Toxicology in the Genome

Scientists have found gene expression patterns that help to explain differences in how people react to drugs; why not do the same for industrial toxins? By Sheldon Krimsky

"Have you ever passed a nail salon gasping from the chemicals seeping through the open door, while a dozen women patrons and their handlers are breathing in those same chemicals without a trace of discomfort?"

There was a time shortly before the human genome was sequenced that many believed genetic science was on the cusp of a medical revolution. Our sequenced DNA was thought to hold the key to understanding the onset of disease. Why are some children afflicted with autism? Why do some adults stop producing enough insulin? Why do some otherwise healthy individuals who reach their senior years lose mental functions and memory? Ten years after the human genome was sequenced, biomedical scientists have become more cautious in their optimism about how DNA sequencing will change medicine by revealing the existence of a disease years before its onset or by introducing new therapies with the tools of molecular medicine and stem cells.

The terms "gene-environment interaction" and "epigenetics" are now recognized as the clue to many disease conditions. The switches that turn genes on and off may be more important in understanding clinical pathology than mutations in coding sequences of DNA. These switches, which may stop or modify gene expression, are in the form of protein complexes that overlay the DNA code, such as histones or methyl groups, or the RNA interference molecules that reside in the genome.

On the website of the National Institute of General Medical Sciences we find the following statement: "A good part of who we are is 'written in our genes,' inherited from Mom and Dad. Many traits, like red or brown hair, body shape and even some personality quirks, are passed on from parent to offspring. But genes are not the whole story. Where we live, how much we exercise, what we eat: These and many other environmental factors can all affect how our genes get expressed."

Despite the growing awareness that environmental factors interact with and affect the human genome, most of the research remains focused on the mechanisms operating at the molecular level. Thus, there is much discussion about sequencing the epigenome to gain an understanding of the genetic switches or to probe deeply into non-coding DNA for discovery of RNA sequences that interfere or modulate gene expression.

Meanwhile, we know that around 100,000 people die from adverse drug reactions. Some people are highly sensitive to chemicals in perfumes or outgassing from carpets or plastic. The detoxification mechanisms of people vary widely. Without a sufficient quantity of enzyme production, our bodies cannot break down certain chemicals fast enough before experiencing harm. If we expect to make any major inroads into preventing the many environmentally-induced diseases, each of which may affect a small percentage of the population, then we must use the human genome and the epigenome to acquire an understanding of why some people are more adversely affected by environmental agents. What we need is a massive effort to unravel the "gene-environment" interaction in disease causation. We have over 100,000 chemicals in current industrial use. Many of these chemicals were introduced into commerce without much toxicological evaluation. It takes between 25-50 years to regulate or ban a chemical that has been shown to be harmful to humans. The United States has only banned about a half dozen chemicals over half a century. In part this is because the regulatory system is geared toward industrial interests. The government requires very minimal safety studies to permit a chemical into industrial use, but demands an extraordinary body of replicable scientific studies and cost-benefit analyses before a chemical is removed from the marketplace.

The one area where there have been major contributions in deciphering the gene-environment interaction is in the study of the genetic effects of ionizing radiation. Perhaps radiation effects on health is the low hanging fruit because of the mutations the radiation produces, although low level radiation effects remains highly controversial.

How can we learn what chemicals are adversely affecting the healthy human genome and what chemicals have differential effects on different genomes? How can we detect the detoxification potential of each individual toward a chemical? The

differences in people's ability to detoxify a chemical may be the result of shorter genes coding for the relevant detoxifying enzymes, or the enzyme-producing gene is switched off.

