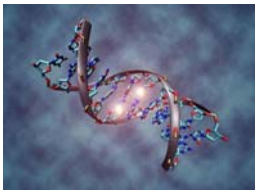
Epigenetics: A Turning Point in Our Understanding of Heredity

By Kara Rogers | January 16, 2012 |



A DNA molecule that is methylated on both strands on the center cytosine. Christoph Bock, Max Planck Institute for Informatics. Image used by permission of its author.

In a study published in late 2011 in *Nature*, Stanford University geneticist Anne Brunet and colleagues described a series of experiments that caused nematodes raised under the same environmental conditions to experience dramatically different lifespans. Some individuals were exceptionally long-lived, and their descendants, through three generations, also enjoyed long lives. Clearly, the longevity advantage was inherited. And yet, the worms, both short- and long-lived, were genetically identical.

This type of finding—an inherited difference that cannot be explained by variations in genes themselves—has become increasingly common, in part because scientists now know that genes are not the only authors of inheritance. There are ghostwriters, too. At first glance, these scribes seem quite ordinary—methyl, acetyl, and phosphoryl groups, clinging to proteins associated with DNA, or sometimes even to DNA itself, looking like freeloaders at best. Their form is far from the elegant tendrils of DNA that make up genes, and they are fleeting, in a sense, erasable, very unlike genes, which have been passed down through generations for millions of years. But they do lurk, and silently, they exert their power, modifying DNA and controlling genes, influencing the chaos of nucleic and amino acids. And it is for this reason that many scientists consider the discovery of these entities in the late 20th century as a turning point in our understanding of heredity, as possibly one of the greatest revolutions in modern biology—the rise of epigenetics.

Epigenetics and the state of chromatin

In Brunet's lab, epigenetic inheritance is a big deal. Their *Nature* paper was the first to describe the phenomenon as it applies to longevity across generations, a breakthrough that emerged out of their quest to better understand the role of chromatin in inheritance.

Chromatin is a compact fiber of proteins and DNA that exists in either a condensed or a relaxed state. It assumes its condensed form during cell division in order to facilitate the splitting of chromosomes for distribution to daughter cells. Segments of the fiber, however, may retain this form when a cell is not dividing, with the result that genes occurring in these segments are fixed in an inactive state. Other stretches of the fiber, on

the other hand, relax and open to allow regulatory proteins to access the DNA and activate genes.

Certain epigenetic modifications, such as the binding of methyl groups to histone proteins, the bobbins around which DNA is wound for chromatin packaging, are responsible for holding the fiber in an open state. But modifications are dynamic. During development, for example, chemical moieties attach to and detach from histones or DNA in an orchestrated fashion, their fluid dance aiding the execution of important functions, such as the establishment of patterns of gene expression for different types of tissues and the silencing of parental genes, a phenomenon known as parental, or genomic, imprinting.

Modifications can also accumulate during an organism's lifetime. Because some of these acquisitions may affect DNA passed through the germline (in eggs and sperm) and may not be beneficial, they are erased at the time of reproduction, and the chromatin is returned to its original state. The process is not faithful, however, so some modifications slip through. In this way, chromatin modifications in parent DNA that are not reprogrammed are transmitted to the next generation.

Epigenetic inheritance of longevity in nematodes

The difference in coat color in these two genetically identical mice is due to epigenetic modifications. Jennifer Cropley, Victor Chang Cardiac Research Institute Image used by permission of its author.

There is increasing evidence that epigenetic modifications are transgenerational (inherited through multiple generations) in a variety of species. Examples include coat color in mammals, eye color in *Drosophila*, symmetry in flowers, and now longevity in *C. elegans*. These findings are exciting and raise intriguing questions about the seemingly limitless nature of epigenetics.

