Environment, not genes, dictates human immune variation, research finds

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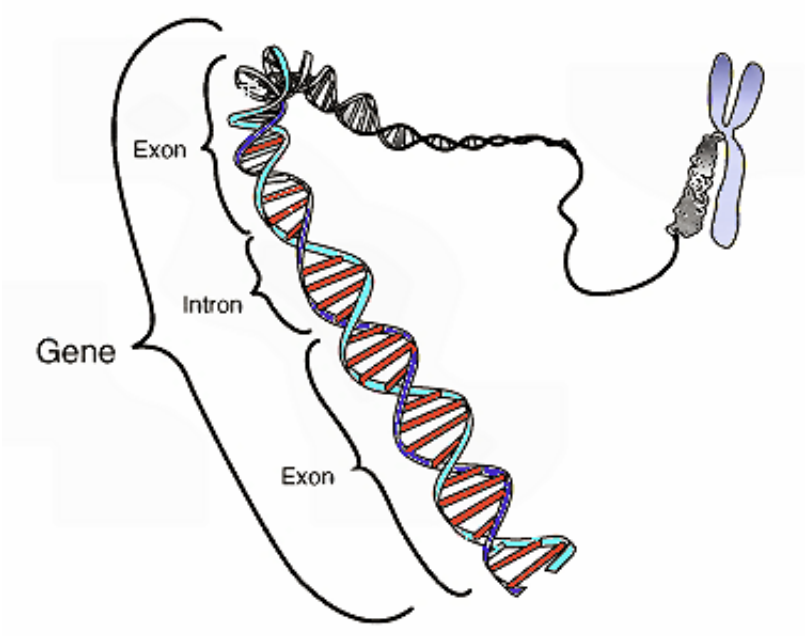

This image shows the coding region in a segment of eukaryotic DNA. Credit: National Human Genome Research Institute

A study of twins conducted by Stanford University School of Medicine investigators shows that our environment, more than our heredity, plays the starring role in determining the state of our immune system, the body's primary defense against disease. This is especially true as we age, the study indicates.

Much has been made of the role genes play in human health. Stunning

advances in gene-sequencing technologies, in concert with their plummeting costs, have turned many scientists' attention to minute variations in the genome—the entire toolbox of genes carried in virtually every cell in the body—in the hope of predicting people's future health. Such studies have revealed a genetic contribution to health outcomes. But, with some notable exceptions, very few individual genetic variants contribute much to particular health conditions.

"The idea in some circles has been that if you sequence someone's genome, you can tell what diseases they're going have 50 years later," said Mark Davis, PhD, professor of microbiology and immunology and director of Stanford's Institute for Immunity, Transplantation and Infection. But while genomic variation clearly plays a key role in some diseases, he said, the immune system has to be tremendously adaptable in order to cope with unpredictable episodes of infection, injury and tumor formation.

"The immune system has to think on its feet," said Davis, senior author of the new study, which will be published Jan. 15 in *Cell*. Lead authorship is shared by former Stanford postdoctoral scholars Petter Brodin, MD, PhD, and Vladimir Jojic, PhD.

Nature versus nurture

"Unlike inbred lab mice, people have broadly divergent genetic heritages," said Davis, who is also the Burt and Marion Avery Family Professor. "And when you examine people's immune systems, you often find tremendous differences between them. So we wondered whether this reflects underlying genetic differences or something else. But what we found was that in most cases, including the reaction to a standard influenza vaccine and other types of immune responsiveness, there is little or no genetic influence at work, and most likely the environment and your exposure to innumerable microbes is the major driver."

To determine nature's and nurture's relative contributions, Davis and his colleagues turned to a century-old method of teasing apart environmental and hereditary influences: They compared pairs of monozygotic twins—best known to most of us as "identical"—and of dizygotic, or fraternal, twins. Monozygotic twins inherit the same genome. Despite inevitable copying errors when cells divide, which cause tiny genetic divergences to accumulate between monozygotic twins over time, they remain almost 100 percent genetically identical. Dizygotic twins are no more alike genetically than regular siblings, on average sharing 50 percent of their genes.

Because both types of twins share the same environment in utero and usually share the same environment in childhood, they make excellent subjects for contrasting hereditary versus environmental influence.

About two decades ago, study co-author Gary Swan, PhD, who was then at SRI Inc. and is now a consulting professor of medicine at Stanford, began curating a registry of twins for research purposes. The registry now includes about 2,000 twin pairs. For the new study, the researchers recruited 78 monozygotic-twin pairs and 27 pairs of dizygotic twins from the registry. They drew blood from both members of each twin pair on three separate visits.

The Stanford team then applied sophisticated laboratory methods to the blood samples to measure more than 200 distinct immune-system components and activities. All samples were sent immediately to Stanford's Human Immune Monitoring Core, which houses the latest immune-sleuthing technology under a single roof.

The power of environment

Examining differences in the levels and activity states of these components within pairs of monozygotic and dizygotic twins, the

Stanford scientists found that in three-quarters of the measurements, nonheritable influences—such as previous microbial or toxic exposures, vaccinations, diet and dental hygiene—trumped heritable ones when it came to accounting for differences within a pair of twins. This environmental dominance was more pronounced in older identical twins (age 60 and up) than in younger twins (under age 20).

Davis and his associates also observed considerable environmental influence over the quantities of antibodies produced in members of twin pairs who had been vaccinated for influenza in a separate Stanford investigation directed by study co-author Cornelia Dekker, MD, professor of pediatric infectious disease and medical director of the Stanford-Lucile Packard Children's Hospital Vaccine Program. While many previous studies have suggested a powerful genetic component in vaccine responsiveness, Davis noted that those studies typically were performed in very young children who had not yet undergone the decades of environmental exposure that appears to reshape the immune system over time.

In a striking example of the immune system's plasticity, the Stanford scientists found that the presence or absence of a single chronic viral infection could have a massive effect on the system's composition and responsiveness. Three out of five Americans and as many as nine out of 10 people in the developing world are chronic carriers of cytomegalovirus, which is dangerous in immune-compromised people but otherwise generally benign. In 16 of the 27 monozygotic twin pairs participating in the study, one member of the pair had been exposed to cytomegalovirus but the other had not. For nearly 60 percent of all the features Davis' group measured, cytomegalovirus' presence in one twin and absence in another made a big difference.

"Nonheritable influences, particularly microbes, seem to play a huge role in driving immune variation," said Davis. "At least for the first 20 or so

years of your life, when your immune system is maturing, this amazing system appears able to adapt to wildly different environmental conditions. A healthy human immune system continually adapts to its encounters with hostile pathogens, friendly gut microbes, nutritional components and more, overshadowing the influences of most heritable factors."

Provided by Stanford University Medical Center

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