# 10

# Social and Behavioral Epigenetics: Evolving Perspectives on Nature-Nurture Interplay, Plasticity, and Inheritance

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## Introduction

Though there has been long-standing division between considerations of the role of nature vs. nurture in determining the origins of variation in personality, behavior, health, and well-being, this traditional view has been revised in light of demonstrated gene-environment interactions (GxE) and their influence on these outcomes. A classic example of this interaction is in the prediction of depression based on stress and genotype: individuals with a specific polymorphism within the gene encoding the serotonin transporter (SLC6A4) are at higher risk for depression *only* when they have experienced elevated lifetime stress (Caspi et al. 2003). Under conditions of low stress, no effects of genotype are observed. Thus, the impact of genes/nature on the traits of an individual is tempered by the environmental experiences of that individual. This shift in understanding of nature and nurture has important implications for how we think about genes and their influences. In particular, gene-environment interactions provide evidence of plasticity and an ability to overcome the constraints of genetic determinism. However, the occurrence of a gene-environment interaction is derived primarily from statistical relationships—the presence of a statistical interaction between genotype and environmental exposure. These interactions suggest a phenomenon but do not provide a mechanism.

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In the past decade there has been a rapidly growing literature focused on the biological mechanisms through which interactions between genes and the environment occur (Champagne 2012; Meaney 2010). At the core of these mechanistic studies is epigenetics. The term "epigenetics" was coined by Conrad Waddington, a developmental biologist, in the 1940s to refer to the interplay between genes and their products that account for variation in phenotype. From this perspective, genes were viewed as being "organized" or "induced" in their activity with resulting consequences for development (Waddington 1940). By the 1980s, biologists had identified possible molecular processes to account for variation in gene regulation through studies of DNA methylation (Razin and Riggs 1980). DNA methylation is the chemical modification of a cytosine within the DNA sequence, resulting in 5-methylcytosine (Culp et al. 1970). Early studies of DNA methylation indicated that the activity of genes can be altered in this way and that this alteration is fundamental to driving diversity of phenotype—albeit at a cellular/molecular level accounting for cellular differentiation (Jones et al. 1983). However, the notion that these molecular epigenetic mechanisms could be modified by the environment to account for the phenomenon of nature-nurture interactions has only been the focus of epigenetic research in the past decade (Weaver et al. 2004; Dolinoy et al. 2006).

The field of social and behavioral epigenetics explores the relationship between the quality of the social environment, epigenetic variation, and behavioral variation and is part of the broader study of how environments (i.e. nutritional, toxicological, social) come to induce phenotypic variation at the level of the organism (i.e. growth, metabolism, health, behavior) via epigenetic mechanisms. Though the initial studies linking social experiences to epigenetic changes in the brain with consequences for behavior were conducted in model organisms, such as rats, there is growing support for the relevance of these mechanisms for humans. Both individual-level social experiences, such as psychosocial stress (Monk et al. 2016), trauma (Yehuda et al. 2014), and exposure to adverse parent-offspring interactions (McGowan et al. 2009), and group-level experiences, such as poverty (Lam et al. 2012) and racial discrimination (Brody et al. 2016a), may exert lasting biological influences through epigenetic variation. Epigenetic studies illustrate the integration of biology and the social world in unprecedented ways by demonstrating the direct effect on DNA function of the social environment. Moreover, there is increasing focus on the transmission of environmentally induced molecular changes across generations. This multigenerational perspective has forced a reconsideration of the narrowness with which we view the biology of inheritance (Danchin et al. 2011) and suggests a broader and more dynamic process of

evolution (Laland et al. 2015). Given the scientific revolution that this body of work has triggered, social and behavioral epigenetics raises many issues of societal relevance, including the biology of social adversity, the relationship between DNA and identity, and intervention as a strategy to target epigenetic plasticity (Brody et al. 2016a, b; Swartz et al. 2016). This chapter will highlight studies within the field of social and behavioral epigenetics, discuss the changing scientific and societal views contributed to by these studies, and speculate about the future implications of this field of study for our evolving understanding of the gene, individuals, and society.

