Women's immune system genes operate differently from men's, study finds

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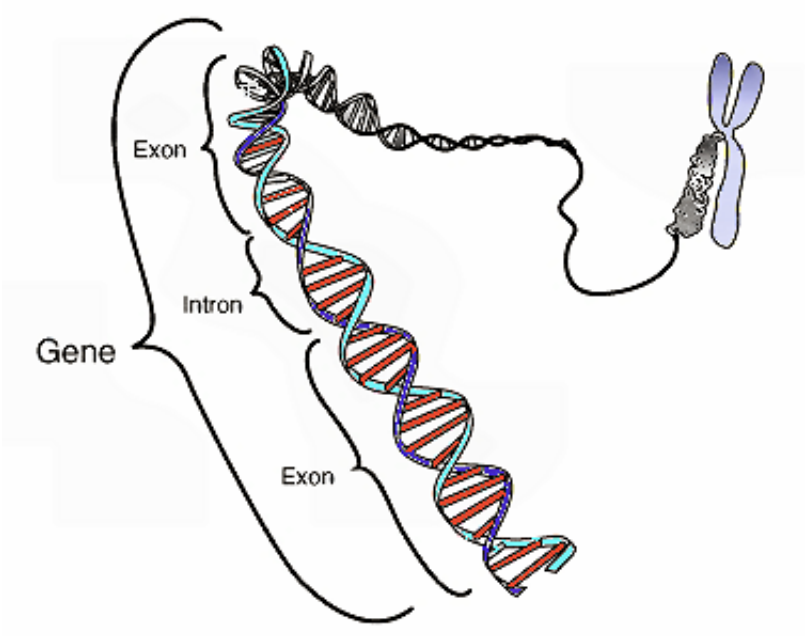

This image shows the coding region in a segment of eukaryotic DNA. Credit: National Human Genome Research Institute

A new technology for studying the human body's vast system for toggling genes on and off reveals that genes associated with the immune system toggle more frequently, and those same genes operate differently in women and men.

Some genes are virtually always on, like the clock light on a microwave; others sit unused for years at a time, like some regrettable appliance you

bought, stuffed into the back of the closet and forgot. Some genes can be always on in one person and always off in another. A minority of genes switch on and off, like a favorite cell phone app. A new technology, which makes it possible to study the molecules that regulate all of that switching in living people as they go about their lives, has revealed some intriguing surprises, according to a study from the Stanford University School of Medicine.

One of those discoveries is that the genes that switch on and off differently from person to person are more likely to be associated with autoimmune diseases. Another is that women and men use different switches to turn on many immune system genes. It's too soon to be sure, but that difference in activity might explain the much higher incidence in women of autoimmune diseases such as scleroderma, lupus and rheumatoid arthritis.

"Part of why this is possible is a new technology that was invented at Stanford for measuring the accessibility of the genome to regulatory elements," explained the study's senior author Howard Chang, MD, PhD, professor of dermatology.

The new technique, called ATAC-seq and developed by Chang's team, lets researchers sample living cells in real time to see what they are up to. "In the past," he said, "people needed a huge number of cells to do this kind of measurement. You'd actually need a pound of flesh to get certain rare cell types. So you can't get that out of a live person—and certainly not more than once, right?"

Examining the source

Researchers coped by growing cells in the lab, so they had enough cells to study. "But now," continued Chang, "you are studying copies of copies; you aren't studying the original cells anymore. Those months of

being grown in the lab completely changes how the cells are behaving and so you are no longer looking at the personal. How the laboratory cells behave has nothing to do with what the person just ate, whether they had a fight with their girlfriend or whether they had an infection," said Chang. With lab-grown cells, the cells haven't experienced any of those things, all of which can alter the regulation of individual genes.

The new study, which will be published July 29 in the new journal *Cell Systems*, took ordinary blood samples from 12 healthy volunteers to measure how certain genes are switched on and off, and how that measure varied from individual to individual. Chang's team also looked at how much change occurred at different times in the same volunteers. The researchers looked exclusively at specialized immune cells called T cells, which are easy to isolate from a standard blood test, easy for volunteers supply and an important component of the immune system.

One goal of the study was to establish a baseline measure of how much this gene-switching activity varies among healthy people. That way, when other researchers make similar measures in people who are ill, they'll have an idea of what is normal. Another goal was to refine the new technique for measuring gene activity in standard blood samples.

"We were interested in exploring the landscape of gene regulation directly from live people and look at differences," said Chang. "We asked, 'How different or similar are people?' This is different from asking if they have the same genes." Even in identical twins, he said, one twin could have an autoimmune disease and the other could be perfectly well. And, indeed, the team reported that over a third of the variation in gene activity was not connected to a genetic difference, suggesting a strong role for the environment. "I would say the majority of the difference is likely from a nongenetic source," he said.

The sex factor

Across the 12 healthy volunteers, 7 percent of the genes were switched on in different patterns from person to person. For each person, these patterns persisted over time, like a unique fingerprint. "But the single greatest predictor for genes' tendency to turn on and off was the sex of the person. In terms of significance," said Chang, "sex was far more important than all the other things we looked at, perhaps even combined." When the team measured gene activity levels from 30 of the top 500 genes the researchers expected would show gender-influenced activity, they found that 20 of the 30 genes showed significant differential activity between men and women.

Chang directs the Center for Personal Dynamic Regulomes at Stanford University, which aims to map the "regulome"—the complete set of all the switches that turn genes on and off in real time.

Provided by Stanford University Medical Center