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By SHARON BEGLEY

Chubby Blonde? Slim and Dark? Lab Mice Take After Mom's Diet

The baby mice looked as different as night and day.

Those in one litter were dirty blondes, while those in the other were, well, mousy brown. Yet the mice's genes for coat color were identical, down to the last A, T, C and G that make up the twisting strands of DNA.

The reason some animals were yellow and some were brown lay deep in their fetal past, biologists at Duke University Medical Center, Durham, N.C., reported this month: Some of the mothers consumed supplements high in very simple molecular compounds that zip around the genome turning off genes. One silenced gene was for yellow fur; when it is turned off, the mouse's fur color defaults to brown. For the mice, it wasn't just that "you are what you eat," but that you are what your mother ate, too.

The ink on the final draft of the complete human genome sequence is hardly dry, but scientists are seeing more and more instances in which the sequence of those celebrated A's, T's, C's and G's constituting the genome is only part of the story.

Biologists have long known that having a particular gene is no guarantee you will express the associated trait, any more than having a collection of CDs will fill your home with music. Like CDs, genes are silent unless they are activated. Because activating and silencing doesn't alter the sequence of the gene, such changes are called epigenetic.

"Epigenetics is to genetics as the dark matter in the universe is to the stars; we know it's important, but it's difficult to see," says geneticist Andrew Feinberg of Johns Hopkins University School of Medicine, Baltimore. "What we're thinking now is that, in addition to genetic variation, there may be epigenetic variation that is very important in human disease."

Epigenetic variation may explain such long-running mysteries as why identical twins are, in many ways, no such thing, including whether they have such supposedly genetic diseases as schizophrenia and cancer. Epigenetics may also help explain how the seeds of many adult diseases may be planted during fetal life. Studies suggest that the nutrition a fetus receives -- as indicated by birth weight -- might influence the risk of adult-onset diabetes, heart disease, hypertension and some cancers. The basis for such "fetal programming" has been largely an enigma, but epigenetics may be key.

There is no doubt that, in the case of the brown or yellow mice, the "you are what your mom ate" phenomenon reflects just such epigenetic influences. The Duke scientists fed female mice dietary

supplements of vitamin B12, folic acid, betaine and choline just before and throughout their pregnancy. Offspring of mice eating a regular diet had yellowish fur; pups of the supplemented mothers, although genetically identical to the yellow mice, were brown.

When they grew up, the brown mice also had much lower rates of obesity, diabetes and cancer, Robert Waterland and Randy Jirtle of Duke's Department of Radiation Oncology report in the journal Molecular and Cellular Biology. Whatever the extra nutrients did to the fetal mice's genes didn't stop with fur color.

Actually, that "whatever" isn't quite fair. The Duke team knows exactly what the supplements did. All of the compounds contain a simple molecule called a methyl group, which is one carbon and three hydrogen atoms. For a little guy, methyl wields a big stick: It can turn genes off.

That's what happened in the brown mice. Methyl from the supplements switched off a gene called Agouti, which both gives a mouse a yellowish coat and makes it obese. The yellowish babies weren't suffering from any nutritional deficiency; it's just that their Agouti gene was still activated. "Nutritional supplementation to the mother can permanently alter gene expression in her offspring without mutating the genes themselves at all," says Prof. Jirtle.

That's the very essence of epigenetics.

The reason the Agouti gene was silenced is that it had the misfortune to lie next to an interloper. Mammalian genomes are riddled with bits of DNA that leap around like so many jumping beans. Called transposons, they sometimes wind up beside the on/off switch for an important gene, and are sitting ducks for those gene-silencing methyl groups. In the offspring of mouse moms eating methyl-rich dietary supplements, just such a jumping gene was silenced, with the result that the Agouti gene it had snuggled up to was also struck dumb.

This isn't just about yellow and brown mice. "About 40% of the human genome is transposons," notes Prof. Jirtle.

That means an awful lot of human genes could be targets of methylation, and so silenced. Whether that is good or bad depends on what the gene does. Silencing a gene that raises the risk of schizophrenia would be welcome. Silencing a tumor-suppressor gene wouldn't be. What's clear, he adds, is that "we, too, have genes -- including those influencing susceptibility to cancer, obesity and diabetes -- that can be turned off or on by epigenetic factors triggered by early nutrition and exposure to chemical agents."