## A Primer of Modern Epigenetics

Advances in the methodological tools available to interrogate biology at a molecular level have enabled rapid scientific discovery within the field of epigenetics. In particular, these advances have revealed the dynamic process of gene regulation—involving multiple types of epigenetic modifications occurring within a temporal-spatial context. DNA methylation is perhaps the most fully explored modification of cytosines within the DNA sequence (Razin and Riggs 1980). The addition of a methyl-group to cytosines within DNA is generally an epigenetic mechanism of gene silencing when occurring within the promoter—the regulatory region of a gene (Razin 1998). This chemical modification of DNA does not alter the DNA sequence. The gene silencing occurring as a consequence of DNA methylation is contributed to by the accumulation of methyl-binding proteins within the methylated genomic region which serves to limit accessibility to the DNA (Fan and Hutnick 2005). DNA methylation patterns are mitotically heritable such that when cells divide they transmit this pattern to daughter cells (Jones et al. 1983). This transmission process is critical to the phenomenon of cellular differentiation, where all cells descend from an omnipotent stem cell that generates more lineage-specific cell types.

In addition to direct chemical modifications to DNA, there are two other main classes of epigenetic mechanisms: post-translational histone modifications and non-coding RNA. Within the cell nucleus, DNA is physically wrapped around a cluster of proteins called histones (e.g. H3, H4). Histone proteins can, like DNA, be modified through the addition of a variety of chemicals, leading, for example, to acetylation, methylation, and ubiquitination (Cheung et al. 2000). Histone chemical modifications serve to either create a more densely packed chromatin structure associated with gene silencing or loosen interactions between DNA and histones to promote gene

activation. The type of chemical added, the location within the histone where the chemical has been added, and the genomic location where the modified histone interacts with the DNA are collectively predictive of the impact of post-translational histone modifications on gene expression (Jenuwein and Allis 2001). Finally, there is increasing understanding of the role of non-coding RNAs—RNA that does not produce a protein product—in gene regulation (Sato et al. 2011). The product of "junk DNA" (Ohno 1972), non-coding RNA molecules can alter the function of a gene by interacting with proteins and mRNA produced from coding regions of the genome (i.e. genes) and may also interact directly with DNA. The function of non-coding RNA molecules in gene regulation has challenged the way in which we define "functional" with regard to the genome—producing a protein may be one of many functions that a genome can have (Tragante et al. 2014; Graur et al. 2015).

Overall, though epigenetics is often described as a molecular "on/off" switch, the complexity of these biological processes is immense. Each of type of epigenetic modification operates within a genomic context and has spatial and temporal features that contribute to their predicted effects. Beyond that initial complexity, there is interaction between different types of epigenetic modifications in the prediction of gene expression (Molina-Serrano et al. 2013). Thus, increasing understanding of epigenetics reveals how highly complex, multilayered, and contextually sensitive these biological mechanisms are, as a first step in the process of generating phenotype from genotype. Though developing simple analogies to communicate the basic principle of epigenetics is important for transmitting emerging scientific ideas, the complexity involved in epigenetics should not be lost. Organisms are complex and epigenetics builds an infinitely complex and dynamic layer of biological information within the genome.

## Mothering the Epigenome

The role of epigenetics in gene regulation and cellular differentiation has been accepted for decades; however, a relatively novel concept to emerge is that these mechanisms can be shaped or "induced" by the environment. Certainly, the cellular environment is important in setting epigenetic state of DNA as it is through cell-signaling and cell-cell interactions that cellular differentiation occurs. However, the question that has moved the study of epigenetics into the realm of the social world is whether the experiences of an individual can shape epigenetic variation within the genome (see Fig. 10.1). Theoretical discussions regarding epigenetic plasticity have existed within the literature for

