The Journal of Mind and Behavior
Winter 2019, Volume 40, Number 1
Pages 53–62
ISSN 0271–0137

Transgenerational Trauma: The Role of Epigenetics

Stanley Krippner

Saybrook University

Deirdre Barrett

Harvard University Medical School

Epigenetics is the study of cellular variations that are caused by external, environmental factors that "switch" genes "on" and "off," making changes in the phenotype of genetic expression without concomitant changes in the DNA sequence or genotype. Epigenetic effects have been noted in the offspring of traumatized parents and there is some evidence that some of these effects can be observed in third generation offspring. However, the latter studies have been conducted with small numbers of non-human animals, with modest effect sizes. Implications for evolutional theory and psychotherapy are discussed.

Keywords: DNA, epigenetics, post-traumatic stress disorder, transgenerational trauma

There is a solid body of literature documenting and characterizing the effects of traumas of one generation upon its children or even subsequent generations (Danieli, 1998). However, physiological mechanisms are not usually discussed, even for the first generation, and later generation effects are assumed to be transmitted through parental behavior. A new field of biological study, epigenetics, offers not only a physiological explanation for how these transgenerational effects take place but also for the growing evidence that some trauma effects are inherited even when offspring are not raised by the traumatized parents. In this article, we will review epigenetic research especially as it applies to trauma and its potential inheritance.

Epigenetics is the study of cellular variations that are caused by external, environmental causes that switch genes "on" or "off," thus making changes in phenotype or genetic expression without concomitant changes in the DNA sequence

The preparation of this paper was supported by the Saybrook University Chair for the Study of Consciousness. Correspondence concerning this article should be addressed to Stanley Krippner, Ph.D., Saybrook University, 475 14th Street, Floor 9, Oakland, California 94612-1943. Email: skrippner@saybrook.edu

or genotype. The term is used to describe the modification of DNA packaging that alters the accessibility of DNA and potentially regulates gene expression without changing the sequence of DNA itself (Jones, Moore, and Kobor, 2018). Epigenetic research attempts to describe dynamic alterations in the transcriptional potential of cells, alterations that may or may not be inherited (Tost, 2008). Epigenetics can be thought of as a very specific sort of memory. Most memories involve the brain storing experiences by altering the connections between brain cells. This ability, often referred to as "plasticity," provides the basis for much alteration of behavior as well as for consciously recalled memories. In contrast, epigenetic changes are mediated by modifications of expression of specific genes and their protein production. These epigenetic changes in gene activity involve DNA and DNA-associated proteins but do not alter the DNA sequence itself. Gene expression can be "turned off" through the action of "repressor proteins" that attach themselves to the DNA, even though the DNA remains unchanged. Some epigenetic changes happen very rapidly as proteins change expression in a 24-hour cycle; however, the ones of interest to transmission of trauma involve much longer lasting alterations of gene expression.

Biologist C.H. Waddington introduced the word "epigenetic" in the 1940s to describe how growing cells acquire and maintain their identity through changing developmental stages. For example, the muscle cells, once differentiated, continue to divide into muscle cells, kidney cells into kidney cells, even though they all start from one universal cell and carry the same DNA after they divide. Waddington (1952) speculated that there was an "epigenetic" effect because all cells continue to have the same chromosomes, the same set of genes, and the same DNA sequencing. "Epigenesis" means "extra growth" (from a Greek noun) and this term, dating back to the seventeenth century, was the basis for Waddington's use of the adjective "epigenetic" because the observed effect is "extra," something in addition to the basic genetic effect.

