cut through this welter, winnowing out the genes or genetic combinations that probably don't lead to asthma and verifying those that look promising. "A lot of my research," he said, "is focused on dealing with this mixed bag of results to get a better biological understanding of asthma." Much of this is done through large-scale statistical analysis of genetic data, looking in big populations for mutations linked to the disease. A recent study that DeWan co-authored, for instance, surveyed the scientific literature to find genes that have been associated with asthma.

DeWan and his colleagues identified 251 of them, then tried to replicate those findings through a genetic analysis of an independent population. (They recently updated their search; the current count of genes reportedly associated with asthma is now over 400.) In their statistical analysis, DeWan and his colleagues got minor hits on several genes and also identified one previously unassociated gene (RAD50), but they were unable to replicate any links to asthma in the vast majority of reported genes.

That doesn't necessarily mean these genes aren't implicated in the disease, noted DeWan, "but the caveat in our paper is that there may be many false positives in our initial literature search. That's one reason genetic epidemiologists require that results be replicated." Though many findings about genetic contributions to asthma may seem inconsistent and ambiguous, the picture is slowly coming into better focus as more studies connect the same genes, such as ADAM33 and ORMDL3, to the disease. "I think the true number of genes that contribute in some way to the risk of developing asthma is well over 100," said DeWan.

To whittle that number further, he will continue to combine the technological power of high-speed sequencing with the growing quantity and availability of genetic data. The sequencing of the human genome, coupled with advances in computer power, has made possible a revolution in genetic analysis. But to continue that progress, researchers such as DeWan need more extensive genetic data.

That's happening. Many large population-based stud- ies in the United States and abroad are genotyping and sequencing their subjects, each of them collecting data on 50,000 to 100,000 individuals. "To detect the small effects of these genetic variants on asthma, we need much larger sample sizes," said DeWan, "and we're now getting to that point. We're trying to understand which inherited genetic variants are contributing to an individual's risk of developing asthma by looking in large populations,

and these big data sets will give us the statistical power to find what is really a needle in a haystack."

The analysis entails sequencing the genomes of thousands of people and then looking for mutations, and combinations of mutations, common to people with asthma. If DeWan and others can identify the ones that contribute to asthma, they may be able to predict who will develop the disease. Once that's possible, so is prevention. "If we can understand the biological processes that cause asthma," said DeWan, "we can develop better treatments for it and intervene at a pharmaceutical level to prevent or lessen the symptoms." Someday genetic markers could help identify which individuals will respond, or not respond, to certain drugs and treatments, opening the way to effective targeted therapies. Genetic knowledge might also make it possible to predict which environmental factors should be avoided by people with a certain combination of mutations. "The goal is to reduce the overall severity of asthma and its public health costs," said DeWan.

Andrew DeWan and Yasmmyn Salinas extract genomic DNA from saliva samples collected as part of FAstGen, a study of genetic variants contributing to asthma susceptibility in families that have multiple children with asthma. The DNA samples are currently being sequenced to reveal all of the genetic variants in the protein-coding regions of the genome.

Why Asthma?

These possibilities lie well into the future. In addition to his statistical analyses of large populations from all over the world, DeWan is conducting a local study named FAstGen (Family-Specific Genetic Variants Contributing to Asthma Susceptibility). Funded by the National Institutes of Health, DeWan and his team have recruited almost 250 two-generation families who have a minimum of three children, at least two

of whom have asthma. This is a narrowly focused study, but these families are more likely to have inherited genetic variants contributing to asthma, due to the fact that multiple family members have asthma. DNA samples have been collected from all participants, and their exomes are being sequenced. "That's the quick part," said DeWan. "We'll probably be analyzing these data for the next couple of years, looking for rare mutations that are contributing to the development of asthma in individual family members." DeWan likes working on asthma because it's a major public health problem with complex causes. "From a methods or analytical perspective, there are a lot of extremely interesting challenges," he said. "And if we can develop methods to detect genetic associations in a really complex trait such as asthma, maybe we can do this with other traits such as cancer or COPD (chronic obstructive pulmonary disease)."

A Ph.D. candidate working in DeWan's lab, Yasmmyn Salinas, is searching for genetic links between asthma and obesity. Researchers have noticed that the two diseases often occur together and seem to instigate each other, but any genetic connection remains unclear. "One of the hypotheses," said Salinas, "is that they are controlled by the same metabolic pathways, so there is probably a set of genes that affects both diseases. I will look for these genes by studying the whole genome of a large adult population." With support from an NIH predoctoral research grant, she will be analyzing a Norwegian cohort of more than 50,000 people. This sort of large-scale genome- wide analysis done simultaneously on multiple diseases is a new development in genetic epidemiology.

Salinas doesn't know what she will find, but the possibilities excite her. If she can identify a gene or genes linked to both asthma and obesity, those genes could be pharmacologically targeted to prevent them from activating the diseases. That could be particularly important, noted Salinas, "because the population of asthmatics who are obese tends to

have much worse outcomes, and the medications available for asthma don't work quite as well in that population. We hope we can find a more targeted therapy for that population." Salinas was drawn to the study of obesity-related conditions like asthma partly for personal reasons. She grew up in a city once called "the fattest city in America"— McAllen, Texas—and has seen her own family members suffer from the wide-ranging health effects of obesity. "That's how I got interested," said Salinas, who plans to pursue a career in academia after graduation in 2019. "I hope to make a difference in the prevention of these diseases."

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