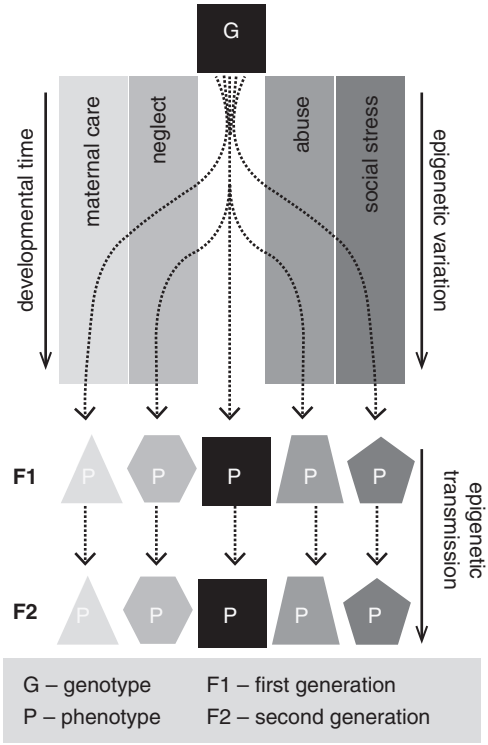


**Fig. 10.1** Illustration of the complex interplay between genotype and social environment in predicting phenotype within and across generations. Epigenetic variation is a mechanism through which divergent phenotypes can arise through interactions of genotype with different environmental conditions across development. This epigenetic variation can be transmitted across generations leading to the inheritance of phenotypic variation

decades—such as the idea that memories might be encoded or "ticketed" within DNA through cytosine modifications (Griffith and Mahler 1969). However, a theoretical stumbling block to a wider appreciation of epigenetic plasticity was present in the hypothesized role of stable epigenetic patterns in defining cell types. How can a mechanism confer both stability of phenotype (i.e. maintenance of a muscle cell type vs. a neuron) and plasticity in response to a lifetime of environmental signals? Though the solution to this dilemma has yet to be elucidated, evidence of epigenetic plasticity and stability exists and is demonstrated by the impact of early life mother-infant interactions.

Mammalian development is characterized by a high level of investment in the care of offspring from the prenatal period through to young adulthood. Though biparental care is present in some species, including humans, mothers are the primary caregivers in most reproductive contexts and invest significant

energetic resources through placentation, lactation, and offspring-directed behaviors (Fowden and Moore 2012; Jenkins et al. 2016). Maternal reproductive investment is essential to offspring growth and development. However, there is significant within-species variation in maternal behavior (Hane et al. 2010; Maestripieri et al. 1997; Champagne et al. 2003). Studies of natural variations in maternal behavior reveal the critical role of mothers in shaping epigenetic outcomes. Offspring of female laboratory rats that engage in low vs. high levels of postpartum maternal licking/grooming (LG) during the first week of life differ significantly on physiological, neurobiological, and behavioral outcomes (Meaney 2001). These effects persist into adulthood. Adult offspring that have experienced low levels of LG during infancy have heightened stress reactivity, behavioral inhibition within novel environments, increased aggressiveness in social interactions, impaired learning/memory capacity, and altered reproductive behavior (Meaney 2001; Cameron et al. 2005). These functional outcomes are associated with altered gene expression within specific neural systems associated with the hypothalamic-pituitary-adrenal (HPA) response to stress, fear, cognition, and maternal/sexual behavior. What is particularly notable about the observed association between early life mother-infant interactions and gene expression is its persistence. The activity of genes within the brain is stably altered by the quality of the social environment occurring early in development. Analyses of DNA methylation levels and post-translational histone modifications within the brain of offspring that differ in their experience of postnatal maternal care reveal the role of maternal behavior in shaping these epigenetic mechanisms (Weaver et al. 2004; Suderman et al. 2012; McGowan et al. 2011). The epigenetic effects of maternal care occur at a broad range of genomic locations, including specific gene promoters involved in stress reactivity. The regulatory region of the gene encoding the glucocorticoid receptor (NR3C1) is hypermethylated in the hippocampus of offspring of low-LG compared to high-LG mothers (Weaver et al. 2004). In concert with increased DNA methylation are decreased levels of histone acetylation which collectively accounts for the decreased NR3C1 gene expression and protein observed in the hippocampus of low-LG offspring (Liu et al. 1997; Francis et al. 1999). The result of this gene regulatory state is to reduce the capacity of low-LG offspring to adapt to stress.