In the following decades, Waddington's central questions were answered by scientists who found that the cells remember their states (e.g., muscle states, kidney states) through specific types of attachments to their DNA. Social insects, which often have an entire hive or anthill of genetic clones, differentiate into phenotypic queen vs. worker vs. drone bees or into forager vs. scout ants based on the same epigenetic programming mechanisms (Simola et al., 2016). There are several mechanisms through which epigenetics operate. Attachments may consist of DNA methylation (the replacement of hydrogen atoms with a methyl group) or through the modification of histones (the proteins that "package" DNA). A third process, involving "micro-DNA" by which small fragments of non-coding attach to the DNA of chromosomes also regulates gene expression and is usually included as a form of epigenetics. This research is important in understanding how life events can change an individual's health and behavior. Epigenetic mechanisms have already been shown to explain the action of disease-causing mechanisms

beyond those explainable by conventional genetics (Chen et al., 2016; Horowitz, 2015; Skinner, 2011; Skinner, Manikkam, and Guerrero–Bosagna, 2010). For example, rats on different diets show epigenetic effects, especially regarding the repair of damaged DNA chains; the same might be true of humans (Fang, Chen, and Yang, 2007). Epigenetic research has discovered instances in which cancer cells do not have the usual DNA mutations, but rather epigenetic changes have turned "off" or "on" genes that promote or block tumor formation (Struhl, 2014).

In an effort to unravel the epigenetic network underlying both short-term and long-term memory, Halder et al. (2016) examined changes in two regions of mice brains before and after contextual learning. They found that histone modifications changed during memory acquisition but showed little correspondence with gene expression. Although long-lasting changes were limited almost exclusively to neurons, learning-related histone modification and NDA methylation changes also occurred in non-neuronal cell types. This finding suggests a functional role for non-neuronal cells in epigenetic learning. These data also provide evidence for a molecular framework of memory acquisition and maintenance, wherein DNA methylation could alter the expression and splicing of genes involved in functional plasticity and wiring of the synapses, those parts of neurons that enable connections with other neurons (Farzadfard and Lu, 2014).

All these phenomena of epigenetics discussed so far depend upon gene expression being altered in an initial generation. However, there is additional research on how these changes may sometimes be passed to future generations.

In Utero Epigenetic Reprogramming

The mildest, but best-established, form of cross-generational epigenetic change is that in which the second generation is conceived or gestated while the parent is being exposed to trauma. An early example of epigenetic impact was the study of maternal stress during the Dutch Famine of 1944–1945 at the end of World War II. Medical records reveal that female offspring exposed to a low-nutrient diet prenatally during the mother's first trimester had a higher risk for both schizophrenia and breast cancer as adults. If the low-nutrient diet had occurred during the second trimester, the offspring had a high rate of lung and kidney problems. These epigenetic effects have been linked to the methylation patterns of a gene that coded for insulin-like growth factor 2 (IGF2); the 442 adults who lived through the famine showed the effect while a control group of 463 adults did not (Kennedy et al., 2014).

Several studies of the offspring of adults with histories of abuse as children, survival of war, and other forms of trauma leading to post-traumatic stress disorder (PTSD), reported a heritability effect. The offspring were more likely than others to develop PTSD through adverse maternal epigenetic-related experiences during pregnancy (Yahyavi, Zarghami, and Marwah, 2014). A study of 38

women who were pregnant when they witnessed the September 11, 2001 attacks on the World Trade Center in New York City demonstrated greater susceptibility to PTSD and lower levels of cortisol than members of a control group. Their offspring also had lower levels of cortisol, a hormone that assists recovery from trauma (Yehuda et al., 2005).

Indirect Transgenerational Epigenetic Inheritance

The studies above demonstrate that epigenetic effects can be observed in the offspring of parents who have survived stressful experiences such as the Holocaust, the September 11 attacks, famine, or other disasters. But can those effects be passed on to a third generation? For a direct biological effect, the affected DNA would have to be in the "germ" cell — the sperm or egg. Further it would also have to survive the "reset" at conception (Hackett et al., 2012). Ordinarily, there are two "cleansing and resetting" stages which remove all tags — one during the generation of the germ cell (egg and sperm) and one just after fertilization before implantation of the embryo. But some "tags" appear to slip through these "cleansing and resetting" stages (Tang et al., 2015). Before we explore this rare phenomenon, perhaps we should discuss the milder sense of multi-generational epigenetic effects: that methylation of DNA in a traumatized parent may result in behaviors around the offspring that cause similar methylation patterns anew in one or more generations.

