

Why Your DNA Isn't Your Destiny

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The remote, snow-swept expanses of northern Sweden are an unlikely place to begin a story about cutting-edge genetic science. The kingdom's northernmost county, Norrbotten, is nearly free of human life; an average of just six people live in each square mile. And yet this tiny population can reveal a lot about how genes work in our everyday lives.

Norrbotten is so isolated that in the 19th century, if the harvest was bad, people starved. The starving years were all the crueler for their unpredictability. For instance, 1800, 1812, 1821, 1836 and 1856 were years of total crop failure and extreme suffering. But in 1801, 1822, 1828, 1844 and 1863, the land spilled forth such abundance that the same people who had gone hungry in previous winters were able to gorge themselves for months.

In the 1980s, Dr. Lars Olov Bygren, a preventive-health specialist who is now at the prestigious Karolinska Institute in Stockholm, began to wonder what long-term effects the feast and famine years might have had on children growing up in Norrbotten in the 19th century — and not just on them but on their kids and grandkids as well. So he drew a random sample of 99 individuals born in the Overkalix parish of Norrbotten in 1905 and used historical records to trace their parents and grandparents back to birth. By analyzing meticulous agricultural records, Bygren and two colleagues determined how much food had been available to the parents and grandparents when they were young.

Around the time he started collecting the data, Bygren had become fascinated with research showing that conditions in the womb could affect your health not only when you were a fetus but well into adulthood. In 1986, for example, the *Lancet* published the first of two groundbreaking papers showing that if a pregnant woman ate poorly, her child would be at significantly higher than average risk for cardiovascular disease as an adult. Bygren wondered whether that effect could start even before pregnancy: Could parents' experiences early in their lives somehow change the traits they passed to their offspring?

It was a heretical idea. After all, we have had a long-standing deal with biology: whatever choices we make during our lives might ruin our short-term memory or make us fat or hasten death, but they won't change our genes — our actual DNA. Which meant that when we had kids of our own, the genetic slate would be wiped clean.

What's more, any such effects of nurture (environment) on a species' nature (genes) were not supposed to happen so quickly. Charles Darwin, whose *On the Origin of Species* celebrated its 150th anniversary in November, taught us that evolutionary changes take place over many generations and through millions of years of natural selection. But Bygren and other scientists have now amassed historical evidence suggesting that powerful environmental conditions (near

death from starvation, for instance) can somehow leave an imprint on the genetic material in eggs and sperm. These genetic imprints can short-circuit evolution and pass along new traits in a single generation.

For instance, Bygren's research showed that in Overkalix, boys who enjoyed those rare overabundant winters — kids who went from normal eating to gluttony in a single season — produced sons and grandsons who lived shorter lives. Far shorter: in the first paper Bygren wrote about Norrbotten, which was published in 2001 in the Dutch journal *Acta Biotheoretica*, he showed that the grandsons of Overkalix boys who had overeaten died an average of six years earlier than the grandsons of those who had endured a poor harvest. Once Bygren and his team controlled for certain socioeconomic variations, the difference in longevity jumped to an astonishing 32 years. Later papers using different Norrbotten cohorts also found significant drops in life span and discovered that they applied along the female line as well, meaning that the daughters and granddaughters of girls who had gone from normal to gluttonous diets also lived shorter lives. To put it simply, the data suggested that a single winter of overeating as a youngster could initiate a biological chain of events that would lead one's grandchildren to die decades earlier than their peers did. How could this be possible?

Meet the Epigenome

The answer lies beyond both nature and nurture. Bygren's data — along with those of many other scientists working separately over the past 20 years — have given birth to a new science called **epigenetics**. At its most basic, **epigenetics** is the study of changes in gene activity that do not involve alterations to the genetic code but still get passed down to at least one successive generation. These patterns of gene expression are governed by the cellular material — the **epigenome** — that sits on top of the genome, just outside it (hence the prefix *epi-*, which means above). It is these epigenetic "marks" that tell your genes to switch on or off, to speak loudly or whisper. It is through epigenetic marks that environmental factors like diet, stress and prenatal nutrition can make an imprint on genes that is passed from one generation to the next.