The determination of an epigenetic consequence of maternal behavior has been the launching point for studies of social and behavioral epigenetics. Moreover, further exploration of the dynamics of epigenetic change within the NR3C1 gene has revealed important principles of environmental interplay within the genome. First, epigenetic variation emerges in response to the cues in the environment. At birth, there are no epigenetic differences in DNA

methylation of NR3C1 in the hippocampus of low- compared to high-LG rat offspring (Weaver et al. 2004). After several days of differential maternal care, group differences in DNA methylation are observed and persist into adulthood. Second, though the epigenetic effects of maternal care persist into adulthood, there is continued epigenetic plasticity in the adult brain whereby NR3C1 gene activity can be "reset" resulting in a shift in the stress reactivity of offspring. Pharmacological manipulations in adulthood that decrease DNA methylation or increase histone acetylation can be used to shift the phenotype of a low-LG rat toward that of a high-LG rat, and the converse can be achieved by increasing DNA methylation (Weaver et al. 2004; Weaver et al. 2005). Thus, reversibility of both epigenetic variation and the phenotype associated with this variation is possible, even when stability has been maintained throughout infancy and adolescence. Finally, studies exploring the link between maternal behavior and NR3C1 DNA methylation have revealed the cascade of sensory, neural circuit, hormonal, and transcriptional events that link this particular aspect of the social environment to a change in DNA methylation (Hellstrom et al. 2012). Somatosensory stimulation features prominently in this cascade as a way through which an organism senses the quality of caregiving (Ferber et al. 2008; Hellstrom et al. 2012).

Though natural variations in maternal behavior have served as the starting point for studies examining epigenetic interplay with the social environment, subsequent studies have examined a broad range of "nurture" cues, including the experience of abuse and neglect. In rodents, disruptions to the postnatal environment result in an increased incidence of abusive caregiving, resulting in altered DNA methylation, histone acetylation, and gene expression within the brain of offspring (Roth et al. 2009; Blaze et al. 2015; Doherty et al. 2016). In humans, a history of childhood abuse is predictive of increased hippocampal DNA methylation within the NR3C1 gene and similar overall patterns of epigenetic variation to what has been observed in the rodent model comparing low- and high-LG offspring (Suderman et al. 2012). Global increases in DNA methylation have been observed in blood samples from institution-reared orphans (Naumova et al. 2012) and analyses of buccal cells indicate hypomethylation in the SLC6A4 gene as a function of increased exposure to institutional care (Non et al. 2016). The ability to detect epigenetic signatures of early life adversity in tissues outside the brain is an important methodological step in translating laboratory-based findings into the real-world analyses of human biobehavioral processes and to field studies of animals exposed to ecological pressures meaningful in discussions of fitness and evolution. Though there is ongoing debate about the relevance of these "peripheral" epigenetic changes in understanding the brain and behavior,

there is increasing evidence of epigenetic concordance across different tissue types in response to environmental cues (Nemoda et al. 2015; Farré et al. 2015; Kundakovic et al. 2015).

