



# **The SAGE Encyclopedia of Lifespan Human Development**

## **Epigenetics**

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Book Title: The SAGE Encyclopedia of Lifespan Human Development

Chapter Title: "Epigenetics"

Pub. Date: 2018

Access Date: April 1, 2018

Publishing Company: SAGE Publications, Inc.

City: Thousand Oaks,

Print ISBN: 9781506307657

Online ISBN: 9781506307633

DOI: <http://dx.doi.org/10.4135/9781506307633.n284>

Print pages: 760-762

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DNA sequence is a critical source of information for all biological processes, but the regulation of gene activity is necessary for this genetic potential to be utilized. Epigenetics refers to molecular mechanisms that contribute to the regulation of gene activity, resulting in either increases or decreases in gene expression (transcription). These mechanisms do not involve modifications to the DNA sequence. In 1942, Conrad Waddington coined the term *epigenetics* to describe the complex interplay between genes and their products, which occur during development to establish the divergence of phenotypes (characteristics) that emerge from a given genotype. An example of the role of epigenetics in development is illustrated by the process of cellular differentiation. An organism has a single genome, and that genome is copied when cells divide, such that each cell within an organism has the same sequence of DNA. However, there are hundreds of different cell types that emerge across development within an organism, such as neurons, muscle cells, and immune cells, which differ from each other in both function and form. This divergence in phenotype of cells is established and maintained through epigenetic modifications.

There are currently three broad types of epigenetic modifications: (a) chemical modifications to cytosine within the DNA sequence (e.g., DNA methylation), (b) posttranslational histone protein chemical modifications (e.g., histone acetylation, methylation), and (c) expression noncoding RNAs. *Histones* are proteins around which DNA is wrapped within the cell nucleus, and *noncoding RNA* refers to RNA molecules that are created through transcription but that do not undergo translation to become a protein. Although each of these types of epigenetic mechanisms alters gene activity via different processes, the collective action of these mechanisms is to alter the levels of gene transcription, in some cases resulting in gene silencing. The study of epigenetic mechanisms has been integrated into the biological sciences, neuroscience, and medicine. Epigenetics may also provide insights into the interplay between genes and environments during the life span of an individual and in the transmission across generations of the effects of environmental exposures (i.e., nutritional, stress, toxins) and social experiences. This entry discusses this interplay and generational transmission, which have broad implications within the social and behavioral sciences, particularly for the study of human development.

### Epigenetic Variation Associated With Early Life Experiences

Comparison of the personality, behavior, and health of monozygotic twins—individuals who share 100% genetic similarity—suggests that these twins display both concordance (similarity) and discordance (dissimilarity) in these phenotypic traits. For example, the concordance in risk of schizophrenia between monozygotic twins has been estimated to be as high as 50%. This concordance rate would suggest that if one twin develops schizophrenia, the co-twin has a 50% likelihood of also developing the disorder. This likelihood of risk is significantly higher than the risk among fraternal twins who are not genetically identical. However, among monozygotic twins, there would also be a 50% likelihood of discordance for the disorder, where one twin develops schizophrenia and the other does not develop the disorder. For decades, twin studies have been used to illustrate the role of genes and environments in shaping phenotype. Comparison of monozygotic twins can also advance understanding of epigenetics. When monozygotic twins are young, they have very similar patterns of DNA methylation and histone modifications within their cells. However, among older twins, these epigenetic patterns are less concordant. This observation suggests that epigenetic variation emerges across the life span, with increasing divergence accumulating with age. Just as cells in the body undergo cellular differentiation via epigenetic mechanisms, so do individuals differentiate epigenetically from each other as they transition from infancy to

old age. Comparison of monozygotic twins who are concordant versus discordant for schizophrenia suggests that epigenetic discordance between twin pairs is associated with discordance for the disorder. The question that these findings raise regards the factors that contribute to increasing epigenetic divergence. Longitudinal studies in humans point to an association between adverse life experiences and epigenetic divergence. Studies in animal models have allowed for the experimental study of the impact of life experiences on epigenetics and the relation between epigenetic variation and behavioral and neurobiological outcomes.

During early embryonic development, dynamic cellular and molecular changes include epigenetic changes. Disruption to the quality of the environment experienced during embryogenesis can have broad epigenetic consequences. For example, toxin exposure during this period can alter the process of genomic imprinting. Although most genes are biallelically expressed (meaning that both the gene copy inherited from the mother and the father produce messenger RNA), there is a subset of genes that is monoallelically expressed (only the maternal or paternal copy is expressed). This parent-of-origin effect on gene activity is referred to as *genomic imprinting*, and the silencing of the maternal or paternal gene copy is achieved via epigenetic mechanisms. Maintaining the parental imprint of an imprinted gene is critical for normal growth and development. Laboratory studies in rodents indicate that exposure to toxins during embryogenesis can disrupt genomic imprinting, leading to the activation of the normally silent parental gene copy. This environmentally induced epigenetic effect has long-term developmental consequences, increasing risk of adverse neurobiological and psychiatric outcomes.

