Roadmap Epigenomics Project reads between DNA's genetic instructions

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Mapping the human genome was a gargantuan task. But it was just the beginning.

Nearly a dozen years after scientists published the first complete draft of human DNA, a global research effort has addressed another profound genetic mystery: how cells throughout the human body interpret the instructions encoded in an individual's DNA.

The international consortium of scientists described the process by which the biological equivalent of Post-it notes attaches to DNA and turns genes on and off and issues instructions to cells throughout the body.

The resulting "Epigenome Roadmap" offers insights into how these molecular marks are able to direct a single gene to produce proteins that give rise to different types of tissue throughout the human body, providing an unprecedented peek into the earliest moments of some diseases, when an errant instruction can knock the behavior of healthy cells terribly off course.

The findings appear in a collection of studies published this week in the journal Nature and its sister publications.

"Building a complex person requires the coordinated activity of thousands of genes, much like coordinating the activities of large numbers of musicians is required to produce a symphony," said Dr. Michael Snyder, director of Stanford University's Center for Genomics and Personalized Medicine, who was not involved in any of the 11 studies.

He said that mapping the DNA in the so-called epigenome and the ways that it coordinates the body's biological activities would help scientists "understand the process that generates a human being — and what goes wrong in disease."

Perhaps more than any other line of scientific research, epigenomics promises to explain how genes and life experience conspire to make us who we are.

The roughly 20,000 genes in the human genome determine whether you're right-handed or left-handed, whether your hair is curly or straight and whether you are colorblind, among hundreds of other traits. These genes account for only about 1.5% of human DNA.

The epigenome modifies the genome. It makes marks that tell genes what to do and when to do it.

"The Human Genome Project gives us a book of life that encodes a human being," said MIT computer scientist Manolis Kellis, who led the seven-year effort to produce the Epigenome Roadmap. "All our cells have a copy of the same book. But they're all reading different chapters, book-marking different pages, and highlighting different paragraphs and words."

The epigenome is responsible for that. By studying the location of its many marks and deciphering the instructions they impart to protein-coding genes, the Roadmap Epigenomics Project offers "an unprecedented view of the living genome," Kellis added.

Unlike genes, which remain largely stable across a person's lifetime, the epigenome is highly dynamic. Preliminary research suggests the epigenome's instructions may be altered by habits such as smoking and eating fatty foods. It also changes in response to experiences, including chronic, severe stress.

To get a better understanding of how this works, Kellis and hundreds of colleagues from around the world studied the epigenomes in 111 different types of human cells and tissues. By comparing their similarities and differences, they identified patterns associated with dozens of complex traits, including height, blood pressure and cholesterol as well as propensity for such conditions as multiple sclerosis, attention deficit and hyperactivity disorder and Alzheimer's disease.

"What's exciting is that we're starting to see how genome sequence expresses itself through the epigenome," said Harvard geneticist Steven McCarroll, who wasn't involved in the studies.

In one of the other new research studies, scientists described an apparent fault in the immune system that may allow Alzheimer's disease to gain a foothold. A genetic propensity to the memory-robbing disease has been recognized for some years now, but scientists led by Stanford University geneticist Anshul Kundaje gleaned that, under the influence of epigenomic marks, the DNA that confers increased risk acts primarily on the cells of the body's immune system, and only indirectly on cells in the brain.

That insight may open up "completely new therapeutic avenues" for the treatment of Alzheimer's that target malfunctioning immune cells rather than focusing on the symptom of brain-cell death, Kellis said.

The epigenome researchers also suggested their road map may plot new courses of treatment for cancer.

Patients with metastatic cancers of unknown origin may be among the earliest beneficiaries, Kellis said. Such patients often receive treatment aimed at a tumor's current location, or based on an oncologist's hunch about where the tumor originated. These treatments are often unsuccessful.

But one of the new studies suggests that cancer-causing mutations often bear the molecular fingerprint of the type of cell that spawned them. That finding may allow physicians to treat these cancers with greater success.

Similar benefits may be found for other diseases, researchers predicted.

"I think we're in for a surprise," Kellis said. "These maps give us a completely unbiased picture of what tissues and cells may be underlying these complex disorders."

And the maps will only get better. Over the next seven to 10 years, the International Human Epigenome Consortium aims to expand on this work by deciphering 1,000 human epigenomes, Kundaje said.

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