Evidence for the profound impact of maternal care on offspring development that extends to epigenetic outcomes has placed increased emphasis on the development of parenting interventions. Despite a recognized need to provide additional support and education to parents (Shuman and Masterpasqua 1981), these interventions have not typically been implemented at a global or national level. However, family-based programs that focus on developing attachment security, managing stress, and treating parental and child psychiatric illness have promise in reducing mental illness and improving child and parent well-being (Cicchetti et al. 2006; Lowell et al. 2011). Though parental neglect or abuse can exert significant "wear and tear" on the biology and behavior of children, it may be possible to shift developmental trajectories through intervention. Moreover, this plasticity may manifest at the level of epigenetic variation. One epigenetic metric that delves into the biological "wear and tear" experienced by an individual is referred to as "epigenetic age" (Horvath 2013). Analyses of DNA methylation from virtually any cell in the body can give an approximate estimate of our chronological age. Thus, our cells have a memory of time. However, in some cases, the epigenetic estimate of chronological age suggests we may be biologically "older" than our chronological age. This phenomenon is referred to as "age acceleration" and is thought to reflect a process of "wear and tear" (Horvath 2013). Epigenetic age acceleration has been observed in response to disease (Horvath and Levine 2015), prenatal adversity (Simpkin et al. 2016), and exposure to parental depression (Brody et al. 2016b). Within intervention studies, programs that reduce harsh parenting can reduce epigenetic age acceleration with potential for improved physical and mental health outcomes (Brody et al. 2016b). Intervention studies have significant potential to "reset" epigenetic outcomes. However, it is important within the context of intervention studies to not lose sight of the cascade of events within the social environment that influence parent-offspring interactions. Studies of maternal behavior in laboratory rodents and in primates provide empirical support for the influence of social stress and social support on the quality of mother-infant interactions (Ruppenthal et al. 1976; Curley et al. 2009; Champagne and Meaney 2007; Champagne and Meaney 2006). Similarly, human parenting occurs within a broader context of socioeconomic pressures, family dynamics, community well-being, and exposures to nutritional and toxicological factors that may alter reproductive systems and stress physiology. Integrating context into the discourse of the impact of mother-infant interactions on the epigenome will

be particularly important for identifying the distal predictors of parenting, identifying society/community level targets for intervention, and lessening the "blame the mother" sentiment that may arise from the focus on the more proximal influences of child development (Winett et al. 2016).

## Psychosocial Stress and Epigenetic Plasticity

Stress is a highly conserved process of coordinating the biology of an organism in response to threat. Psychosocial stress and mood during pregnancy can have a lasting impact on offspring development with consequences for psychiatric risk (Koubovec et al. 2005; Weinstock 2008). These psychological states are associated with heightened HPA activation, resulting in increased glucocorticoid levels within the mother—a classic physiological response to threat (Kane et al. 2014; O'Connor et al. 2014). In humans, objective stress exposure, maternal perceived stress, anxiety, and depression can epigenetically alter offspring via three distinct yet interactive routes (Monk et al. 2012). The first pathway is through epigenetic variation within the placenta. During pregnancy, the placenta acts as a critical interface between the mother and the fetus (Burton and Jauniaux 2015). Gene expression and epigenetic profiles within the placenta change during the course of pregnancy (Novakovic et al. 2010; Sitras et al. 2012), and variation in these profiles is predictive of fetal growth restriction (Jensen et al. 2014; Roifman et al. 2016). Among mothers that report elevated perceived stress during pregnancy, there is increased placental DNA methylation within the 11HSD2B gene—a gene encoding an enzyme that buffers the fetus from maternal stress hormone (Monk et al. 2016). Moreover, increased 11HSD2B DNA methylation within the placenta is predictive of impaired neurodevelopment in the fetus. Variation in 11HSD2B DNA methylation is also observed as a consequence of socioeconomic status (SES)—though this association suggests decreased DNA methylation of 11HSD2B in response to stress (Appleton et al. 2013). Epigenetic variation in several other placental gene targets is predictive of stress responsivity, self-regulation, and sensory development (Paquette et al. 2014; Conradt et al. 2015). A second route of prenatal epigenetic influence is the direct impact of maternal psychosocial stress on fetal tissues—including the brain. In humans, analyses of epigenetic effects in offspring who have experienced prenatal stress have primarily relied on blood, buccal cells, or saliva. Altered DNA methylation within stress-related genes such as NR3C1 and neural plasticity-related genes such as brain-derived neurotrophic factor (BDNF) has been detected in these tissues associated with prenatal exposure to maternal

