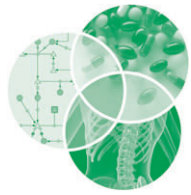
Primer



Behavioral epigenetics

David S. Moore*

Why do we grow up to have the traits we do? Most 20th century scientists answered this question by referring only to our genes and our environments. But recent discoveries in the emerging field of behavioral epigenetics have revealed factors at the interface between genes and environments that also play crucial roles in development. These factors affect how genes work; scientists now know that what matters as much as which genes you *have* (and what environments you encounter) is how your genes are *affected* by their contexts. The discovery that what our genes *do* depends in part on our experiences has shed light on how Nature and Nurture interact at the molecular level inside of our bodies. Data emerging from the world's behavioral epigenetics laboratories support the idea that a person's genes alone cannot determine if, for example, he or she will end up shy, suffering from cardiovascular disease, or extremely smart. Among the environmental factors that can influence genetic activity are parenting styles, diets, and social statuses. In addition to influencing how doctors treat diseases, discoveries about behavioral epigenetics are likely to alter how biologists think about evolution, because some epigenetic effects of experience appear to be transmissible from generation to generation. This domain of research will likely change how we think about the origins of human nature.

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INTRODUCTION

How do we come to have our characteristics, from eye color to height to personality? Although theorists traditionally referred to Nature and Nurture when answering this question—or, more recently, genes and environments—we now know that a third factor, 'epigenetics,' plays a central role in trait development. Serving as the interface between genetic and environmental factors, epigenetic processes illustrate how Nature and Nurture work together in development. The implication of this discovery is that genes cannot have effects that are independent of context. Just as all of our phenotypes depend on our genes for their development, they also depend on non-genetic factors; thus, there really cannot be any traits that are *strictly* genetic, because a gene's context always matters (see Lickliter, Developmental evolution, *WIREs Cogn Sci*, also in the collection How We Develop). Epigenetic processes have been linked to diverse phenomena, including memory and learning, cancer, addiction, diabetes, aging, and the effects of such factors as exercise, nutrition, environmental toxins, and early-life experiences…and this is just a partial list.[1]

DEFINING EPIGENETICS

'Epigenetics' is an old word—Aristotle believed all of our characteristics arise in a process he called 'epigenesis'—and it has had several definitions through the years. In the 1940s, the biologist Conrad Waddington began using the word in a modern way, to refer to how genes interact with their local environments to build organisms.[2] Waddington understood that we each begin life as a fertilized egg, and that as development unfolds, this egg divides into trillions of cells that each contain the same genetic information. Therefore, in order to develop into *different* kinds of cells—blood cells and brain cells and bone cells—there has to be a way for *nongenetic* factors to turn different genes on or off. Although different contemporary theorists define epigenetics in different ways,

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scientists agree that epigenetics is fundamentally about development. And one way in which development can be influenced is via the effects of contextual factors on genetic activity. In fact, genetic activity can be regulated somewhat like a light bulb controlled by a *dimmer* switch: it can be turned off completely, or can be turned on to greater or lesser degrees. And because contexts influence genetic activity by physically attaching various chemicals to our genes, these chemicals are literally 'epi'-genetic: they are '*on*' genes. What has made recent research on epigenetics so exciting is the discovery that the environments in which we develop—how we are nurtured—can influence the epigenetic state of our DNA, and, therefore, who we become.[3]

IT'S NOT JUST ABOUT THE GENES YOU *HAVE*, IT'S ABOUT WHAT YOUR GENES ARE *DOING*

Because of how most parents, teachers, and the media talk about genes, it is easy to imagine that genes are agents that make active decisions about how to build bodies and minds. But the fact is that the DNA that contains our genes is not capable of independent action; if you put a bowl of naked DNA on your desk, it will just sit there, inert (see Ref 4 for additional information). This is why genetic *regulation* is so important. What your genes are induced to *do* by their contexts—which include other genes, of course—is just as important as what genes you *have*; a gene you have inherited from your parents is of no consequence if that gene remains turned off by epigenetic processes, so you might as well not have the gene at all.

