

Using DNA methylation to examine epigenetic changes

By Robin Arnette

Before the advent of epigenetics, the study of heritable changes that don't alter DNA sequence, scientists wondered how genetically identical organisms could display different physical characteristics. It turns out that environmental exposures, such as cigarette smoke, pollution, or even nutritional intake, place chemical tags on DNA that alter gene function. Among the best studied DNA tags is the addition of a methyl group, or methylation.

One researcher who is studying the effects of DNA methylation on gene function is Cathrine Hoyo, Ph.D., associate professor and chief of the Division of Clinical Epidemiology in the Department of Obstetrics and Gynecology at Duke University School of Medicine. She came to the Institute Nov. 18 to present "Testing the Developmental Origins of Adult Diseases Hypothesis: The Durham Newborn Epigenetics Study," as part of the Keystone Science Lecture Seminar Series. Cindy Lawler, Ph.D., branch chief of the Genes, Environment, and Health Branch in the NIEHS Division of Extramural Research and Training, hosted the talk.

Gene inactivation is necessary for normal development

Hoyo

(<http://obgyn.duke.edu/faculty/details/0295388>)

studies insulin-like growth factor 2 (IGF2), a gene required for proper embryonic and fetal growth. Unlike the majority of human genes, IGF2 undergoes an essential physiological process called imprinting, in which one allele, or copy of the gene, is epigenetically silenced, usually through methylation.

In designing her experiments, Hoyo theorized that since the working copy of IGF2 should not be methylated, and the inactive copy should be 100 percent methylated, she should be able to detect any measurable deviation in IGF2 methylation levels in response to environmental stress.

"Previous research has shown that children born to mothers who smoked during pregnancy exhibit lower birth weights," Hoyo said, "so we wanted to see if we could do a study looking for epigenetic changes using DNA methylation."

Hoyo and her collaborators not only wanted to examine DNA methylation in response to cigarette smoke, but also other environmental exposures, such as psychotropic drugs, folic acid, and organic and inorganic compounds. To measure human exposures, as early as they possibly could, the team focused on the prenatal environment.

The Newborn Epigenetics Study

The Newborn Epigenetics Study (NEST)

(<http://sites.duke.edu/nest/>)

was made up of two cohorts of pregnant women - one with 1,000 participants and another with 2,500. The research team isolated DNA from 2,300 samples of umbilical cord blood at birth and analyzed IGF2 methylation patterns.

Among women who smoked during pregnancy, Hoyo saw significant differences in IGF2 DNA methylation levels that were also accompanied by slight gene expression differences. She also saw an association between lower infant IGF2 DNA methylation born to women who had taken folic acid before and during pregnancy, consistent with a threshold effect.

Further analysis of circulating maternal folate revealed a similar pattern of association between folate levels and DNA methylation at multiple differentially methylated regions, including IGF2 regulatory sequences.

"Those that had moderate amounts of folate had a lower DNA methylation profile compared to those with the lowest levels of folate," Hoyo said.

By following the children over several years, Hoyo will be able to determine if these differences in methylation, which are driven by *in utero* exposures, can be evaluated in relation to common chronic diseases including autism. Lawler, who oversees extramural research involving autism, believes the work has great promise for helping determine whether altered DNA methylation that may occur as a result of environmental exposures contributes to neurodevelopmental conditions, such as



One year after gathering samples from newborns in the study, Hoyo and her team members obtained the infants' height and weight, new diagnoses through medical records, and updated contact information. They are currently doing a 3-5 year update, and will do another when the children reach age 7. (Photo courtesy of Steve McCaw)

autism spectrum disorders.

"There is a growing body of scientific literature that suggests improper methylation could be playing a role in the expression of genes vital to normal brain development," Lawler said. "Hoyo's analysis may shed new light on a possible link."

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