Epigenetics brings both good news and bad. Bad news first: there's evidence that lifestyle choices like smoking and eating too much can change the epigenetic marks atop your DNA in ways that cause the genes for obesity to express themselves too strongly and the genes for longevity to express themselves too weakly. We all know that you can truncate your own life if you smoke or overeat, but it's becoming clear that those same bad behaviors can also predispose your kids — before they are even conceived — to disease and early death.

The good news: scientists are learning to manipulate epigenetic marks in the lab, which means they are developing drugs that treat illness simply by silencing bad genes and jump-starting good ones. In 2004 the Food and Drug Administration (FDA) approved an epigenetic drug for the first time. Azacitidine is used to treat patients with myelodysplastic syndromes (usually abbreviated, a bit oddly, to MDS), a group of rare and deadly blood malignancies. The drug uses epigenetic marks to dial down genes in blood precursor cells that have become overexpressed. According to Celgene Corp. — the Summit, N.J., company that makes azacitidine — people given a diagnosis of serious MDS live a median of two years on azacitidine; those taking conventional blood medications live just 15 months.

Since 2004, the FDA has approved three other epigenetic drugs that are thought to work at least in part by stimulating tumor-suppressor genes that disease has silenced. The great hope for ongoing epigenetic research is that with the flick of a biochemical switch, we could tell genes that play a role in many diseases — including cancer, schizophrenia, autism, Alzheimer's, diabetes and many others — to lie dormant. We could, at long last, have a trump card to play against Darwin.

The funny thing is, scientists have known about epigenetic marks since at least the 1970s. But until the late '90s, epigenetic phenomena were regarded as a sideshow to the main event, DNA. To be sure, epigenetic marks were always understood to be important: after all, a cell in your brain and a cell in your kidney contain the exact same DNA, and scientists have long known that nascent cells can differentiate only when crucial epigenetic processes turn on or turn off the right genes in utero.

More recently, however, researchers have begun to realize that epigenetics could also help explain certain scientific mysteries that traditional genetics never could: for instance, why one member of a pair of identical twins can develop bipolar disorder or asthma even though the other is fine. Or why autism strikes boys four times as often as girls. Or why extreme changes in diet over a short period in Norrbotten could lead to extreme changes in longevity. In these cases, the genes may be the same, but their patterns of expression have clearly been tweaked.

Biologists offer this analogy as an explanation: if the genome is the hardware, then the epigenome is the software. "I can load Windows, if I want, on my Mac," says Joseph Ecker, a Salk Institute biologist and leading epigenetic scientist. "You're going to have the same chip in there, the same genome, but different software. And the outcome is a different cell type."

How to Make a Better Mouse

As momentous as epigenetics sounds, the chemistry of at least one of its mechanisms is fairly simple. Darwin taught us that it takes many generations for a genome to evolve, but researchers have found that it takes only the addition of a methyl group to change an epigenome. A methyl group is a basic unit in organic chemistry: one carbon atom attached to three hydrogen atoms. When a methyl group attaches to a specific spot on a gene — a process called DNA methylation — it can change the gene's expression, turning it off or on, dampening it or making it louder.

The importance of DNA methylation in altering the physical characteristics of an organism was proposed in the 1970s, yet it wasn't until 2003 that anyone experimented with DNA methylation quite as dramatically as Duke University oncologist Randy Jirtle and one of his postdoctoral students, Robert Waterland, did. That year, they conducted an elegant experiment on mice with a uniquely regulated agouti gene — a gene that gives mice yellow coats and a propensity for obesity and diabetes when expressed continuously. Jirtle's team fed one group of pregnant agouti mice a diet rich in B vitamins (folic acid and vitamin B12). Another group of genetically identical pregnant agouti mice got no such prenatal nutrition.

The B vitamins acted as methyl donors: they caused methyl groups to attach more frequently to the agouti gene in utero, thereby altering its expression. And so without altering the genomic structure of mouse DNA — simply by furnishing B vitamins — Jirtle and Waterland got agouti mothers to produce healthy brown pups that were of normal weight and not prone to diabetes.

Other recent studies have also shown the power of environment over gene expression. For instance, fruit flies exposed to a drug called geldanamycin show unusual outgrowths on their eyes that can last through at least 13 generations of offspring even though no change in DNA has occurred (and generations 2 through 13 were not directly exposed to the drug). Similarly, according to a paper published last year in the *Quarterly Review of Biology* by Eva Jablonka (an epigenetic pioneer) and Gal Raz of Tel Aviv University, roundworms fed with a kind of bacteria can feature a small, dumpy appearance and a switched-off green fluorescent protein; the changes last at least 40 generations. (Jablonka and Raz's paper catalogs some 100 forms of epigenetic inheritance.)