Advocates of this explanation frequently point to studies of Holocaust survivors involving effects on their grandchildren. In one study, children and grandchildren of 32 men and women who survived the Holocaust were compared to descendants of Jewish parents who lived abroad during the Second World War. Members of the first group of parents had been tortured, imprisoned in concentration camps, or had remained hidden for several years. Members of the second parental group had undergone none of these traumatizing events. Both children and grandchildren of Holocaust survivors demonstrated symptoms of PTSD, more so if the mother had been the only survivor, but even if the father (and not the mother) had been oppressed by the Nazis (Yehuda, 2011). To explain the epigenetic effects on the grandchildren of Holocaust survivors, Yehuda noted that one region of a gene has been associated with the hormone cortisol, associated with the ability to recover from stress and trauma. Hypomethylation of this gene was found for both the children and grandchildren, but not for members of a control group. However, these children and grandchildren were being raised within their families, so the epigenetic markers may have been reinforced by behavioral interactions with the affected parents.

One rat study provides a model for how such effects might operate. Trauma to female rats affects how much contact they have with their pups, especially in terms of licking them. Researchers demonstrated that hormonal signals in the brain

of rats were related to the amount of licking the rats received as pups (Skinner and Guerrero–Bosagna, 2009; Weaver et al., 2004). Rats that received less licking during infancy displayed markedly less gregarious and exploratory behavior and showed lower methylation on genes responsible for regulation of corticosteroids. There's no demonstration that the methylation patterns were passed on by the germ cells in this case, but rather that traumatized maternal behavior instigates the methylation patterns anew. In further research by this group, they found that the effects of traumatizing mother rats decreased across each generation and disappeared entirely after five generations. They also observed that fostering the rat pups out to mothers who licked more completely prevented the effects on the offspring (Weaver, Meaney, and Szyf, 2006).

Most discussions of this study have referred to "inadequate maternal care" resulting in "impaired exploratory" behavior. However, from an evolutionary point of view, a mother rat who has lived her life in a relatively safe world grooming pups in a way that makes them explore and a mother who's faced severe dangers and grooms hers in ways that produce cautious offspring are equally adaptive and highlight the manner in which epigenetics can respond to environmental situations with adaptions in one generation vs. the centuries genes would take to alter (Barrett, 2010).

In a postmortem study on humans, the same research group found that this methylation pattern was seen to varying degrees in people who had either died of natural causes, died by suicide without a history of childhood abuse, and those who died by suicide with a history of childhood abuse (McGowan et al., 2009). Normal individuals showed less methylation in key areas of the hippocampus than those who died by suicide and those who died by suicide with a history of childhood abuse showed the greatest degree of methylation. The genes affected in these areas are again responsible for glucocorticoid regulation. Interactive effects between parental genes and offspring phenotype have also been supported in more strictly evolutionary research as well (Wolf, 2000).

Direct Transgenerational Epigenetic Transmission of Trauma

Direct epigenetic transmission by germ cells across multiple generations has been demonstrated most frequently for toxic exposures. Men who begin smoking before puberty have a higher chance of fathering obese sons than those who start smoking after puberty — an effect that cannot be accounted for by the smoke or nicotine exposure during sperm formation which would be equal for the two groups (Fang, Chen, and Yang, 2007). Epigenetic effects have also been documented for environmental toxins such as vinclozolin (an endocrine disrupter); the DNA methylation pattern of the sperm for three generations after the initial exposure (F3 males) is altered at specific promoter regions (Guerrero–Bosagna et al., 2010). Third generation epigenetic alteration of sperm was also observed

following exposure to pesticides, plastics, dioxin, and jet fuel (Guerrero–Bosagna et al., 2010; Manikkam, Guerrero–Bosagna, Tracey, Haque, and Skinner, 2012; Manikkam, Tracey, Guerrero–Bosagna, and Skinner, 2012a, 2012b, 2013).