stress (Radtke et al. 2011; Hompes et al. 2013; Braithwaite et al. 2015; Unternaehrer et al. 2016). Moreover, studies in laboratory rodents provide experimental support for the presence of these epigenetic effects within the brain (Mueller and Bale 2008; Peña et al. 2012). A third route through which prenatal epigenetic effects may be mediated is via alterations in the quality of postnatal mother-infant interactions. Stress during pregnancy may alter mental health of the mother during the postpartum period, and there is a heightened risk of impaired mother-infant interactions associated with postpartum depression (Brummelte and Galea 2016; Dollberg et al. 2016). Influence of prenatal stress on the quality of the postnatal environment highlights the interplay between experiences occurring at different developmental time points.

Epigenetic plasticity in response to stress continues during postnatal development and persists into adulthood. The deprivation of maternal care during infancy can be perceived as a threat and activate the HPA response to stress with epigenetic consequences. In laboratory rodents, prolonged postnatal maternal separation, often referred to as early life stress, leads to increased activity of stress-related genes (Murgatroyd et al. 2009; Chen et al. 2012) and epigenetic silencing of genes involved in moderating stress responses (Kember et al. 2012; Kundakovic et al. 2013) within the hypothalamus and hippocampus. Moreover, the effects of maternal separation occurring during infancy can be ameliorated if offspring are placed on a diet that alters DNA methylation in adulthood (Paternain et al. 2016). Histone modifications and non-coding RNA expression are also altered by early life stress. For example, activity of the BDNF gene is decreased by maternal separation, and this effect coincides with decreased histone acetylation within the hippocampus (Seo et al. 2016). Altered expression of microRNA—a small non-coding RNA—is observed in the frontal cortex of offspring exposed to maternal separation (Uchida et al. 2010). Early life stress-associated epigenetic variation may account for increased stress vulnerability in response to subsequent stressors as both behavioral and epigenetic variations are exacerbated when maternal separation is combined with adult chronic stress exposure (Seo et al. 2016). Finally, studies in primates illustrate the integration of environment, genetics, and epigenetics in the study of stress vulnerability. Among rhesus macaques that possess the risk SLC6A4 gene variant, DNA methylation of the SLC6A4 gene rather than SLC6A4 gene sequence predicts heightened effects of maternal separation on behavioral stress reactivity in infants (Kinnally et al. 2010). Putative risk genotypes may thus mediate their effects via altered epigenetic variation, suggesting that the phenotypic effects of genes may be shifted through targeting of the epigenome.

Plasticity is typically a phenomenon associated with being young. However, it is apparent that, despite the potential stability of epigenetic effects of early life experiences, epigenetic plasticity can persist across the life span in response to social stress. In humans, adult trauma exposure is associated with epigenetic age acceleration (Boks et al. 2015), and altered DNA methylation is associated with adult SES (Subramanyam et al. 2013). Studies of SES have typically focused on the link between childhood SES and health outcomes; however, given the plasticity of the epigenome, a lifecourse perspective may be more informative in predicting, for example, indices of biological weathering such as epigenetic age acceleration (Simons et al. 2016). Studies in laboratory rodents indicate that a variety of social stressors in adulthood, including social exclusion (Krause et al. 2015) and exposure to aggressive social interactions (Jung et al. 2015; Kenworthy et al. 2014), can impact the epigenome, and pharmacological targeting of histones may ameliorate the effects of social stress (Covington et al. 2015). Moreover, resilience to stress can be described from an epigenetic perspective. Among adult mice exposed to social stress, there is decreased DNA methylation within the corticotropin-releasing factor (CRF) gene—a key player within the HPA response to stress (Elliott et al. 2010). However, among individual mice that are resilient to social stress (i.e. do not display social avoidance or depressive-like behaviors following social stress exposure), there is no alteration in DNA methylation of CRF—the gene remains epigenetically silent. Overall, increasing evidence for epigenetic plasticity in adulthood suggests that intervention and reversal of both genetic and environmentally mediated effects may be possible long after the sensitive period of early development. Further, it may be possible to "re-open" plasticity beyond classic critical periods occurring prenatally or in childhood, leading to improved biobehavioral functioning (Takesian and Hensch 2013).

