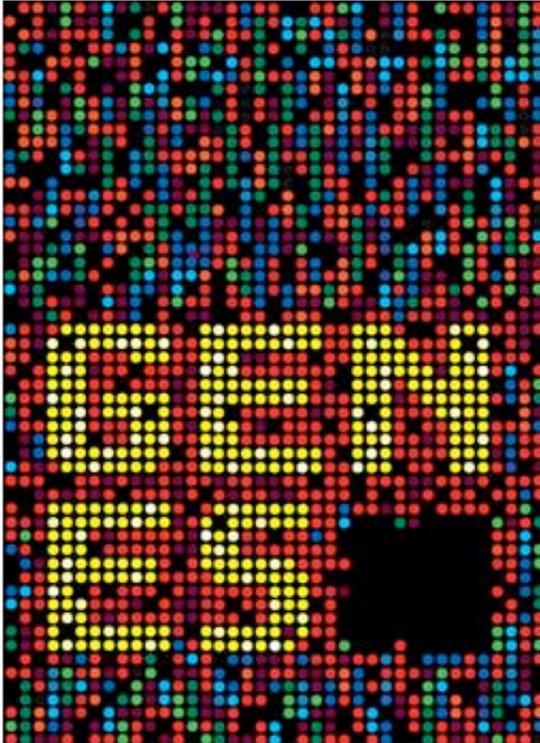


## Looking Deep, Deep Into Your Genes

by Laura Wright

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### Discoveries about the impact of the environment on our DNA could revolutionize our concept of illness.

Martha Herbert, a pediatric neurologist at Boston's Massachusetts General Hospital, studies brain images of children with autism. She was seeing patients one day a few years ago when a 3-year-old girl walked in with more than the usual cognitive and behavioral problems. She was lactose intolerant, and foods containing gluten always seemed to upset her stomach. Autistic children suffer profoundly, and not just in their difficulty forming emotional bonds with family members, making friends, or tolerating minor deviations from their daily routines. Herbert has seen many young children who've had a dozen or more ear infections by the time they made their way through her door, and many others -- "gut kids" -- with chronic diarrhea and other gastrointestinal problems, including severe food allergies. Such symptoms don't fit with the traditional explanation of autism as a genetic disorder rooted in the brain, and that was precisely what was on Herbert's mind that day. She's seen too many kids whose entire systems have gone haywire.

During the course of the little girl's appointment, Herbert learned that the child's father was a computer scientist -- a bioinformatist no less, someone trained to

crunch biological data and pick out patterns of interest. She shared with him her belief that autism research was overly focused on examining genes that play a role in brain development and function, to the exclusion of other factors -- namely, children's susceptibility to environmental insults, such as exposure to chemicals and toxic substances. Inspired by their conversation, Herbert left the office that day with a plan: She and the girl's father, John Russo, head of computer science at the Wentworth Institute of Technology, would cobble together a team of geneticists and bioinformaticists to root through the scientific literature looking for genes that might be involved in autism without necessarily being related to brain development or the nervous system.

The group scanned databases of genes already known to respond to chemicals in the environment, selecting those that lie within sequences of DNA with suspected ties to autism. They came up with more than a hundred matches, reinforcing Herbert's belief that such chemicals interact with specific genes to make certain children susceptible to autism.

Although some diseases are inherited through a single genetic mutation -- cystic fibrosis and sickle cell anemia are examples -- the classic "one gene, one disease" model doesn't adequately explain the complex interplay between an individual's unique genetic code and his or her personal history of environmental exposures. That fragile web of interactions, when pulled out of alignment, is probably what causes many chronic diseases: cancer, obesity, asthma, heart disease, autism, and Alzheimer's, to name just a few. To unravel the underlying biological mechanisms of these seemingly intractable ailments requires that scientists understand the precise molecular dialogue that occurs between our genes and the environment -- where we live and work, what we eat, drink, breathe, and put on our skin. Herbert's literature scan was a nod in this direction, but actually teasing out the answers in a laboratory has been well beyond her or anyone else's reach -- until now.

Consider for a moment that humans have some 30,000 genes, which interact in any number of ways with one or more of the 85,000 synthetic, commercially produced chemicals, as well as heavy metals, foods, drugs, myriad pollutants in the air and water, and anything else our bodies absorb from the environment. The completion of the Human Genome Project in 2003 armed scientists with a basic road map of every gene in the human body, allowing them to probe more deeply into the ways our DNA controls who we are and why we get sick, in part by broadening our understanding of how genes respond to external factors. In the years leading up to the project's completion, scientists began developing powerful new tools for studying our genes. One is something called a gene chip, or DNA microarray, which came about through the marriage of molecular biology and computer science. The earliest prototype was devised about a decade ago; since then these tiny devices, as well as other molecular investigative tools, have grown exponentially in their sophistication, pushing medical science toward a new frontier.