Of more direct relevance to transgenerational effects of trauma is a mouse experiment conducted by Dias and Ressler (2014) examining how the olfactory (smell) experience of male parent mice might influence their offspring. The parent mice were conditioned to manifest fear when they smelled cherry blossoms. This was accomplished by pairing the odor with a shock to the foot. This fear changed the organization of the animal's nose, leading to more cells that were sensitive to that particular smell. This structural alteration was also found in future generations as was a fear-generated "startle" when the mice were exposed to the odor. The reaction to other odors was not affected. Their pups were found to be afraid of the odor and passed that fear down to their pups. The results suggest that the experiences of a parent, before conceiving offspring, markedly influence both structure and function in the nervous system of subsequent generations. The authors hypothesized that micro-RNA involved in gene expression enter the bloodstream and deliver odor information to sperm cells. From an evolutionary point of view, the offspring learned how to avoid a smell that had negative effects on their parents and grandparents. Dias and Kessler maintained that these behavioral and olfactory effects "were inherited and were not socially transmitted from generation to generation" (p. 89). They reached this conclusion after conducting in vitro fertilization so that there would be no contact between parent mice and their offspring. Micro-RNA maintains the activity of the gene and it is possible that these activities can be inherited, even when the original stimulus for their expression is no longer present (Mattick et al., 2009).

Another example highly analogous to human trauma involves a mouse model of early life stress by unpredictable maternal separation and maternal stress. This manipulation affects behavior severely across multiple generations (Franklin, Linder, Russig, Thorny, and Mansay, 2010; Franklin et al., 2011; Weiss, Franklin, Vizi, and Mansuy, 2011). Behavioral changes due to maternal separation and stress are accompanied by persistent molecular changes in the stress pathway as well as serotonergic signaling that are transmitted for three generations. The authors examined the sperm and found that DNA methylation was altered at gene promoters that correlated with changes observed in the brains of the stressed males from the subsequent generations (Franklin et al., 2010; Weiss et al., 2011). Another research group found that stress during the first week of gestation caused dysmasculanization in the male offspring that lasted multiple generations (Morgan and Bale, 2011). An X-linked placental gene, O-linked-N-acetylglucosamine, which regulates proteins involved with chromatin remodeling, was decreased following prenatal stress (Howerton, Morgan, Fischer, and Bale, 2013) and it is believed to play a role in the phenotype of masculinity. Another rodent model, using the chronic social defeat paradigm in adult male rats, also shows a

stress-related phenotype being passed on to subsequent generations with both male and female offspring displaying increased anxiety and depressive-like behaviors (Dietz et al., 2011). However, it appears that at least some of these behavioral phenotypes are transmitted behaviorally, with only the forced swim test phenotype persisting following in vitro fertilization.

There has been criticism of these studies, based on small sample sizes and the nature of the sample. Ptashne (2013) noted that some transgenerational claims are based on experiments with a few dozen mice (e.g., Dias and Ressler's experiment) or humans (e.g., Yehuda's studies). Another critic (Callaway, 2013) singled out the Dias and Ressler experiment for special criticism alleging that some of the mice were not siblings, that the sample size was small, and that the effect size was low.

Implications for Evolution

Advocates of "transgenerational epigenetic inheritance" argue that genes contained in DNA are the standard way that biological information is transmitted from one generation to succeeding generations but now point to the epigenetic "tags" that attach themselves to the DNA, as a further mechanism for inheritance. It is generally agreed that some of these "tags" can be inherited by children, but the inheritance by grandchildren has only a few established examples in animals such as mice. In addition, there is agreement that "micro-RNA" can impact sperm cells and affect offspring. But to what extent may they affect future generations? And, will this demand changes in evolutionary theory?

