SCIENCE LIFE

University of Chicago Medical Center: A blog of news and ideas in biomedicine

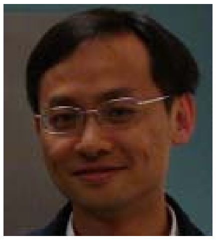
Nature Takes One Back from Nurture

Posted by Rob Mitchum at 8:36 am CT on March 17, 2010

Genetically identical mice with different DNA Methylation produce different tail types (photograph courtesy of Emma Whitelaw, U. of Sydney, Australia / Wikimedia Commons).

Ah, nature and nurture, those eternal enemies. What once used to be the domain of philosophy and English classes has migrated over the past century to the sphere of science, culminating in the completion of The Human Genome Project in 2003. But far from settling this age-old battle, the HGP may have reinvigorated it. Now that scientists know the roughly 24,000 genes that code for proteins in the human genome, they also know that those genes alone cannot explain the complexity of the human body. Many are now looking for the missing parts of the story in regulatory sequences hidden in "non-coding" DNA, but others are looking at a concept, called epigenetics, where nurture/environmental factors have a chance to make a comeback.

Epigenetics - "upon" genetics, if you're into word dissection - is the modification of genes without changing their DNA sequence. There are several different epigenetic mechanisms that can modify a gene's expression, many of which are too complex to tackle in one article. But one epigenetic process is relatively simple at heart - DNA methylation, where the addition of a methyl group to the nucleotide cytosine can effectively silence genes. Those methylated genes can then be handed down to offspring cells or offspring people, a form of non-genetic heritability sometimes known as "cell memory" or "genetic imprinting." DNA methylation also creates a space for environmental factors, which could presumably change the methylation of genes during a person's life and thus have dramatic effects upon gene expression.



But is DNA methylation purely a tool for nurture to scramble nature? Not so fast, says Chunyu Liu, Ph.D. (left), Assistant Professor of Psychiatry and Behavioral Neuroscience at the University of Chicago Medical Center. In a paper published last week in the American Journal of Human Genetics, Liu and colleagues discovered that, for some genes, DNA methylation is under genetic control - that is, genes control the methylation of other genes, and thus their expression.

"Previously, we thought that genetics and epigenetics were two separate things," Liu said. "When you talk about epigenetics, people think it's more environmental. Basically, this is the first time we go deep into the genetic components of DNA methylation. I think it's an important bridge."

The secret to finding the genes pulling the strings of epigenetics was to think about DNA methylation in a different way: not as a process, but as a genetic trait. Quantitative traits are characteristics determined by multiple genes producing a spectrum of outcomes, as in height or blood pressure. These are all complex traits that are administered by multiple genes, but genetic analysis methods can be used to find particular stretches of DNA important for determining the ultimate outcome.

Using human brain samples from people with psychiatric disorders and normal controls, Liu and his colleagues found that there was indeed high variability of DNA methylation between individuals. That allowed the researchers to treat the methylation state of specific genes as a quantitative trait - in different people, a particular gene could be methylated a lot, a little, or somewhere in between. Comparing that methylation state to sequence variations located elsewhere in the person's DNA revealed segments that appear to control methylation state, some very far away in genetic distance from the gene being methylated. That demonstrates genetic control of epigenetics, but leaves open the question of how exactly the control is taking place.

"This is just the first step, it's just the mapping," Liu said. "Right now, the only thing we can see is that there's a strong genetic component inside. We don't know the detail of the machinery. There's still lots and lots of mystery."

Mysterious, but still consequential. The methylated genes that Liu and his team studied can have dramatic effects on a person. One gene, called IRF6, is thought to be involved in the birth defect of a cleft palate, and mice with the gene deleted show abnormal skin, limb and head development. Silencing the gene with methylation at a key point in a person's growth could have dramatic medical consequences.

Under healthier circumstances, the genetic control of DNA methylation can make sure that the right genes are turned on or off at the right time, leading to the intricate construction of the human body. But don't count out nurture yet; Liu said that he doesn't think all DNA methylation is so tightly scripted, and that there remains room for the environment to exert an influence on other important genes.

"You can imagine it's like a spectrum," Liu said. "Some genes have strong genetic programming inside so that at a particular stage their methylation is strictly genetically determined. Some other genes are more responsive to the environment - they'll maybe have half genetic component, half environmental factors [determining methylation]. And there may be some others that are completely responsive to the environment."

"Whenever we talk about epigenetics, we need to think about how much contribution comes from the genetic part or the environment part. That's the major thing we should get out of this paper."

See**:** Zhang D, Cheng, L, Badner J, Chen C, Chen Q, Luo W, Craig D, Redman M, Gershon E, & Liu C. Genetic Control of Individual Differences in Gene-Specific Methylation in Human Brain *The American Journal of Human Genetics, 86* (3), 411-419, 2010.

To see a copy of this article, place this link in your browser:

http://linkinghub.elsevier.com/retrieve/pii/S000292971000087X

For more on research in Psychiatry and Other Fields at the University of Chicago Medical Center, please visit: http://sciencelife.uchospitals.edu