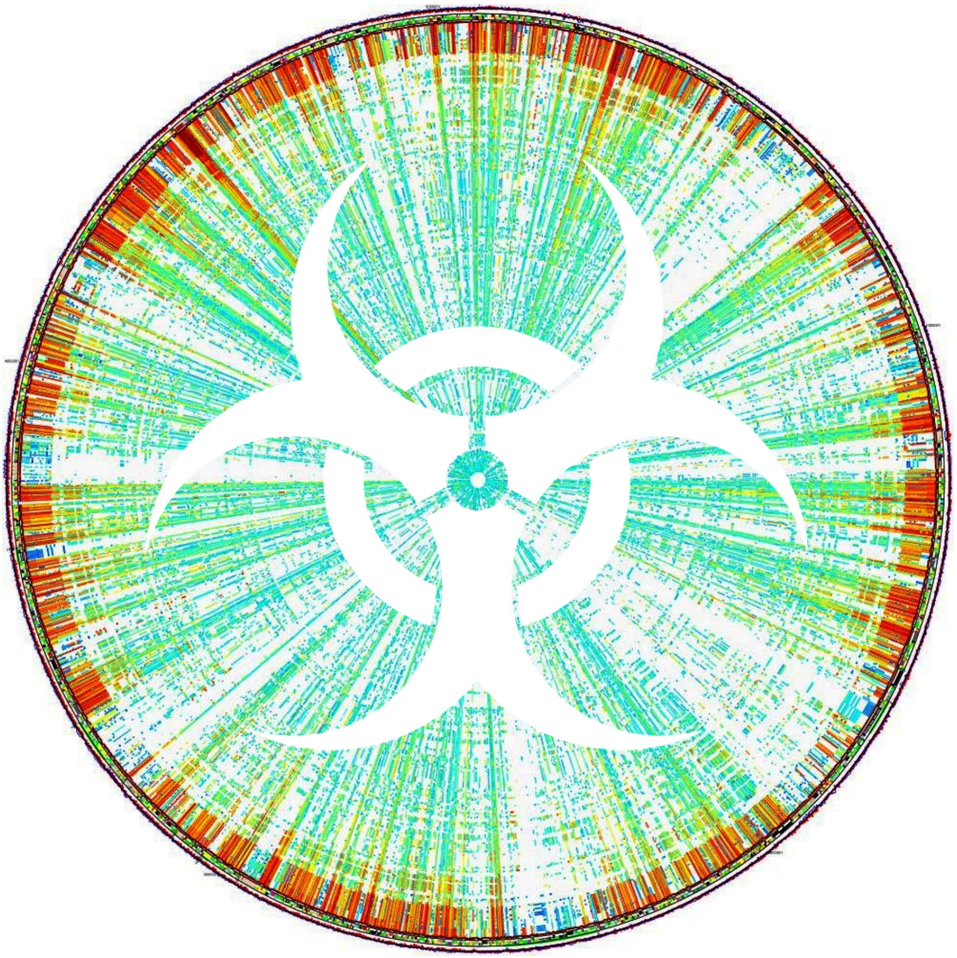
Most of the commercial interest in the sequenced human genome has been focused on risk factors for certain diseases that are read from the individual's DNA. There is nothing in direct-to-consumer testing kits that reveals the cause of any disease other than what is encrypted in the code itself. And there are only a small number of illnesses where there is a one-to-one correlation between having a particular form of a gene and a disease, such as cystic fibrosis, sickle cell anemia and Canavan's disease.

Of course, a massive effort to determine how chemicals interact with the human genome may have unintended consequences. Instead of banning the chemical, it may result in a genetic classification of people—those hypersensitive to chemical X, those with peanut allergies, etc.—putting the onus on them about how to navigate through life. Many people have figured out they are hypersensitive to new carpets, latex or perfumes and learn how to keep away. But if we had a mechanism that showed us these people were not psychologically challenged but rather had a normal genome with less capacity to metabolize chemical toxins, we would have a new regulatory mechanism for removing the chemicals from the environment.

Biomedical scientists have been able to titrate chemotherapy agents to individuals based on genomic information. Gene expression patterns associated with sensitivity and/or resistance to chemotherapy may be used to help provide more effective treatment.

Scientists have used genetic testing to identify patients at high risk of bleeding from the drug warfarin. Two genes account for most of the risk. Recently, genetic variants in the gene encoding Cytochrome P450 enzyme CYP2C9, which metabolizes warfarin, and the Vitamin K epoxide reductase gene (VKORC1), has enabled more accurate dosing that takes account of the genome of an individual. Genotyping variants in genes encoding Cytochrome P450 enzymes (CYP2D6, CYP2C19, and CYP2C9), which metabolize antipsychotic medications, have been used to improve drug response and reduce side-effects. Pain killers like codeine affect people differently. Tests for certain enzymes (P450-2D6) can determine whether someone will be an ultra-rapid metabolizer of codeine, which could induce life-threatening toxicity.

If we can understand through certain enzyme pathways that individuals react differently to drugs and that some of us cannot efficiently metabolize certain chemicals, why couldn't we do the same for industrial toxins within the next 20 years? Once we learn that many people cannot detoxify a chemical that bioaccumulates in their body, it provides new grounds for finding a substitute for that chemical rather than waiting a quarter century to complete hundreds of studies with mixed results.



***Sheldon Krimsky**, PhD, is Chair of the Board of Directors and a founder of the Council for Responsible Genetics. He is a Professor of Urban and Environmental Policy and Planning at Tufts University.*