Gene chips are small, often no larger than your typical domino or glass laboratory slide, yet they can hold many thousands of genes at a time. Human genes are synthesized and bound to the surface of the chip such that a single copy of each gene -- up to every gene in an organism's entire genome -- is affixed in a grid pattern. The DNA microarray allows scientists to take a molecular snapshot of the

activity of every gene in a cell at a given moment in time.

The process works this way: Every cell in your body contains the same DNA, but DNA activity -- or expression -- is different in a liver cell, say, than it is in a lung, brain, or immune cell. Suppose a scientist wishes to analyze the effect of a particular pesticide on gene activity in liver cells. (This makes sense, since it is the liver that processes and purges many toxins from the body.) A researcher would first expose a liver cell culture in a test tube to a precise dose of the chemical. A gene's activity is observed through the action of its RNA, molecules that convey the chemical messages issued by DNA. RNA is extracted from the test tube, suspended in a solution, then poured over the gene chip. Any given RNA molecule will latch on only to the specific gene that generated it. The genes on the chip with the most RNA stuck to them are the ones that were most active in the liver cells, or most "highly expressed." The genes that don't have any RNA stuck to them are said to be "turned off" in those cells. Scientists use the microarray to compare the exposed cells to non-exposed, control cells (see sidebar). Those genes that show activity in the exposed cells but not in the control cells, or vice versa, are the ones that may have been most affected by the pesticide exposure.

DNA microarrays open the door to an entirely new way of safety-testing synthetic chemicals: Each chemical alters the pattern of gene activity in specific ways, and thus possesses a unique genetic fingerprint. If a chemical's genetic fingerprint closely matches that of another substance already known to be toxic, there is good reason to suspect that that chemical can also do us harm. Ultimately, government agencies charged with regulating chemicals and protecting our health could use this method, one aspect of a field called toxicogenomics, to wade through the thousands of untested or inadequately studied chemicals that circulate in our environment. In other words, these agencies could make our world safer by identifying -- and, one hopes, banning -- hazardous substances.

For such a young field, toxicogenomics has already begun to challenge some fundamental assumptions about the origins of disease and the mechanisms through which chemicals and various environmental exposures affect our bodies. Consider the case of mercury, which was identified as poisonous many centuries ago. Its potential to wreak havoc on the human nervous system was most tragically demonstrated in the mass poisoning of the Japanese fishing village of Minamata in the 1950s. More recently, scientists have begun to amass evidence suggesting that mercury also harms the immune system. In 2001, Jennifer Sass, a neurotoxicologist and senior scientist at the Natural Resources Defense Council (NRDC), who was then a postdoctoral researcher at the University of Maryland, designed an experiment that included the use of microarrays and other molecular tools to figure out how, exactly, mercury was interfering with both our nervous and immune systems. She grew cells in test tubes -- one set for mouse brain cells, another for mouse liver cells -- and exposed them to various doses of mercury so that she could see which genes were being switched on and off in the presence of the toxic metal. In the brain and the liver cells, she noticed unusual activity in the gene interleukin-6, which both responds to infection and directs the development of neurons.

"We thought we had mercury figured out," says Ellen Silbergeld, a professor of environmental health sciences at Johns Hopkins University, who collaborated with

Sass on the study. Genomic tools may identify effects of other chemicals by allowing scientists to "go fishing," as Silbergeld puts it, for things they didn't know to look for.

The findings of Sass, Silbergeld, and others indicate that mercury might play a role in the development of diseases involving immune system dysfunction. These diseases perhaps include autism -- think of Herbert's patients with their inexplicable collection of infections and allergies -- but also the spate of autoimmune disorders that we can't fully explain, from Graves' disease and rheumatoid arthritis to multiple sclerosis and lupus.

"Do we need to reevaluate our fish advisories?" Silbergeld asks. "Are our regulations actually protecting the most sensitive people?" We target pregnant women and children because we've presumed that mercury's neurotoxic effects are most damaging to those whose brains are still developing. Sass and Silbergeld's findings don't contradict that assumption, but they do suggest that there might be other adults who are far more vulnerable than we'd realized -- who simply can't tolerate the more subtle effect the metal has on their immune system because of a peculiarity in their genetic makeup. Designing fish advisories for those people, whose sensitivities are coded in their DNA, is a challenge we've never tackled before. Translating new findings about how chemicals affect gene activity into something of broader public health value will require that we understand precisely the tiny genetic differences among us that make one person or group of people more vulnerable than others to certain environmental exposures. One way to do that is by slightly modifying the gene chip to allow researchers to scan up to a million common genetic variants -- alternate spellings of genes, so to speak, that differ by just a single letter -- to look for small differences that might make some people more likely to get sick from a toxic exposure. Our attempts to identify those who are most genetically susceptible to developing a particular disease as a result of environmental exposures have already yielded important insights. Patricia Buffler, dean emerita of the School of Public Health at the University of California, Berkeley, has found that children with a certain genetic variant may be susceptible to developing leukemia in high-traffic areas, where they're likely to be exposed to benzene compounds in auto exhaust. Other studies have found that a particular genetic variation in some women who drink chlorinated municipal water leads to an increased likelihood that they'll give birth to underweight babies. Still others have found that a specific version of an immune gene, HLA-DP, renders people vulnerable to the toxic effects of the metal beryllium, which causes a chronic lung condition in the genetically sensitive population. This particular vulnerability raises some sticky workplace issues. Toxic exposure to beryllium occurs almost exclusively in industrial settings where welders and other machinists come in contact with the metal while making defense industry equipment, computers, and other electronics. Should employers test their workers for genetic variants that may put them at risk for developing a disease? Could that information be used to bar someone from a job? Such ethical considerations, and their legal and public policy ramifications, will only multiply as we learn more.

