New tool pinpoints genetic sources of disease

20 March 2014

Many diseases have their origins in either the genome or in reversible chemical changes to DNA known as the epigenome. Now, results of a new study from Johns Hopkins scientists show a connection between these two "maps." The findings, reported March 20 on the website of the *American Journal of Human Genetics*, could help disease trackers find patterns in those overlays that could offer clues to the causes of and possible treatments for complex genetic conditions, including many cancers and metabolic disorders.

"By showing the connections between genetic variants and epigenetic information, we're providing epidemiologists with a road map," says Andy Feinberg, M.D., M.P.H., a Gilman Scholar, the King Fahd Professor of Medicine and the director of the Center for Epigenetics in the Institute for Basic Biomedical Sciences at the Johns Hopkins University School of Medicine. "Epigenetic tags show how disease-causing genetic variants might affect distant genes that in turn contribute to the disease."

Feinberg says it has long been known that individual genetic variants in sections of DNA that don't contain blueprints for proteins (once thought of as "junk DNA") seem to alter the quantity of proteins produced far afield. That phenomenon has made it very hard for researchers to pinpoint the source of some genetic diseases or targets for their treatment. This study, Feinberg says, shows that these genetic variants may be acting on distant protein-forming genes by influencing epigenetic tags, or chemical add-ons, atop the DNA.

Feinberg; co-leader Dani Fallin, Ph.D., professor and chair of the Department of Mental Health at the Bloomberg School of Public Health and director of the Wendy Klag Center for Autism and Developmental Disabilities; and their team analyzed genetic data from hundreds of healthy participants in three studies to first figure out what a normal epigenetic pattern looks like. Although it's now common to compare the genomes of healthy and sick populations to identify predispositions for diseases, it has not been possible to compare epigenomes this way. The researchers zoomed in on one type of epigenetic change, the attachment of a chemical tag called a methyl group to a particular site on DNA. Known as methylation, these tags affect whether genes produce any protein, and if so, how much.

The team then looked for the relationship between the resulting epigenetic data and genetic data. Human genetic code is marked by telltale blocks of DNA that children tend to inherit from their parents in unbroken chunks called haplotypes. One of these blocks is often fingered as a suspect when a genetic disease arises. However, since the blocks are comprised of hundreds of thousands of "letters" of DNA code, researchers are not often able to identify the culprit mutation, or the protein-forming genes it affects, which may lie somewhere else in the block.

Epigenetic signatures like methylation patterns also occur in blocks, which the team dubbed "GeMes," for methylation blocks controlled by genes. The researchers found that the GeMes overlapped with the long genetic blocks but were much shorter.

That led them to suspect that the protein-coding genes turned on or off by those tags must be at the root of the disease associated with a particular genetic variant found elsewhere in the block.

"Previously, people could not pinpoint the variants within a long stretch of DNA that were responsible for the disease," says Yun Liu, Ph.D., a postdoctoral fellow in Feinberg's laboratory. "But now, by detecting just one variation in DNA methylation, or one GeMe, a researcher will know that one or more of the few hundred methylated nucleotides are possibly causing the disease."

"These corresponding genetic and epigenetic maps provide new insights about the architecture of the genome and its regulatory epigenetic marks. This can inform the integration of multiple types of data in future large-scale epidemiologic studies," says Fallin.

Feinberg says he hopes that researchers will see these findings as a reason to add epigenetic analyses to ongoing genetic analyses of disease. His group's next step, he says, will be to look for GeMes associated with specific diseases, such as Crohn's and cirrhosis, in which researchers have struggled to isolate the problematic part of the genetic code. "Researchers—ourselves included—can use this information to see if the implicated gene is turned on or off in patients compared to healthy people," Feinberg says.

Provided by Johns Hopkins University School of Medicine