Transgenerational transmission of epigenetic programming does not violate the major theses of biological evolution. Mechanisms such as DNA methylation and histone modification are still genetically inherited under the aegis of natural selection (Lynch, 2007). At the same time the rate of change due to epigenetics can be more rapid than rates due to adaptive mutations, especially for plants and insects (e.g., Rando and Verstrepen, 2007). A frequently cited example is how Mourning Cloak butterflies will change color through hormone changes in response to experimentally-induced changes of temperature (Davies, 2008). The two forms of heritable information, namely genetic and epigenetic, can be collectively denoted as dual inheritance. There is an overlap in molecular mechanisms, but — according to mainstream scientists — nothing that justifies premature application of the data to extensive transgenerational epigenetic effects (The Guardian, 2014).

There is a growing body of research for this possible "dual inheritance" with humans and other animals seeming to inherit a predisposition for fear from their ancestors on a longer time scale presumably mediated by the DNA itself, and then a more specific fear conditioning through epigenetics. Primates' brains are uniquely tuned to recognize spiders and snakes. Human infants are not afraid of snakes and spiders at birth but learn to fear them more quickly than they learn

to fear other stimuli such as rabbits. Another study found that unborn crickets whose mothers were stalked by wolf spiders demonstrated a greater fear of those spiders after they were born than crickets whose mothers had not been exposed. Furthemore, the former offspring were more likely to survive than were crickets who did not avoid the lethal spiders (e.g., Barrett, 2010; Gruber, 1974). In his own age, Jean-Baptise Lamarck (1809) was reviled for his notion that acquired characteristics could be inherited. Today he is being hailed as ahead of his time.

Implications for Psychotherapy

Epigenetics in general, and especially its behavioral effects, are fast-expanding research areas, so many implications will be emerging over the next decades. At present, the most important consequence for psychotherapists conceptualizing psychopathology is the knowledge that severe trauma may be passed along through direct germ line alterations rather than simply through parenting. Therapists working with children adopted out of war zones or dysfunctional families may want to consider that these patients may be reacting to traumas of their parents even if they have not been raised by them. While there are no human treatment implications at this time, these may be on the horizon. One study has already demonstrated that the maternal stress in mice affecting subsequent generations as described above can be erased by infusion of l-methionine, an amino acid widely available in oral form at health food stores. L-methionine eliminated both hypo-methylation patterns in DNA and the trauma-produced behaviors in offspring (Weaver et al., 2005). This has obvious implications for human dietary and pharmacological intervention pending further studies. It is also possible that methylation studies of cortisol-associated genes or micro-RNA attachment might become a means of assessing whether therapeutic interventions are working.

References

Barrett, D. (2010). *Supernormal stimuli: How primal urges overran their evolutionary purpose.* New York: W.W. Norton.

Callaway, E. (2013). Fearful memories passed down to mouse descendants: Genetic imprint from traumatic experiences carries through at least two generations. *Nature Magazine,* Dec. 1. Retrieved from: https://www.scientificamerican.com/article/fearful-memories-passed-down/

Chen, Q., Yan, M., Cao, Z., Li, X., Zhang, Y., Shi, J., ... and Qian, J. (2016). Sperm tsRNAs contribute to intergenerational inheritance of an acquired metabolic disorder. *Science*, *351*(6271), 397–400.

Danieli, Y. (Ed.).(1998). *International handbook of multigenerational legacies of trauma*. New York: Plenum.

Davies, H. (2008). *Do butterflies bite? Frequently asked questions about butterflies and moths.* Camden, New Jersey: Rutgers University Press.

Dias, B.G., and Ressler, K.J. (2014). Parental olfactory experience influences behavior and neural structure in subsequent generations. *Nature Neuroscience, 17,* 89–97.

Dietz, D. M., Laplant, Q., Watts, E. L., Hodes, G. E., Russo, S. J., Feng, J., … and Nestler, E. J. (2011). Paternal transmission of stress-induced pathologies. *Biological Psychiatry, 70*, 408–414.

Fang, M. Chen, D., and Yang, C. S. (2007, January). Dietary polyphenols may affect DNA methylation. *Journal of Nutrition, 137* (Suppl.), 223S–228S.