Can epigenetic changes be permanent? Possibly, but it's important to remember that epigenetics isn't evolution. It doesn't change DNA. Epigenetic changes represent a biological response to an environmental stressor. That response can be inherited through many generations via epigenetic marks, but if you remove the environmental pressure, the epigenetic marks will eventually fade, and the DNA code will — over time — begin to revert to its original programming. That's the current thinking, anyway: that only natural selection causes *permanent* genetic change.

And yet even if epigenetic inheritance doesn't last forever, it can be hugely powerful. In February 2009, the *Journal of Neuroscience* published a paper showing that even memory — a wildly complex biological and psychological process — can be improved from one generation to the next via epigenetics. The paper described an experiment with mice led by Larry Feig, a Tufts University biochemist. Feig's team exposed mice with genetic memory problems to an environment rich with toys, exercise and extra attention. These mice showed significant improvement in long-term potentiation (LTP), a form of neural transmission that is key to memory formation. Surprisingly, their offspring also showed LTP improvement, even when the offspring got no extra attention.

All this explains why the scientific community is so nervously excited about epigenetics. In his forthcoming book *The Genius in All of Us: Why Everything You've Been Told About Genetics, Talent and IQ Is Wrong*, science writer David Shenk says epigenetics is helping usher in a "new paradigm" that "reveals how bankrupt the phrase 'nature versus nurture' really is." He calls epigenetics "perhaps the most important discovery in the science of heredity since the gene."

Geneticists are quietly acknowledging that we may have too easily dismissed an early naturalist who anticipated modern epigenetics — and whom Darwinists have long disparaged. Jean-Baptiste Lamarck (1744-1829) argued that evolution could occur within a generation or two. He posited that animals acquired certain traits during their lifetimes because of their environment and choices. The most famous Lamarckian example: giraffes acquired their long necks because their recent ancestors had stretched to reach high, nutrient-rich leaves.

In contrast, Darwin argued that evolution works not through the fire of effort but through cold, impartial selection. By Darwinist thinking, giraffes got their long necks over millennia because genes for long necks had, very slowly, gained advantage. Darwin, who was 84 years younger than Lamarck, was the better scientist, and he won the day. Lamarckian evolution came to be seen as a scientific blunder. Yet epigenetics is now forcing scientists to re-evaluate Lamarck's ideas.

Solving the Overkalix Mystery

By early 2000, it seemed clear to Bygren that the feast and famine years in 19th century Norrbotten had caused some form of epigenetic change in the population. But he wasn't sure how this worked. Then he ran across an obscure 1996 paper by Dr. Marcus Pembrey, a prominent geneticist at University College London.

Published in the Italian journal *Acta Geneticae Medicae et Gemellologiae*, Pembrey's paper, now considered seminal in epigenetic theory, was contentious at the time; major journals had rejected it. Although he is a committed Darwinist, Pembrey used the paper — a review of available epigenetic science — to speculate beyond Darwin: What if the environmental pressures and social changes of the industrial age had become so powerful that evolution had begun to demand that our genes respond faster? What if our DNA now had to react not over many generations and millions of years but, as Pembrey wrote, within "a few, or moderate number, of generations"?

This shortened timetable would mean that genes themselves wouldn't have had enough years to change. But, Pembrey reasoned, maybe the epigenetic marks atop DNA would have had time to change. Pembrey wasn't sure how you would test such a grand theory, and he put the idea aside after the *Acta* paper appeared. But in May 2000, out of the blue, he received an e-mail from Bygren — whom he did not know — about the Overkalix life-expectancy data. The two struck up a friendship and began discussing how to construct a new experiment that would clarify the Overkalix mystery.

Pembrey and Bygren knew they needed to replicate the Overkalix findings, but of course you can't conduct an experiment in which some kids starve and others overeat. (You also wouldn't want to wait 60 years for the results.) By coincidence, Pembrey had access to another incredible trove of genetic information. He had long been on the board of the Avon Longitudinal Study of Parents and Children (ALSPAC), a unique research project based at the University of Bristol, in England. Founded by Pembrey's friend Jean Golding, an epidemiologist at the university, ALSPAC has followed thousands of young people and their parents since before the kids were born, in 1991 and 1992. For the study, Golding and her staff recruited 14,024 pregnant mothers — 70% of all the women in the Bristol area who were pregnant during the 20-month recruitment period.