## Revisiting the Inheritance of Acquired Characteristics

The discovery of DNA canalized the gene-centric view of inheritance. This view was inconsistent with the notion of the inheritance of acquired characteristics that was historically integrated into theories of inheritance (Zirkle 1935) and was developed further by Jean Baptiste Lamarck into a theory of evolution (Lamarck 1809). Lamarck posited that the characteristics of an organism were driven by the "habits of life"—a statement describing the dynamic developmental process whereby environments shape the individual. Lamarck also described a process whereby if the environmental exposures that

are driving the "habits of life" were to be sustained over chronological time and repeated across several generations, the phenotypes that emerged would be passed to descents and preserved by heritability. The notion of the inheritance of acquired characteristics, within the context of Lamarckian theory, rests heavily on the idea that the phenotypic adaptations that emerge within an individual are important for the development and survival of that individual. To lose those adaptations from one generation to the next was to compromise the development and survival of generations to come. As Paul Kammerer, a biologist and proponent of Lamarckian theory, once wrote: "If acquired characteristics cannot be passed on … then no true organic progress is possible. Man lives and suffers in vain. Whatever he might have acquired in the course of his lifetime dies with him. His children and his children's children must ever and again start from the bottom" (Kammerer 1914). However, without mechanistic support, the idea of the inheritance of acquired characteristics failed to flourish and was supplanted by the more rapidly developing ideas within quantitative and subsequently molecular genetics.

Within epigenetics, the inheritance of acquired characteristics has gained new momentum, primarily due to experimental studies illustrating the transmission of environmentally induced phenotypes from one generation to the next (see Fig. 10.1).

Critical examples of epigenetic inheritance come from studies within social and behavioral epigenetics. For example, male mice exposed to social instability (i.e. changing social groups repeatedly to prevent the establishment of stable social groups) are altered in their phenotype—this manipulation leads to increased indices of stress (Saavedra-Rodríguez and Feig 2013). Grand-offspring and great-grand-offspring of stressed males exhibit increased indices of anxiety. This transmission is remarkable given that laboratory male mice have no postnatal contact with their offspring and that the transmission to great-grand-offspring occurs exclusively through the patriline (i.e. via male descendants). Though this transmission does not reveal a biological mechanism, it strongly suggests a germline inheritance of an environmentally induced effect. Analyses of sperm from males exposed to stress in early life or in adulthood indicate epigenetic variation, including altered DNA methylation and increased microRNA expression (Franklin et al. 2010; Gapp et al. 2014; Rodgers et al. 2013). Further, these epigenetic changes are also observed in the offspring of exposed males, and the phenotypes observed in offspring can be generated by manipulating epigenetic variation in the developing embryo (Rodgers et al. 2015; Gapp et al. 2014). Though the issue of how these epigenetic marks survive the epigenetic reprogramming that is occurring post-fertilization remains, there is increasing support for the hypothesis that

epigenetic inheritance is possible and may have adaptive consequences for offspring (Zeybel et al. 2012).