Farzadfard, F., and Lu, T.K. (2014). Genomically encoded analog memory with precise in vivo DNA writing in living cell populations. *Science, 346*(6211), 1256272.doi: 10.1126/science.1256272

Franklin, T. B., Linder, N., Russig, H., Thony, B., and Mansuy, I. M. (2011). Influence of early stress on social abilities and serotonergic functions across generations in mice. *PLoS One, 6*, e21842.

Franklin, T. B., Russig, H., Weiss, I. C., Graff, J., Linder, N., Michalon, A., Vizi, S., and Mansuy, I. M. (2010). Epigenetic transmission of the impact of early stress across generations. *Biological Psychiatry, 68*, 408–415.

Gruber, H. E. (1974). *Darwin on man: A psychological study of scientific creativity.* New York: E.P. Dutton.

The Guardian. (2014). Beware the pseudo game. Retrieved from http://www.theguardian.com/july/1

Guerrero–Bosagna, C., Settles, M., Lucker, B., and Skinner, M. K. (2010). Epigenetic transgenerational actions of vinclozolin on promoter regions of the sperm epigenome. *PLoS One*, *5*, e13100.

Hackett, J. A., Sengupta, R., Zylicz, J. J., Murakami, K., Lee, C., Down. T. A., and Surani, M. A. (2012). Germline DNA demethylation dynamics and imprint erasure through 5-hydoxymethylcytosine. *Science, 339,* 448–452.

Halder, R., Hennion, M., Vidal, R.D., Shomroni, O., Rahman, R., Rajput, A., … and Bonn, S. (2016). DNA methylation changes in plasticity genes accompany the formation and maintenance of memory. *Nature Neuroscience, 19*, 102–110.

Horowitz, S. (2015). Epigenetics and its clinical applications. *Journal of Alternative and Complementary Therapies, 21,* 269–275.

Howerton, C. L., Morgan, C. P., Fischer, D. B., and Bale, T. L. (2013). O-GlcNAc transferase (OGT) as a placental biomarker of maternal stress and reprogramming of CNS gene transcription in development. *Proceedings of the National Academy of Sciences, 110*, 5169–5174.

Jones, M. J., Moore, S. R., and Kobor, M. S. (2018). Principles and challenges of applying epigenetic epidemiology to psychology. *Annual Review of Psychology, 69,* 459–485.

Kennedy, B. K., Berger, S. L., Brunet, A., Campisi, J., Cuervo, A. M., Epel, E. S., … and Rando, T. A. (2014). Geroscience: Linking aging to chronic disease. *Cell, 159*(4), 709–713.

Lamarck, J.-B. (1809). *Philosophie zoologique.* [Zoological Philosophy: Exposition with Regard to the Natural History of Animals]. Paris, France: Museum d'Histoire Naturelle.

Lynch, M. (2007). The frailty of adaptive hypotheses for the origins of organismal complexity. *PNAS, 104* (suppl. 1), 8597–8604.

Manikkam, M., Guerrero–Bosagna, C., Tracey, R., Haque, M. M., and Skinner, M. K. (2012). Transgenerational actions of environmental compounds on reproductive disease and identification of epigenetic biomarkers of ancestral exposures. *PLoS One, 7*, e31901.

Manikkam, M., Tracey, R., Guerrero–Bosagna, C., and Skinner, M. K. (2012a). Dioxin (TCDD) induces epigenetic transgenerational inheritance of adult onset disease and sperm epimutations. *PLoS One, 7*, e46249.

Manikkam, M., Tracey, R., Guerrero–Bosagna, C., and Skinner, M. K. (2012b). Pesticide and insect repellent mixture (permethrin and DEET) induces epigenetic transgenerational inheritance of disease and sperm epimutations. *Reproductive Toxicology, 34*, 708–719.

Manikkam, M., Tracey, R., Guerrero–Bosagna, C., and Skinner, M. K. (2013). Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. *PLoS One, 8*, e55387.