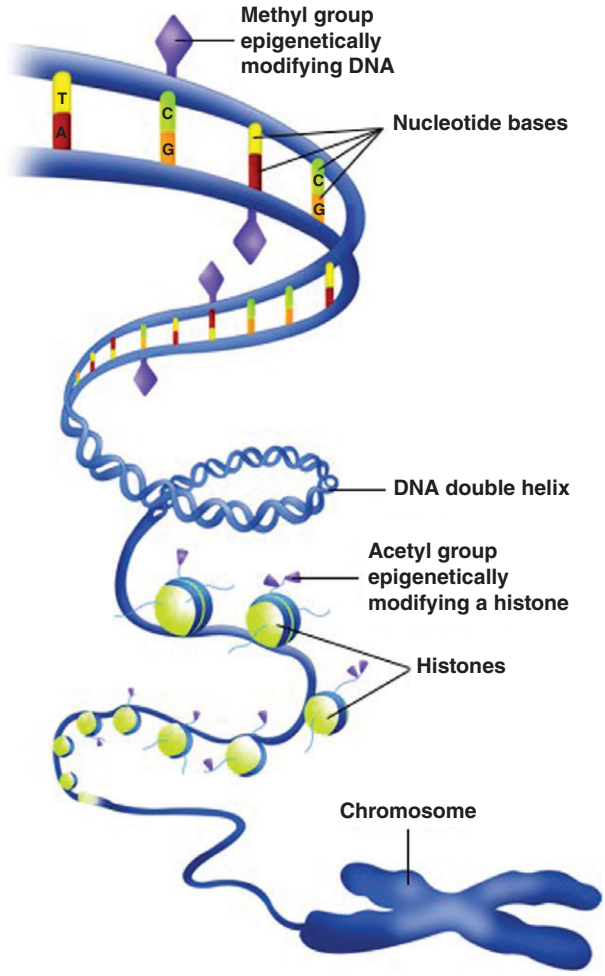

FIGURE 1 | A schematic diagram of DNA pulled from a chromosome, showing the double helix wrapped around histones, and some epigenetic modifications to both the DNA and the histones.

EPIGENETIC MECHANISMS

The genetic information in our DNA is unavailable in certain circumstances. For instance, if a DNA segment is bunched up very tightly, the cellular 'machinery' that ordinarily accesses that information will be unable to make adequate contact with the segment. When that happens, the bunched-up DNA segment will be unavailable for use, and the proteins normally produced using that segment will not be produced.

Epigenetic factors can alter access to genetic information in several ways (Figure 1). Large molecules called 'histones' are associated with DNA, and these can be modified through a variety of processes. One of these processes is called 'acetylation'; histone acetylation generally causes DNA segments to become *more* accessible, and thereby leads to increased gene expression and ultimately to the production of more of the proteins associated with those DNA segments. In contrast, chemicals called 'methyl groups' can attach to DNA segments and thereby decrease access to those segments; when this happens, the segments are said to be 'methylated,' leading to decreased gene expression and ultimately to reduced production of proteins associated with those DNA segments. Thus, histone acetylation effectively turns genes on (or speeds up rates of protein production), whereas DNA methylation effectively turns genes off (or slows down rates of protein production). Other epigenetic processes—such as histone methylation, phosphorylation, or ubiquitination, to name a few—can likewise promote or suppress gene expression, but these processes have not yet received as much research attention as DNA methylation or histone acetylation. Regardless, in each of these cases, the genome is 'marked' by the addition of

chemicals that influence genetic activity without actually changing the coded information in the DNA.

Several factors contribute to cells' epigenetic states. First, different cell types are epigenetically different. For instance, blood cells have certain genes activated and other genes deactivated, and this combination is what gives those cells the distinctive characteristics of blood cells. In contrast, neural cells have *other* combinations of activated and deactivated genes, and this combination is what makes these cells neurons. Second, additional epigenetic marks are located at random throughout the genome.[5] Third, the locations of some epigenetic marks are related to variations in individuals' DNA sequences.[6] And finally, the epigenetic state of particular DNA segments in particular cells can sometimes reflect an individual's prior *experiences*.[7,8]

FIGURE 2 | A photograph of a calico cat. Image courtesy of Howard Cheng.

