Photo of the day

DNA Is Not Destiny

The new science of epigenetics rewrites the rules of disease, heredity, and identity.

By Ethan Watters
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Back in 2000, Randy Jirtle, a professor of radiation oncology at Duke University, and his postdoctoral student Robert Waterland designed a groundbreaking genetic experiment that was simplicity itself. They started with pairs of fat yellow mice known to scientists as agouti mice, so called because they carry a particular gene—the agouti gene—that in addition to making the rodents ravenous and yellow renders them prone to cancer and diabetes. Jirtle and Waterland set about to see if they could change the unfortunate genetic legacy of these little creatures.

Typically, when agouti mice breed, most of the offspring are identical to the parents: just as yellow, fat as pincushions, and susceptible to life-shortening disease. The parent mice in Jirtle and Waterland's experiment, however, produced a majority of offspring that looked altogether different. These young mice were slender and mousy brown. Moreover, they did not display their parents' susceptibility to cancer and diabetes and lived to a spry old age. The effects of the agouti gene had been virtually erased.

Remarkably, the researchers effected this transformation without altering a single letter of the mouse's DNA. Their approach instead was radically straightforward—they changed the moms' diet. Starting just before conception, Jirtle and Waterland fed a test group of mother mice a diet rich in methyl donors, small chemical clusters that can attach to a gene and turn it off. These molecules are common in the environment and are found in many foods, including onions, garlic, beets, and in the food supplements often given to pregnant women. After being consumed by the mothers, the methyl donors worked their way into the developing embryos' chromosomes and onto the critical agouti gene. The mothers passed along the agouti gene to their children intact, but thanks to their methyl-rich pregnancy diet, they had added to the gene a chemical switch that dimmed the gene's deleterious effects.

"It was a little eerie and a little scary to see how something as subtle as a nutritional change in the pregnant mother rat could have such a dramatic impact on the gene expression of the baby," Jirtle says. "The results showed how important epigenetic changes could be."

Our DNA—specifically the 25,000 genes identified by the Human Genome Project—is now widely regarded as the instruction book for the human body. But genes themselves need instructions for what to do, and where and when to do it. A human liver cell contains the same DNA as a brain cell, yet somehow it knows to code only those proteins needed for the functioning of the liver. Those instructions are found not in the letters of the DNA itself but on it, in an array of

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chemical markers and switches, known collectively as the epigenome, that lie along the length of the double helix. These epigenetic switches and markers in turn help switch on or off the expression of particular genes. Think of the epigenome as a complex software code, capable of inducing the DNA hardware to manufacture an impressive variety of proteins, cell types, and individuals.

In recent years, epigenetics researchers have made great strides in understanding the many molecular sequences and patterns that determine which genes can be turned on and off. Their work has made it increasingly clear that for all the popular attention devoted to genome-sequencing projects, the epigenome is just as critical as DNA to the healthy development of organisms, humans included. Jirtle and Waterland's experiment was a benchmark demonstration that the epigenome is sensitive to cues from the environment. More and more, researchers are finding that an extra bit of a vitamin, a brief exposure to a toxin, even an added dose of mothering can tweak the epigenome—and thereby alter the software of our genes—in ways that affect an individual's body and brain for life.

The even greater surprise is the recent discovery that epigenetic signals from the environment can be passed on from one generation to the next, sometimes for several generations, without changing a single gene sequence. It's well established, of course, that environmental effects like radiation, which alter the genetic sequences in a sex cell's DNA, can leave a mark on subsequent generations. Likewise, it's known that the environment in a mother's womb can alter the development of a fetus. What's eye-opening is a growing body of evidence suggesting that the epigenetic changes wrought by one's diet, behavior, or surroundings can work their way into the germ line and echo far into the future. Put simply, and as bizarre as it may sound, what you eat or smoke today could affect the health and behavior of your great-grandchildren.

All of these discoveries are shaking the modern biological and social certainties about genetics and identity. We commonly accept the notion that through our DNA we are destined to have particular body shapes, personalities, and diseases. Some scholars even contend that the genetic code predetermines intelligence and is the root cause of many social ills, including poverty, crime, and violence. "Gene as fate" has become conventional wisdom. Through the study of epigenetics, that notion at last may be proved outdated. Suddenly, for better or worse, we appear to have a measure of control over our genetic legacy.

"Epigenetics is proving we have some responsibility for the integrity of our genome," Jirtle says. "Before, genes predetermined outcomes. Now everything we do—everything we eat or smoke—can affect our gene expression and that of future generations. Epigenetics introduces the concept of free will into our idea of genetics."

Scientists are still coming to understand the many ways that epigenetic changes unfold at the biochemical level. One form of epigenetic change physically blocks access to the genes by altering what is called the histone code. The DNA in every cell is tightly wound around proteins known as histones and must be unwound to be transcribed. Alterations to this packaging cause certain genes to be more or less available to the cell's chemical machinery and so determine whether those genes are expressed or silenced. A second, well-understood form of epigenetic signaling, called DNA methylation, involves the addition of a methyl group—a carbon atom plus three hydrogen atoms—to particular bases in the DNA sequence. This interferes with the chemical signals that would put the gene into action and thus effectively silences the gene.

Until recently, the pattern of an individual's epigenome was thought to be firmly established during early fetal development. Although that is still seen as a critical period, scientists have lately discovered that the epigenome can change in response to the environment throughout an individual's lifetime.

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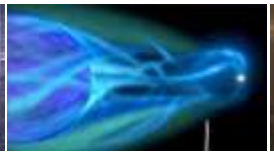

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