The plasticity of epigenetic mechanisms was initially thought to be limited to early embryonic development, but studies of environmental exposures occurring during fetal development suggest that these mechanisms remain sensitive to a broad range of exposures occurring during this period. There is extensive research in humans indicating that prenatal exposure to maternal stress or altered maternal mood (e.g., depression, anxiety) is associated with altered birth outcomes and with long-term consequences for stress sensitivity of offspring. In rodents, prenatal stress exposure can lead to epigenetic changes in genes involved in the hypothalamic–pituitary–adrenal (HPA) response to stress. These epigenetic alterations lead to increased expression of genes that heighten the HPA response to stress and decreased expression of genes that can downregulate the HPA response to stress. One particular gene that has been found to be epigenetically sensitive encodes the glucocorticoid receptor. Activation of glucocorticoid receptors within the hippocampus leads to a downregulation of the HPA response to stress. When there is an elevated level of hippocampal expression of the *Nr3c1* gene, which encodes for the glucocorticoid receptor, there is an increased ability to decrease levels of circulating glucocorticoids. Thus, levels of *Nr3c1* expression can determine an individual's ability to recover from exposure to stress. Among human newborns and infants born to depressed mothers, there is increased DNA methylation within the *Nr3c1* gene in blood and buccal cells. Increased DNA methylation is typically associated with gene silencing. Increased DNA methylation of the *Nr3c1* gene in the newborn associated with maternal depression is also predictive of elevated stress responses in infants at 3 months of age. This example highlights the potential mediating role of environmentally induced epigenetic changes in subsequent phenotypes that confer increased risk of psychiatric outcomes.

Social experiences can have a profound impact on development. In particular, the quality of mother–infant interactions occurring during the postnatal period has been found to shape stress responsivity, fearfulness, and cognition in offspring. Variation in the quality of mother–infant interactions has been observed across species, including laboratory rodents.

Comparison of rodent offspring born to mothers who engage in low versus high levels of maternal care, particularly levels of tactile stimulation, reveals gene expression changes triggered by this stimulation within the brain that persist into adulthood. Epigenetic analyses of the hippocampus of offspring born to mothers who engage in low levels of maternal care indicate that this early life experience is associated with epigenetic silencing of the *Nr3c1* gene. Reduced activity of this gene is predictive of increased stress responses and likely accounts for many behavioral indicators of fearfulness and avoidance of novelty observed in offspring that have received low levels of postnatal maternal care. However, hundreds of genes are altered in their activity as a consequence of variation in postnatal maternal care, and epigenetic variation associated with this early life experience encompasses the entire genome. These genome-wide effects of parental care are also observed when comparing human infants reared by their biological parents versus those reared within institutions. Whole-genome profiling of DNA methylation patterns indicates that institutional rearing, typically characterized by deficits in caregiver–infant social interactions, results in increased DNA methylation throughout the genome. Thus, the epigenetic effects of parental care are relevant for understanding the biological pathways through which these early experiences shape human development.

### Epigenetic Plasticity in the Adult Brain

Although there are sensitive periods within development during which time the environment may have particularly profound effects, plasticity continues across the life span. This plasticity is evident in studies of learning and memory. The adult brain is capable of learning associations and in adapting to new information. The cellular and neurobiological processes that account for this capacity have been studied extensively, and analyses of the molecular basis of learning and memory suggest the critical role of epigenetic mechanisms. Gene expression is dynamically altered when we learn something new. These dynamic changes are mediated by epigenetic changes, including both increased gene activity and gene silencing. Studies in rodents indicate that, without the ability to alter the epigenetic state of DNA, it may not be possible to retain new information within the brain. One approach to studying learning and memory in laboratory rodents is to use a contextual fear-conditioning paradigm. In this experimental design, a rodent is placed in a novel context and administered a brief electric shock (an adverse experience). Exposure to a shock results in a fear response—typically freezing behavior. Following this learning trial, the rodent will typically freeze whenever placed in the context in which the shock was received. This behavioral response indicates memory of the adverse experience. However, if a rodent is treated with a drug that prevents DNA methylation from occurring following the learning trial, freezing behavior is less likely to occur. This finding suggests that, by preventing the process of DNA methylation, memory formation can be prevented. This strategy may have important implications for understanding fear learning in humans, which is relevant for post-traumatic stress disorder.