AN EARLY INSIGHT INTO EPIGENETIC REGULATION

In the 1960s, scientists were grappling with a perplexing question: Why do a woman's *two* X chromosomes not produce twice the number of proteins as a man's single X chromosome? We now know that early in embryonic development, epigenetic processes disable one of the X chromosomes in each cell of female mammals, and whichever one is inactivated stays inactivated for a lifetime.[9] X-Inactivation occurs at random, so some of a woman's cells have an inactivated X chromosome originally provided by her father, but others have an inactivated X chromosome originally provided by her mother; so, women are 'epigenetic mosaics,' because the X chromosomes in different cells are in different epigenetic states.[10] When genes that contribute to *coloration* are located on X chromosomes, we can actually *see* this mosaicism; a calico cat has multiple fur colors arranged in patches in her coat, and this patterning reflects the random inactivation of one X chromosome in some cells and the other X chromosome in other cells (Figure 2). Two important lessons emerge from considering calicos. First, epigenetic effects can be bold; even individuals with identical genomes can have very different appearances owing to epigenetics. Second, a particular calico's coat-color pattern doesn't change as she ages, so epigenetic modifications can be extremely stable.

EPIGENETIC EFFECTS OF EXPERIENCE

Similarly bold effects of epigenetics occur in other species, too, and the effects can sometimes be traced to experiences. For example, genetically identical female honeybees can develop into either infertile workers with small bodies and short lifespans or fecund queens with larger bodies and longer lifespans; these stark differences reflect epigenetic effects of their distinctive diets.[11] Likewise, mice with identical genomes can nonetheless have very different characteristics. In one well-studied strain, some of the mice are yellow, obese, and at risk of developing tumors and diabetes, while others are brownish, thin, and healthy; the rest fall along continua between these extremes.[12] The differences between these mice are epigenetic, reflecting DNA methylation (Figure 3). Although these differing epigenetic states result from random processes to some extent, they can also be influenced during embryonic development by dietary factors. Specifically, providing pregnant mice of this strain with a diet containing supplemental methyl groups causes pups developing *in utero* to be more likely to develop brownish coats and healthy constitutions; the supplemented diet contributes to DNA methylation in the not-yet-born offspring, which silences DNA that contributes to a yellow coat, obesity, and cancer.[14]

Studies of people, too, have revealed epigenetic effects of experience. Groundbreaking research revealed that identical twins—who share identical genomes—have differing epigenetic profiles. Importantly, although epigenetic profiles for pairs of identical twins were *similar* when they were young, the twins' profiles diverged as they had unique experiences. Specifically, older twins who spent more of their lives apart had more epigenetic differences throughout their genomes.[15] Thus, experiences can leave 'marks' on DNA that affect how genes are expressed.[16]

FIGURE 3 | A photograph of mice that are genetically identical, but nonetheless have a spectrum of coat colors. (Reprinted with permission from Ref 13. Copyright 2012)

Some of the most compelling data on the epigenetic effects of experience have come from the labs of Michael Meaney, Moshe Szyf, and their colleagues at McGill University. These researchers discovered that natural variations in behaviors of mother rats affect how newborn offspring react to stress later in life. Specifically, although all normal mother rats lick and groom their newborn pups, mothers that lick and groom their pups a *lot* have offspring that grow up better able to tolerate mild stressors in adulthood; pups that are not licked and groomed as much ultimately behave more fearfully when stressed.[17] When the McGill researchers looked for epigenetic effects of these early experiences, they discovered that reduced exposure to postnatal licking and grooming leaves particular DNA segments highly methylated in cells within the brain's hippocampus. Therefore, these DNA segments are downregulated in the affected hippocampal cells, which ultimately leads to reduced production of a particular protein—called the glucocorticoid receptor, or GR—that helps regulate stress.[18] Subsequent work with rodents revealed similar epigenetic effects of early experiences on other DNA segments in other brain areas as well.[19,20]

Analogous effects occur in humans and other primates. For instance, in one study, when compared to people who did not experience child abuse, adults abused as children had hippocampal cells with DNA that was more methylated in a region associated with the GR.[7] Thus, in this correlational study, there was reduced expression of a stress-moderating protein in the brains of people who experienced bad parenting years earlier. Similarly, an *experimental* investigation examined the epigenetic effects of maternal deprivation on newborn monkeys. When these monkeys were adults, they had hundreds of locations in blood DNA—and thousands of locations in brain DNA—where the patterns of methylation varied depending on how the monkeys were reared.[8] Another experimental study of monkeys revealed that subtler manipulations can also produce epigenetic changes in blood-derived DNA.[21] This study found that the stress experienced by low-ranking animals in a troop's dominance hierarchy affects DNA methylation. Thus, in our primate relatives, methylation—and hence gene expression—is responsive to changes in social status. Finally, there appears to be a correlation between one's socioeconomic status in childhood and one's epigenetic profile decades later; among 45-year-olds currently in various socioeconomic conditions, those who experienced poverty in childhood had different amounts of methylation (compared to unimpoverished children) in over one thousand regions of blood-derived DNA.[22] All of these studies suggest that some epigenetic alterations can serve as *records* of previous experiences.[23] Epigenetics helps explain how our experiences literally get under our skin.