Next week: How epigenetics might explain certain puzzles from cancer to birth defects.

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By SHARON BEGLEY

Diet During Pregnancy May Have Effects Lasting Into Adulthood

As mysteries go, these don't seem to have much in common: A child born underweight has a higher than normal risk of developing heart disease, diabetes, obesity and hypertension as an adult.

One identical twin develops schizophrenia, which studies of families show is a genetic disease, but the other twin is spared.

Last week's column[1] looked at scientists' growing realization that, when it comes to important changes in the genome -- if I may corrupt an old political mantra -- "It's not just the sequence, stupid."

Mice with identical genes for fur color can be brownish or yellow, depending on whether their gene for fur color has been silenced by what their mother ate during pregnancy. It's beginning to look as if such "epigenetic" changes, defined as those having no effect on the sequence of molecules that make up a genome, may be major players in determining traits and disease risk.

"The completion of the human genome project is a monumental event, but there's still an enormous amount that we have not yet fleshed out," says psychiatrist James Potash of Johns Hopkins University School of Medicine, Baltimore. "Epigenetic variation is one."

Take the enigma of fetal programming, in which nutrition during gestation seems to affect the risk of disease decades later. At a June conference on the subject, attended by some 700 scientists, "What came shining through is that birth weight affects the risk of diabetes, coronary heart disease, obesity, hypertension and breast or prostate cancers," says David Barker of England's University of Southampton. Scrawny newborns, in general, grow up to have a higher incidence of the first four; chubby ones, a higher risk of the latter.

At first, scientists thought the reason was physiology, not genetics. For example, newborns who are small for their length probably have fewer kidney cells than they should. Since the kidneys regulate blood pressure, undersized kidneys can increase later risk of hypertension and thus heart disease, explains Dr. Barker.

But fetal programming "almost certainly" reflects epigenetic changes, too, says Craig Cooney of the University of Arkansas for Medical Sciences. That's because, much as in the mice whose color reflects what mom ate while pregnant, nutrients reaching the human fetus can include more or fewer of the molecules that silence or activate genes. Maybe too few nutrients during gestation might mean not enough of the molecules that silence heart-disease-causing genes.

"The nutrition an embryo receives at crucial stages of development can have important and lasting effects on the expression of various genes, including those involved in health and disease," says Randy Jirtle of Duke University Medical Center, Durham, N.C.

One target of such silencing must have Gregor Mendel turning over in his grave. The Austrian monk, regarded as the founder of genetics, concluded that which parent a gene comes from is irrelevant. True, we carry two copies of every gene (except those on the Y chromosome), one from mom and one from dad. But dozens of genes in sperm or ova are tagged with the biochemical equivalent of "don't mind me." Throughout life, those genes are silenced, or "imprinted." If mom's gene is imprinted, only dad's counts; if dad's is imprinted, only mom's counts.

The gene sequence hasn't changed, so imprinting is epigenetic -- and something you don't want to mess up. When the gene for insulin-like growth factor 2 (IGF2) loses its imprinting, for instance, the once-silenced copy is activated, loosing a flood of growth factor that promotes childhood and adult cancers. Yet if you were to sequence that IGF2 gene, it would look just fine.

Such imprinting mistakes may be affecting some test-tube babies. The incidence of a rare genetic disease called Beckwith-Wiedemann syndrome was six times as high as in children conceived the traditional way, according to a study published in January. This syndrome occurs when IGF2 loses its "keep quiet" marker.

"There is reason to believe, from animal studies, that assisted-reproductive technology can lead to more frequent imprinting errors," says Hopkins geneticist Andrew Feinberg. One suspect: the broth in which ova and embryos grow before being implanted in the mother's womb. It may somehow unsilence imprinted genes.

Epigenetics might also solve the puzzle of identical twins who do not have the same "genetic" diseases, especially psychiatric ones. "You wonder if the difference might be that something causes a gene related to mental illness to be silenced in one twin but not the other," says Dr. Potash.

In the old joke, a drunk searches for his lost keys under a streetlight, not because he dropped them there, but because the light is good. The search for genetic variants -- differences in DNA sequences -- underlying complex diseases is starting to look like that. Sequence variants are easy to find; the light's good there, so scientists have found more than a million sequence variants. But they don't correspond too well with genetically based complex diseases. No wonder the spotlight is turning from genetics to epigenetics, the pattern of gene silencing and activation.

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