Though developmental studies of social and behavioral epigenetics have focused primarily on mothers, it is notable that studies of epigenetic inheritance focus almost exclusively on fathers. The rational for this parental divide is in the relative role of mothers vs. fathers in mammalian reproduction. While mothers create the context of development during prenatal and postnatal life, the role of fathers is limited to fertilization. Thus, for an epigenetic inheritance to occur via the patriline, it is assumed that the only route possible is via sperm/seminal fluid (Curley et al. 2011). However, mothers are also capable of transmitting traits across generations via epigenetic mechanisms. In contrast to fathers, mothers achieve this transmission through their interactions with offspring (Champagne 2011). For example, variation in maternal LG is transmitted across generations via the matriline, such that offspring and grand-offspring of low-LG mothers also engage in low levels of LG. This transmission occurs in response to the effects of postnatal LG on epigenetic regulation of the estrogen receptor alpha gene (ESR1) within the developing hypothalamus. The experience of low levels of LG results in epigenetic silencing of ESR1, and this effect persists into adulthood, rendering female offspring less sensitive to estrogens and less primed to engage in maternal behavior (Champagne et al. 2006; Peña et al. 2013). As a consequence, the LG phenotype persists in the next generation. Similar cycles have been observed in laboratory rats in response to abusive maternal care mediated through epigenetic regulation of BDNF (Roth et al. 2009). Maternal transmission of epigenetic effects across generations is entirely experience-dependent and can be modified by stress or social support (Champagne and Meaney 2007; Champagne and Meaney 2006) allowing for heightened responsiveness to intervention and changing environmental conditions. Finally, though paternal and maternal inheritance systems are often dissociated—either experimentally or theoretically—it is important to take an integrative perspective when considering how parents can epigenetically influence their offspring. Much like genes and environments, parents interact to produce phenotypic outcomes.

## Epigenetics and the Gene

Given changing views of development and inheritance contributed to by advances in the study of epigenetics—how should we think about the gene? Genetics is certainly thriving and is central to many new health initiatives

including the Precision Medicine Initiative in the United States (Goodman et al. 2016) and the global Human Variome Project (Burn and Watson 2016). These initiatives focus on genome-wide sequencing of DNA as a strategy for improved diagnosis and treatment of disease. There is also increased availability of direct-to-consumer genetic sequencing resources aimed at defining the origins of individual traits or characterizing an individual's ancestry (Niemiec and Howard 2016; Phillips 2016). Thus, "identity" is still largely linked to DNA despite growing acceptance of the role of gene regulatory processes in shaping development and inheritance. A significant barrier to a better integration of epigenetics and genetics is likely methodological. DNA is stable and identical across tissues. Epigenetic variation is tissue specific and can vary within and across days. The divergent properties of these two molecular features within our cells create challenges when trying to generate a cohesive predictive model of phenotypic outcomes. Overcoming these challenges will be essential to better understand how knowledge of DNA and knowledge of epigenetic profiles can be better used in the design of interventions and to shape public views on the plasticity vs. stability of our biology in response to the social environment.

## Future Directions in Social and Behavioral Epigenetics

Research within the field of social and behavioral epigenetics is rapidly evolving through incorporation of novel methods in the analyses of epigenetic variation and broader application of these analyses to humans. Though DNA is still the primary focus of much of the diagnostic work in the biomedical sciences, within the social and behavioral sciences, there has been more substantial integration of epigenetics. Behavior is complex and dynamic—much like the epigenome—and it is perhaps this complexity that has motivated biological explanations to span beyond the constraints of DNA sequence. Epigenetic variation provides a molecular context to DNA, and there is increasing evidence that the phenomenon of GxE interactions is accounted for by epigenetic mechanisms. One of the many challenges ahead for social and behavioral epigenetics is in the integration of multiple levels of the social environment. The tactile interactions between a human mother and infant that trigger epigenetic effects are the consequence of a cascade of individual- and group-level factors that characterize the environment of families, communities, institutions, and nations. Though animal studies can be used to strip away that context to examine the proximal influences on development,

translating these studies to humans requires a better understanding of the relationship between proximal and distal influences. A second challenge to the field involves the integration of genetics and epigenetics. The goal of studies within the field of epigenetics is not to replace the study of DNA. Rather, the goal is to integrate these molecular factors into a more comprehensive theory of the origins and inheritance of phenotype. This integrative approach will be necessary to avoid perpetuating nature vs. nurture dichotomies and to create a framework for understanding the coexistence of stability and plasticity of phenotypic variation.

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