EPIGENETICS, ALL DAY, EVERY DAY

Epigenetic processes remain important beyond our formative years, and they do not only register exceptional events. In fact, epigenetic events are unfolding in your body right now: if you retain any information after reading this essay, it will be because your brain changed in a physical way that allowed you to store the information in your long-term memory.[24] And these kinds of physical changes require the construction of new proteins in your brain's neurons, a process that requires genes to be epigenetically 'turned on.'[25]

Other behaviors also influence our epigenetic states. For example, exercise causes changes in DNA methylation in muscle cells.[26] Likewise, what we eat and drink can have epigenetic effects.[27] One reason is because methyl groups are present in food, specifically foods that contain B-complex vitamins or a nutrient called choline; B_9, for example, is present in asparagus, eggs, and dark green leafy vegetables, whereas choline is present in cauliflower, meats, and milk. These methyl-rich foods can influence DNA methylation. In addition, some foods influence histone acetylation. For example, broccoli sprouts or turmeric—a spice related to ginger—can affect histone acetylation in some cell types.[28] Consequently, some theorists think these effects explain how certain foods lower the risk of developing colon cancer.[29] Even simply providing people with a daily nutritional supplement containing methyl groups has been found

in some experiments to reduce symptoms of both clinical depression and degenerative arthritis (see Refs 30 and 31, respectively).

Some research has examined how the diets of *pregnant* animals influence the epigenetic states of their offspring. Just as supplementing the diet of some pregnant mice can affect the coat colors and constitutions of the next generation, manipulating the diet of pregnant sheep can influence DNA methylation in offspring and leave them obese, resistant to insulin, and suffering from high blood pressure.[32] Correlational studies have also uncovered epigenetic abnormalities in 60-year-old *people* who were exposed to famine while developing *in utero*.[33] The discovery that prenatal experience can be recorded in the epigenome has stoked interest in the developmental origins of health and disease,[34] and contributed to dawning comprehension about how prenatal experience can produce long-term effects on phenotypes, from body size,[35] to metabolic functioning,[36] to a person's likelihood of developing schizophrenia.[37]

THIS IS NOT YOUR FATHER'S BIOLOGY … BUT YOU MIGHT STILL CARRY HIS EPIGENETICS

DNA methylation is relatively stable; once a segment of DNA is methylated, it typically stays that way. In addition, even when a cell in a body divides, it generally gives rise to two 'daughter' cells that each have the same DNA methylation profile that characterized the 'parent' cell; this is known as 'cellular inheritance' of epigenetic marks. However, things are very different when we consider *transgenerational* epigenetic inheritance—transmission of epigenetic marks not from cell to cell during an organism's life, but from organism to organism when a new generation is produced. Normally, most epigenetic marks are 'erased' between generations, shortly after conception of a new embryo (Figure 4); this process ensures that new embryos will be composed of stem cells able to become any of the different cell types in a mature body.[38] This process is consistent with biology's dominant theory, which holds that an animal's experiences cannot affect the traits inherited by its offspring. Nonetheless, there is now compelling evidence that DNA methylation in mammalian sperm or eggs can sometimes elude between-generation 'erasure,' and thereby be transmitted to offspring.[12,38,39] Some theorists argue that transgenerational epigenetic inheritance via sperm or eggs is rare but others believe 'epigenetic inheritance is ubiquitous' (see Refs 38 and 40, p. 131, respectively). Why the discrepancy?