The ALSPAC parents and kids have undergone extensive medical and psychological testing every year since. Recently, I met an ALSPAC baby, Tom Gibbs, who is now a sturdy 17-year-old. I accompanied him as clinicians measured his height (178 cm, or 5 ft. 8 in., not including spiked blond hair), the bone density of his left femur (1.3 g/sq cm, which is above average) and a host of other physical traits.

All this data collection was designed from the outset to show how the individual's genotype combines with environmental pressures to influence health and development. ALSPAC data have offered several important insights: baby lotions containing peanut oil may be partly responsible for the rise in peanut allergies; high maternal anxiety during pregnancy is associated with the child's later development of asthma; little kids who are kept too clean are at higher risk for eczema.

But Pembrey, Bygren and Golding — now all working together — used the data to produce a more groundbreaking paper, the most compelling epigenetic study yet written. Published in 2006 in the *European Journal of Human Genetics*, it noted that of the 14,024 fathers in the study, 166 said they had started smoking before age 11 — just as their bodies were preparing to enter puberty. Boys are genetically isolated before puberty because they cannot form sperm. (Girls, by contrast, have their eggs from birth.) That makes the period around puberty fertile ground for epigenetic changes: If the environment is going to imprint epigenetic marks on genes in the Y chromosome, what better time to do it than when sperm is first starting to form?

When Pembrey, Bygren and Golding looked at the sons of those 166 early smokers, it turned out that the boys had significantly higher body mass indexes than other boys by age 9. That means the sons of men who smoke in prepuberty will be at higher risk for obesity and other health problems well into adulthood. It's very likely these boys will also have shorter life spans, just as the children of the Overkalix overeaters did. "The coherence between the ALSPAC and Overkalix results in terms of the exposure-sensitive periods and sex specificity supports the hypothesis that there is a general mechanism for transmitting information about the ancestral environment down the male line," Pembrey, Bygren, Golding and their colleagues concluded in the *European Journal of Human Genetics* paper. In other words, you can change your epigenetics even when you make a dumb decision at 10 years old. If you start smoking then, you may have made not only a medical mistake but a catastrophic genetic mistake.

Exploring Epigenetic Potential

How can we harness the power of epigenetics for good? In 2008 the National Institutes of Health (NIH) announced it would pour \$190 million into a multilab, nationwide initiative to understand "how and when epigenetic processes control genes." Dr. Elias Zerhouni, who directed the NIH when it awarded the grant, said at the time — in a phrase slightly too dry for its import — that epigenetics had become "a central issue in biology."

This past October, the NIH grant started to pay off. Scientists working jointly at a fledgling, largely Internet-based effort called the San Diego Epigenome Center announced with colleagues from the Salk Institute — the massive La Jolla, Calif., think tank founded by the man who discovered the polio vaccine — that they had produced "the first detailed map of the human epigenome."

The claim was a bit grandiose. In fact, the scientists had mapped only a certain portion of the epigenomes of two cell types (an embryonic stem cell and another basic cell called a fibroblast). There are at least 210 cell types in the human body — and possibly far more, according to Ecker, the Salk biologist, who worked on the epigenome maps. Each of the 210 cell types is likely to have a different epigenome. That's why Ecker calls the \$190 million grant from NIH "peanuts" compared with the probable end cost of figuring out what all the epigenetic marks are and how they work in concert.

Remember the Human Genome Project? Completed in March 2000, the project found that the human genome contains something like 25,000 genes; it took \$3 billion to map them all. The human epigenome contains an as yet unknowable number of patterns of epigenetic marks, a number so big that Ecker won't even speculate on it. The number is certainly in the millions. A full epigenome map will require major advances in computing power. When completed, the

Human Epigenome Project (already under way in Europe) will make the Human Genome Project look like homework that 15th century kids did with an abacus.

But the potential is staggering. For decades, we have stumbled around massive Darwinian roadblocks. DNA, we thought, was an ironclad code that we and our children and their children had to live by. Now we can imagine a world in which we can tinker with DNA, bend it to our will. It will take geneticists and ethicists many years to work out all the implications, but be assured: the age of epigenetics has arrived.