But the work of teasing out epigenetic modifications and their effects is arduous. To uncover the involvement of methylation in nematode longevity, Brunet and colleagues began by assessing the lifespans of *C. elegans* that were deficient in one of three genes, *ash-2*, *wdr-5*, or *set-2*; decreased or absent expression of these genes previously had been found to increase longevity in the species. They then crossed nematodes with genetic deficiencies with nematodes of normal genetic composition, pairings that in typical Mendelian fashion yielded wild-type (genetically normal) individuals, as well as individuals carrying the genetic alterations. Measurements of longevity were recorded for each of these populations and were compared with those of control populations (wild-type nematodes descended from wild-type parents). The findings revealed that the

controls lived an average lifespan, whereas wild-type nematodes genetically identical to the control population but descended from mutant parents lived 20 to 30 percent longer.

Thus, the genetic deficiencies, though not inherited, had effected some type of change that endowed the genetically normal offspring of mutants with the same length lifespan that the mutants themselves experienced. The change, the Stanford team deduced, was methylation.

The proteins encoded by *ash-2, wdr-5* and *set-2* are part of a histone methylation complex known as H3K4me3, which is found across species ranging from yeast to humans. But the mechanisms underlying the inheritance of longevity are not clear. As Brunet explained, "We did not observe a global decrease in H3K4me3 levels in genetically wild-type descendants from mutants that are deficient in H3K4me3. We interpret that as saying there is not a global dearth of H3K4me3 that is inherited epigenetically." Thus, the team's current model is that when the proteins are scarce or absent, H3K4me3 methylation is lost at specific locations in the genome, and longevity-associated modifications in chromatin state, or possibly other types of modifications (e.g., non-coding RNAs), are passed to the next generation.

Transgenerational inheritance of acquired characters in humans

Epigenetics has given life to Lamarckism and the previously discarded idea that characteristics acquired during an individual's life are heritable. In fact, many scientists already have warmed up to this idea. "There seems to be a renewed acceptance for the Lamarckian concept (in limited cases)," Brunet said. "This could change our understanding of inheritance in that it would add another component, probably minor, but present, in addition to Mendelian genetics."

It also adds another layer of significance to our daily lives. A number of environmental factors, from nutrients to temperature to chemicals, are capable of altering gene expression, and those factors that manage to penetrate germline chromatin and escape reprogramming could, in theory, be passed on to our children and possibly our grandchildren.

But while several studies have suggested that transgenerational epigenetic inheritance can occur in humans, actual evidence for it is scant. Among the more convincing cases thus far involves the synthetic estrogen compound diethylstilbestrol (DES), which was used in the mid-20th century to prevent miscarriages in pregnant women. DES, however, dramatically increases the risk of birth defects. It is also associated with an increased risk for vaginal and breast cancers in daughters and an increased risk of ovarian cancer in maternal granddaughters of women exposed to DES during pregnancy. Studies in mice have suggested that neonatal DES exposure causes abnormalities in the methylation of genes involved in uterine development and uterine cancer; in mice these abnormalities were still present two generations down the line, suggesting a transgenerational effect.

Given the elusive nature of inherited epigenetic modifications, it seems that, despite decades of investigation, scientists remain on the brink of understanding. The possibilities, however, seem endless, even with the constraint that, to be inherited, epigenetic modifications must affect gene expression in the germline, a feat that even genetic mutations rarely accomplish. **But with the skyrocketing prevalence of conditions such as obesity, diabetes, and autism, which have no clear genetic etiology in the majority of cases, as Brunet pointed out, "It seems that all complex processes are affected by epigenetics."**

While scientists continue to search for definitive evidence of transgenerational epigenetic inheritance in humans, the implications so far suggest that are our lifestyles and what we eat, drink, and breathe may directly affect the genetic health of our progeny.

 **About the Author:** Kara Rogers is a freelance science writer and the senior editor of biomedical sciences at Encyclopaedia Britannica, Inc. She is the author of Out of Nature: Why Drugs From Plants Matter to the Future of Humanity (University of Arizona Press, 2012), which explores the human relationship with nature and its relevance to plant-based natural products drug discovery and the loss of biodiversity. She holds a Ph.D. in Pharmacology/Toxicology and enjoys reading and writing about all things science. Follow her on Twitter at @karaerogers, and visit her website. Follow on Twitter @karaerogers.

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