### Epigenetics and Aging

The role of epigenetics in the aging process is being increasingly explored. One area of research within the study of epigenetic mechanisms is epigenetic age. Epigenetic variation within cells is highly correlated with chronological age. However, there is evidence that adverse experiences occurring across the life span can accelerate epigenetic age, with possible implications for life expectancy. For example, maternal depression during childhood is predictive of accelerated epigenetic age in adolescents. Disease state may also accelerate the *epigenetic clock*, and individuals with chromosomal abnormalities, as in the case of Down

syndrome, have accelerated epigenetic aging. Although chronological age cannot be reversed, it is possible that the pace of epigenetic aging can be attenuated through social interventions. For example, maternal depression in childhood is associated with increased epigenetic age, however, this effect is not observed if a family-based program is implemented to reduce the occurrence of harsh parenting. Although epigenetic age may be indicative of the *weathering* of our biology, the dynamic nature of epigenetics and gene regulation also confers plasticity in response to life events that can promote healthy aging.

### Inheritance of Epigenetic Effects

Traditional views of inheritance focus on DNA as the sole biological basis of the transmission of phenotypes across generations. However, as our understanding of epigenetics continues to expand, there is increasing evidence that, in addition to DNA sequence, epigenetic variation within the genome may be inherited. Evidence for epigenetic inheritance is derived primarily from animal models. For example, if a pregnant female rat is exposed to the pesticide vinclozolin, reproductive impairments and increased disease risk is observed in offspring (F1 generation), grand-offspring (F2 generation), and great-grand-offspring (F3 generation). Epigenetic variation is also observed in each generation as a consequence of initial exposure (F0 generation). Similar transgenerational effects have been observed as a function of maternal exposure to a high-fat diet during pregnancy and to postnatal exposure to stress or disruptions in the quality of mother–infant interactions. This transmission is observed primarily in the patriline such that descendants of an exposed male (e.g., F1 male exposed in utero to vinclozolin or stress) inherit the epigenetic variation, and only males transmit this variation to subsequent generations. Although females in each generation can display altered functioning, including increased anxiety or deficits in social behavior, only males have the capacity to transmit these phenotypes to the next generation. This phenomenon of paternal transgenerational epigenetic inheritance has led to increasing focus on epigenetic changes that occur in sperm as a consequence of environmental exposure to stress, toxins, and nutritional variation. Research in this area has revealed a broad range of epigenetic effects, including DNA methylation, histone modifications, and expression of noncoding RNAs that occur in sperm following an environmental event that is also observed in the sperm and other tissues of descendants of exposed males.

Although environmental exposures in females have also been observed to influence the development of F1 generation offspring and their descendants, this phenomenon appears to be a social transmission rather than a germline transmission. In the case of a social transmission, the inheritance of phenotype depends on a change in the social context of development. For example, the experience of low versus high levels of maternal care in rodents leads to epigenetic and neurobiological changes within the brains of female offspring. The neural systems affected by this experience are critical to shaping maternal behavior. As a consequence of these neural changes, the female offspring (F1 generation) of a mother that engages in low levels of maternal care will engage in low levels of maternal care toward her own offspring (F2 generation). This transmission of maternal care from F1- to F2-generation females will then shape postnatal mother–infant interactions of the F3 generation. This *experience-dependent* route of inheritance may be particularly relevant to understanding the transmission of attachment styles, parental bonding, and abusive caregiving across generations. Epigenetic variation plays a critical role in this transmission by maintaining the effects of early caregiving experiences on gene activity from infancy to adulthood.

Advances in molecular biology have contributed to the rapidly evolving study of the role of epigenetic mechanisms in development, behavior, and the inheritance of variations in

phenotype. Ongoing research in this field of study suggests that, despite the potential stability of epigenetic variation—stability necessary for processes such as cellular differentiation—there is also tremendous plasticity in the epigenome that allows for shifts in developmental trajectories. This plasticity is an important consideration in studies of the long-term effects of early life adversity. It has been proposed that epigenetic mechanisms serve as a mechanism of adaptation to environmental challenges, and the transmission of these adaptations to subsequent generations may better prepare individuals to cope with environmental conditions. Thus, both the genome and epigenome may confer developmental advantages, and there is increasing focus on the interplay between these two biological factors and the implications of this interplay for a more integrated notion of development and evolution.

**See also** [Behavior Genetics](#); [Developmental Plasticity](#); [Gene–Environment Interplay](#); [HPA \(Hypothalamic–Pituitary–Adrenal\) Axis](#); [Inheritance](#); [Intergenerational Transmission](#); [Nature–Nurture](#)

- epigenetics
- methylation
- genes
- rodents
- twins, monozygotic
- DNA
- plasticity

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<http://dx.doi.org/10.4135/9781506307633.n284>

10.4135/9781506307633.n284

### Further Readings

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