But first, a more fundamental question: Do we even understand what today's chronic diseases are? It is beginning to appear that what we call autism may in fact be many illnesses that we've lumped together because those who are afflicted seem to behave similarly. Doctors base their diagnosis on behavioral symptoms, not on

what caused those symptoms. Some scientists now refer to the condition as "autisms," acknowledging that we've yet to find a single, unifying biological mechanism, despite the identification, in some studies, of a handful of genes that may confer increased vulnerability. But then, genes or environmental exposures that appear to be important causal factors in one study may not show up at all in another. This leaves scientists to wonder whether the problem isn't that the disease is so diverse in its biological origins that only a truly massive study -- involving many thousands of patients -- would have the statistical power to tease apart the various factors involved.

The same difficulty probably holds true for many chronic diseases, explains Linda Greer, a toxicologist and director of the health program at NRDC. "What we think of as asthma, for example, is probably not one condition at all. It's probably many different diseases that today we simply call asthma." Seemingly contradictory explanations for the epidemic could all turn out to be true. Until we are able to sift out what makes one asthmatic child different from the next -- how and why their respective molecular makeups differ -- treatments or preventive measures that work for one child will continue to fail for another.

At the Centers for Disease Control and Prevention, Muin Khoury, the director of the National Office of Public Health Genomics, has created theoretical models to try to figure out just how many different factors may be involved in most chronic diseases. His findings suggest that some combination of 10 to 20 genes plus a similar number of environmental influences could explain most of the complex chronic diseases that plague the population. But to analyze how even a dozen genes interact with a dozen environmental exposures across large populations requires vast studies: immense numbers of people and huge volumes of data -- everything from precise measurements of gene activity inside cells to exact recordkeeping of subject exposure to environmental hazards. Microarrays and other molecular tools now make such studies possible.

In 2003, Columbia University and the Norwegian government together launched the Autism Birth Cohort, one of the largest autism investigations in history. The study will track 100,000 Norwegian mothers and children -- from before birth through age 18 -- collecting clinical data, blood, urine, and other biological materials. It will also collect RNA in order to analyze gene activity. Though initial results are due in 2011, it will take decades to complete this study, and RNA samples will have to be painstakingly archived while the investigators await additional funding. Although the current study is not focused on environmental health per se, researchers plan to measure a variety of biological exposures -- including infection, environmental toxins, and dietary deficiencies -- in each mother and child. As the children grow up, and as some among them develop disease, scientists will have complete records to analyze for key commonalities and differences. Which genes do the sick children have in common? Which chemical exposures were most meaningful? The answers may provide clues not only to the origins of autism, but to many other disorders, from cerebral palsy to asthma to diabetes. Other archiving projects are even more ambitious, such as the U.K. Biobank project, which has begun to enroll 500,000 people to create the world's largest resource for studying the role of the environment and genetics in health and disease.

As vital to our understanding of human disease as such studies may prove to be, a 50-year-old taking part in the U.K. Biobank project isn't likely to reap the rewards. "It will take a long time to make sense of the data," says Paul Nurse, a 2001 Nobel laureate in medicine and the president of Rockefeller University. According to Nurse, it may well be that most of the researchers starting these studies today won't see the final results -- the data will be analyzed by their children. In his estimation, that's all the more reason "to get on with it."

In response to concern that environmental exposures were affecting children's health, the Clinton administration in 2000 launched the National Children's Study, the largest such undertaking in the United States, under the auspices of the National Institutes of Health. The goal was to enroll 100,000 children; a genetic biobanking component has since been added. Investigators have not yet recruited participants, in part because of financial uncertainties. The Bush administration's 2007 budget proposal completely eliminated money for the study, though Congress reinstated funding in February.

The irony is that cutting funding for such projects may be the most expensive option of all. Even if we successfully address campaign-dominating political issues like skyrocketing medical costs and the growing ranks of the uninsured, our failure to consider the fundamental mechanisms of disease -- the interplay between our genes and the environment -- could still bankrupt us, socially if not financially. Until we're able to interrupt the slide toward disease much earlier, based on our developing knowledge of how genes and the environment interact, medicine will remain the practice of "putting people back together after they've been hit by the train," says Wayne Matson, a colleague of Martha Herbert's who studies Huntington's and other neurodegenerative diseases at the Edith Nourse Rogers Memorial Veterans Hospital in Bedford, Massachusetts. "It would be a lot better if we knew how to pull that person off the tracks in the first place."

#### TAGS

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