Epigenetics and disease: No easy answers

The link between DNA and disease is by now obvious. But it's also obscure. A zillion moving parts go into disorders like cancer and Alzheimer's disease, and only a comparative few are known for sure.

Researchers believe something called the Epigenome Roadmap a cascade of two dozen papers published last year is gradually changing that. The Roadmap is a catalog of the millions of epigenetic switches that control gene action. It's pretty clear that epigenetics is key to really understanding disease as well as normal human traits. Eventually, that is; nailing down those connections is going to take time.

For one thing, disease mutations and other DNA variations, it turns out, are hardly ever where you would expect them to be: in genes that make the proteins that run the show. Ninety percent of disease-related mutations are in the regions of DNA that lie outside those genes, the regulatory regions that control protein-coding gene action. The working hypothesis is that variation in disease susceptibility–or any other trait–depends mostly on subtle differences in the expression of protein-coding genes, which is under epigenetic control.

Mutations associated with Alzheimer's disease, in a surprising and immediately practical finding among those new papers, turned out to be active not so much in brain cells, where you might expect activity. Instead, they altered epigenomic activity in cells of the immune system.

"Our results suggest that repression of neural pathways does not represent genetic predisposition, even though it is a hallmark of Alzheimer's," senior author Li-Huei Tsai of MIT said in a statement. "Instead, it may occur as a consequence of environmental factors and aging, and result from interactions with the altered immune pathways."

This was work done in mice, so we don't know for sure that it applies to humans. But it gives scientists a hopeful new target for figuring out how to prevent and treat this devastating disease, which every day grows more urgent in our aging populations.

Epigenome researchers also reported advances in asthma and allergy research. They identified more than two dozen genes that regulate IgE, the antibody that provokes allergic reactions. In some people, epigenetic mechanisms interfere with shutting down those genes at the right time. The result is the overproduction of IgE, which triggers asthma attacks. Miriam Moffatt, a senior investigator on the project, said in a statement, "The genes we identified represent new potential drug targets for allergic diseases as well as biomarkers that may predict which patients will respond to existing expensive therapies."

What is the epigenome?

But what is the epigenome anyway? The epigenome is the reason that all your body cells, which started out identical when your mother's fertilized egg began splitting into daughter cells, were able to turn themselves into specialists: brain, liver, heart, skin, etc. The epigenome is the reason identical twins,

which have identical genomes, are always different from each other (sometimes very different), grow more different as they age, and often have different diseases. The epigenome is a reason that we humans are utterly unlike chimpanzees, even though our DNA differs very little.

The simplest way to think about the epigenome is that it's all about the biochemical switches that turn genes on and off in particular cells at particular times of life. Epigenetics seeks to explain how the environment—what you eat, how your parents treated you, all of your life events and possibly even your ancestors' life events—has made you into you. Those biochemical switches are how nurture shapes nature.

Explaining the relationship of the genome and the epigenome at a press conference announcing the papers (all published in *Nature* and associated journals), study coauthor Manolis Kellis of MIT said, "All our cells have a copy of the same book [the genome], but they're all reading different chapters, bookmarking different pages, and highlighting different paragraphs and words."

The bookmarks Kellis spoke of are biochemical mechanisms that change the behavior of genetic material without changing any DNA sequences. The two best known and most studied of these mechanisms are DNA methylation and histone modification.

Histones are the proteins DNA is wrapped tightly around. Histone modifications usually involve attachment of an acetyl group (CH3CO.) Acetylation helps tightly coiled DNA unwind a bit, making genes easier to get to and turn on.

In methylation, methyl groups (CH3) stick to DNA and usually suppress gene expression. That's what was going on in the asthma study described above. Among asthma patients, the researchers found low methylation at 36 places in 34 genes. Low methylation meant the genes didn't get turned off. Hence overproduction of IgE antibodies that trigger asthma attacks.

For the National Institutes of Health's Roadmap Epigenomics Program, hundreds of scientists around the world studied epigenetic events in more than 100 types of body tissues from healthy adults, fetal cells, and stem cells, assembling reference epigenomes for each one. These epigenetic patterns characteristic of each tissue can be compared to other samples, including tissue from people with dozens of diseases. Examples: type 1 diabetes, Crohn's disease, high blood pressure, inflammatory bowel disease and Alzheimer's disease. Comparisons permit scientists to see epigenetic abnormalities in particular cell types.

Naysaying and cautions

Not everybody thinks the epigenome project is awesome. An anonymous scientist blogging at Homolog.us – Bioinformatics complained, "Nothing managed to derail this expensive boondoggle over the last four years, including powerful critics of the scientific principle behind it, fraud allegation against the leader, public humiliation of its sister project ENCODE, NIH cost-cutting and protest of the scientists, and so on."

As for the idea that diet, toxic exposures, parental behavior, and other lifestyle factors determine health, "not a single claim is backed by any science. We have gone through many of the relevant studies, and they were often based on poor-quality association studies of 30 or 40 persons and no further study of

causal mechanism."

That fulmination is a minority view, and it's not accurate to claim that all epigenetics studies are weak. But it is certainly the case that, despite the hoopla surrounding these papers, realizing gains to human health from research on the epigenome is a long way away. These studies need to be replicated and, in the case of studies done on animals, replicated in humans. But to date, epigenetics findings have been difficult to repeat.

Also, epigenetic activity varies throughout the lifespan, and so epigenetic investigations tied to the aging process will be required. Studies of 1000 additional cell type epigenomes are being planned.

Kellis, a leader of the Epigenome Roadmap Consortium roundly savaged at Homolog.us, certainly, can be counted a fan of epigenome research. But even his forecast, which is presumably optimistic, predicts that figuring out how one person's epigenome differs from another will take the next decade.

Tabitha M. Powledge is a long-time science journalist and a contributing columnist for the Genetic Literacy Project. She also writes On Science Blogs for the PLOS Blogs Network. Follow her @tamfecit.