Mattick, J. S., Amaral, P. P., Dinger, M. E., Mercer, T. R., and Mehler, M. F. (2009). RNA regulation of epigenetic processes. *BioEssays, 31,* 51–59.

McGowan, P. O., Sasaki, A., D'Alessio, A. C., Dymov, S., Labonté, B., Szyf, M., ... and Meaney, M. J. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neuroscience*, *12*(3), 342–348.

Morgan, C. P., and Bale, T. L. (2011). Early prenatal stress epigenetically programs dysmasculinization in second-generation offspring via the paternal lineage. *Journal of Neuroscience*, *31*, 11748–11755.

Ptashne, M. (2013). Epigenetics: Core misconcept. *PNAS, 110,* 7101–7103.

Rando, O. J., and Verstrepen, K. J. (2007). The evolution of reversible switches in the presence of irreversible mimics. *Evolution, 63,* 2350–2362.

Simola, D. F., Graham, R. J., Brady, C. M., Enzmann, B. L., Desplan, C., Ray, A., … and Berger, S. L. (2016). Epigenetic (re)programming of caste-specific behavior in the ant *Camponotus floridanus*. *Science*, *351*(6268), aac6633.

Skinner, M. K. (2011). Role of epigenetics in developmental biology and transgenerational inheritance. *Birth Defects Research Part C: Embryo Today, 93*, 51–55.
Skinner, M. K., and Guerrero–Bosagna, C. (2009). Environmental signals and transgenerational epigenetics. *Epigenomics, 1*, 111–117.
Skinner, M. K., Manikkam, M., and Guerrero–Bosagna, C. (2010). Epigenetic transgenerational actions of environmental factors in disease etiology. *Trends in Endocrinology and Metabolism, 21*, 214–222.
Struhl, K. (2014). Is DNA methylation of tumour suppressor genes epigenetic? *Elife*, *3*, e02475.
Tang, W. W., Dietmann, S., Irie, N., Leitch, H. G., Floros, V., Bradshaw, C., … and Surani, M. A. (2015). A unique gene regulatory network resets the human germline epigenetics for development. *Biological Psychiatry, 16,* 1453–1464.
Tost, J. (2008). *Epigenetics.* Norfolk, United Kingdom: Caister Academic Press.
Waddington, C.H. (1952). *The epigenetics of birds.* Cambridge: Cambridge University Press.
Weaver, I., Cervoni, N., Champagne, F., D'Alessio, A., Sharma, S., Seckl, J., … and Meaney, M. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience, 7,* 847–854.
Weaver, I., Champagne, F. A., Brown, S. E., Dymov, S., Sharma, S., Meaney, M. J., and Szyf, M. (2005). Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: Altering epigenetic marking later in life. *Journal of Neuroscience*, *25*(47), 11045–11054.
Weaver I., Meaney, M. J., and Szyf, M. (2006). Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. *Proceedings of the National Academy of Science, 103,* 3480–3485.
Weiss, I. C., Franklin, T. B., Vizi, S., and Mansuy, I. M. (2011). Inheritable effect of unpredictable maternal separation on behavioral responses in mice. *Frontiers in Behavioral Neuroscience, 5*, 3.
Wolf, J. (2000). Gene interactions from maternal effects. *Evolution, 54,* 1882–1898.
Yahyavi, S. T., Zarghami, M., and Marwah, U. (2014). A review on the evidence of transgenerational transmission of post-traumatic stress disorder. *Revista Brasileira Psychiatra, 36,* 89–94.
Yehuda, R. (2011). Are different biological mechanisms involved in the transmission of maternal versus paternal stress-induced vulnerability of offspring? *Biological Psychiatry, 70,* 402–403.
Yehuda, R., Daskalakis, N. P., Lehrner, A., Desarnaud, F., Bader, H. N., Makotkine, I., … and Meaney, M. J. (2005). Influences of maternal and paternal PTSD on epigenetic regulation of the glucoticoid receptor gene on Holocaust survivor offspring. *American Journal of Psychiatry, 173,* 872–880.