

Recent discoveries have shed light on how genes alternate between silent and active states. These activity patterns appear to be susceptible to environmental influences, with serious health consequences that stretch across generations.



Epigenetics flipping the genetic “switch”

Epigenetics – What you need to know:

- Genes are specific segments of DNA that contain the instructions for creating proteins.
- Genes can switch between active (directing protein production) or silent (no protein produced) phases.
- Patterns of activation and silencing, known as the epigenome, exist across all the genes in a cell. The study of these patterns is called epigenetics.
- Changes in the epigenome do not change a gene’s sequence, but rather its activity status.
- The environment can alter the epigenome, changing the activity level of genes. These changes may raise or lower the risk for developing diseases like cancer, obesity and diabetes.
- Some environmental factors, such as diet, not only change an individual’s epigenome, but appear to influence the epigenome of future generations.
- The environmental triggers that alter the epigenome and lead to disease are only beginning to be discovered.

Activating genes to begin the protein-making process is a key area of study in genetics and biotechnology. By identifying the signals that turn genes “on” and “off”, investigators hope to understand not only gene function under normal conditions, but also how improper on/off signaling may lead to disorders such as cancer, diabetes, heart disease and obesity.

To illustrate the importance of gene activity, consider another set of “twins” – in this case two laboratory mice. At birth, these twins, while genetically identical, look nothing alike. One has the brown-colored fur typically associated with mice while the other has yellow fur. As the yellow mouse, also called an “agouti mouse” grows to adulthood, it becomes obese, often developing diabetes and various types of tumors. The agouti gene responsible for these differences produces a protein that regulates a number of other genes. Typically, the agouti gene makes this regulatory protein only briefly during mouse development. This quick period where the agouti gene is “on” results in the brown coat color. If the agouti gene is always “on” however, the other genes are continually activated. Consequently, the mice develop yellow fur, obesity and tumors.

Amazingly, the difference between the healthy brown mouse and its overweight yellow twin is not a change in the DNA sequence of the agouti gene. Instead, the difference stems from a tiny molecular tag made of carbon and hydrogen. In the healthy mice, this tag, called a methyl group, binds to the agouti gene, silencing it during the majority of development (figure 1). No methyl groups are present at the agouti gene of the yellow

Identical twins (who share the same genetic information) are exactly alike – or are they? While they generally look alike when young, as twins age obvious differences often emerge. The differences may be due to the varied environment of each twin – for example, one may lift weights and become very muscular while the other never exercises and gains weight. Recent advances in the relatively new field of epigenetics suggest an additional role for the environment in health and disease by altering the activity of particular genes.

Want more information:

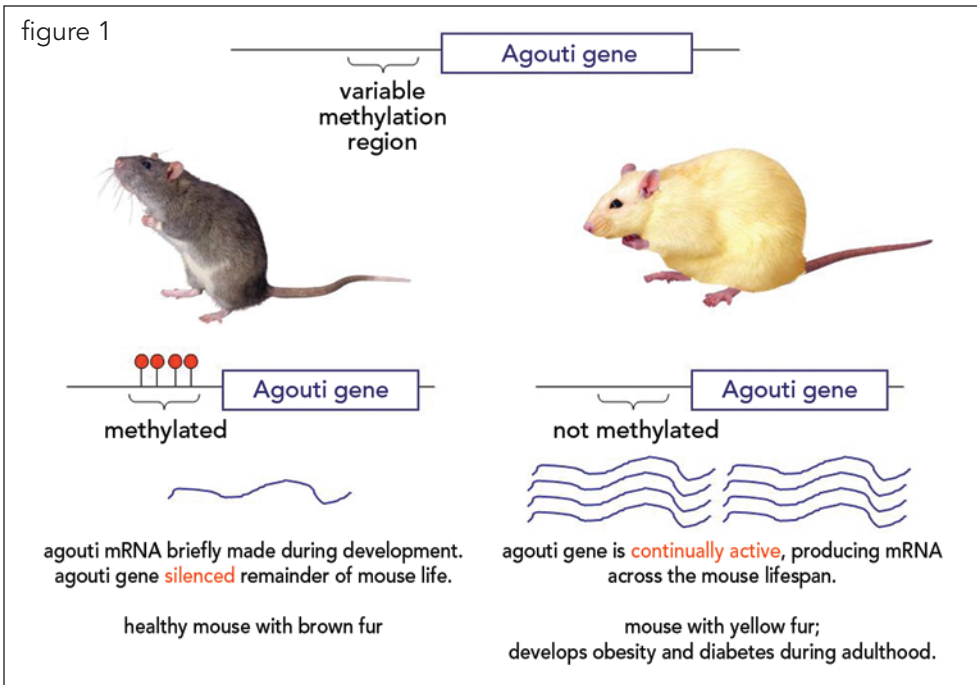
www.pbs.org/wgbh/nova/science-now/3411/02.html

Epigenetics – a recent NOVA program providing an excellent overview of epigenetics and the agouti mouse experiments

discovermagazine.com/2006/nov/cover

DNA Is Not Destiny – an article from the November 11, 2006 issue of Discover magazine that not only discusses the agouti mouse, but a number of epigenetic findings in other organisms, including humans

figure 1



mice and the gene remains active. The cells of living creatures contain millions of methyl tags, working as switchboard operators to control which genes are active and which are silenced.

Methyl groups represent just one of the epigenetic mechanisms cells use to oversee gene activity. These mechanisms account for the very specific patterns of silencing and activation that exist in every cell. For example, skin cells have an activation pattern of genes different from muscle or nerve cells, based on which genes have been silenced. It is this unique combination of genes that are "on" which leads to the individual shape and specific work performed by each cell type.

The epigenetic patterns can be adjusted as cells grow and divide by altering the environment around the cells. If a female yellow mouse is fed a diet rich in methyl groups before and during her pregnancy, she will produce primarily brown-furred newborn mice with a silenced agouti gene (figure 2). The extra methyl groups protect the offspring from obesity and other adult-onset health problems. Surprisingly, this protection extends beyond the offspring and into the next generation of mice (the grandchildren of the initial yellow-furred mother). This finding suggests that epigenetic modifications can be passed across generations – a "memory" of

environmental influence that occurred many years previously.

In humans, there is also evidence of epigenetic modification. A handful of genetic diseases, known as "imprinting disorders" have been linked to improper methylation of key developmental genes. Studies of identical twins suggest that at birth, twins share similar epigenomes. As they age and are exposed to different diets and environments, the twin's epigenomes become markedly different, leading to altered activation and silenc-

ing patterns. Preliminary findings suggest that environment alterations to the epigenome change an individual's risk for disease. Similar to the mouse studies, evidence in humans indicates some epigenetic changes may be "remembered" across multiple generations.

Epigenetics is still in its infancy and a complete understanding of these mechanisms is many years away. Regardless, it appears clear that epigenetic modifications can influence disease susceptibility, potentially lasting through several generations. Future studies will be aimed at identifying all epigenetic modifications, clarifying the environmental triggers that modify the epigenome, and determining which genes are most susceptible to the changes. On the distant horizon, knowledge of the triggers and their genetic targets offers the possibility of early disease diagnosis, as well as the hope that the epigenome may someday be modified to treat the disease once symptoms have appeared, or even prevent its occurrence altogether. ■

– Dr. Neil Lamb

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figure 2