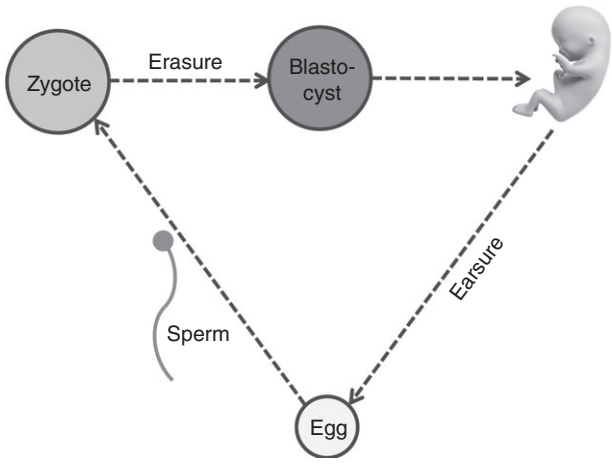

FIGURE 4 | A schematic diagram of the 'life cycle' of methylation under normal circumstances. DNA methylation is 'erased' once shortly after a new organism is conceived (a zygote is a newly conceived organism and a blastocyst is an early embryo), and once more in the primordial germ cells that will become that new organism's sperm or egg cells. (Reprinted with permission from Ref 1. Copyright 2015 Oxford University Press)

One reason transgenerational epigenetic inheritance is controversial is because theorists have different ideas about what should count as 'inheritance.'[1,4] Some writers insist that transgenerational epigenetic inheritance requires transmission of epigenetic marks that are on sperm or egg cell DNA. But a phenomenon described by the McGill researchers suggests that transgenerational transmission of epigenetic marks can sometimes occur independently of genome transmission. In this phenomenon, female rat pups that were licked and groomed a lot grew up to be adults that—because of their epigenetic state—were less reactive in stressful situations. In addition, these rats matured into more attentive mothers, licking and grooming *their* offspring in ways that produced the same distinctive epigenetic characteristic found in the mothers. Thus, even though the epigenetic marks were not actually transmitted with the genome in sperm or eggs, they were nonetheless reliably reproduced in one generation after another, via a behavioral mechanism.[3,41]

Regardless of *how* it occurs, it is now clear that in some species, ancestors can beget descendants that share the ancestors' distinctive epigenetic states. For instance, epigenetic phenomena are responsible for so-called 'parent-of-origin' effects, in which a gene's activity depends on whether it originated in a father or a mother.[42] In addition, some fascinating circumstantial evidence suggestive of epigenetic inheritance across multiple generations has recently been uncovered in a human population.[43,44] Studies of the transgenerational inheritance of epigenetic marks will continue to draw

researchers' attention for at least two reasons. First, such effects have evolutionary significance.[45] In fact, one research team has already described how exposure to a pesticide produces epigenetic effects in rats that are transmitted across generations in a way that these investigators believe provides 'direct experimental evidence for a role of epigenetics as a determinant factor in evolution.'[46,47] Second, because the transgenerational transmission of epigenetic marks provides a mechanism by which individuals' experiences can affect their *descendants*' characteristics, this phenomenon permits a quasi-Lamarckian mode of inheritance that would have been unthinkable to most 20th century biologists.[5] Incorporating transgenerational epigenetic inheritance into a comprehensive theory of biology will be a challenge, as the reigning theory of evolution—the neo-Darwinian Modern Synthesis—cannot accommodate this sort of phenomenon.[48] Therefore, new ideas about inheritance will be an area of active exploration in coming years.

CONCLUSION

Research on behavioral epigenetics has helped explain some long-standing enigmas, and driven home some important points. By revealing how gene expression is controlled, this research has re-emphasized that genetic and nongenetic factors always collaborate to produce our characteristics; there are no features of our bodies or minds that are determined strictly by our DNA. By revealing how contexts can influence epigenetics, this research has explained how early-life experiences can produce lifelong effects, and has clarified how 'identical' twins come to differ. And by revealing how exposure to novel events can lead to the epigenetic initiation of structural changes in our brains, this research has illuminated how learning is implemented in the nervous system, thereby further clarifying the relationship between mind and body.

Behavioral epigenetics has the potential to have an enormous impact on our world. This research will likely alter how psychiatrists treat people with psychological disorders, how physicians practice their art, how public health organizations promote healthy lifestyles, and how government agencies evaluate the risk of pesticides, nutritional supplements, and medications.[1] Research on epigenetics will have consequences that are this wide-ranging because the human epigenome is central to human nature.

FURTHER READINGS

"Genetics" (http://www.nature.com/scitable/topic/genetics-5).

"Translation/RNA Translation" (http://www.nature.com/scitable/definition/translation-173).

"Epigenetics" (http://www.nature.com/scitable/spotlight/epigenetics-26097411).

"Early concepts of evolution: Jean Baptiste Lamarck" (http://www.blackwellpublishing.com/ridley/a-z/Lamarckian_inheritance.asp).

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