Epigenetics Revolution: The Power to Self-regulate and Control Human Behavior

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Abstract

Many people believe that our specific DNA code represents our life destiny with respect to longevity, disease onset, and behavioral characteristics. This is not 100% scientifically true. One of the most exciting areas of genetics is the study of what mechanisms turn genes on or off in regulating our "DNA destiny." One critical process involved in gene regulation is epigenetics. The first section of this article discusses the scientific basis of epigenetics and the latter section will discuss the Jewish ethical issues and *mussar* lessons that are associated with epigenetics as a means to self-regulate and control human behavior.

Introduction

It is common knowledge that all organisms, including human beings, have a specific set of genes or instructions that directs how the organism develops from a fertilized egg until death. Genes can determine physical characteristics such as eye color or hair color, susceptibility to many diseases, longevity, and even human behavior and moods. One of the most controversial and exciting areas in genetic research is the identification of at least hundreds of genes that significantly influence human sexuality (e.g., adultery genes or homosexuality genes), violent behavior, depression, happiness and even spirituality. Yet, even though genes do influence many human physiological and behavioral traits, recent studies in epigenetics have shown that genes can be regulated to turn on or off to help determine who we become in many significant ways. While the Jewish

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tradition has always recognized that humans are more than simply our genetic and physical makeup, these findings in epigenetics have provided a new means to explain how this truth of the Jewish tradition operates, even at a genetic level.

Before discussing how epigenetics operates, it is vital to review basic tenets about genetics and highlight some selected traditional dogmas that are currently being scientifically challenged. The first genetic principle is that our genetic code is presented as a set of four nucleotides (letters) that translate into a set of genetic instructions. Often different cells in the body may develop mutations in their specific genetic code. Unless mutations occur, all cells in each human being will possess the same set of genetic instructions **that are unique** to that person.[1] What is less commonly appreciated is that possessing one set of genes does not mean that a specific characteristic (or phenotype) will be expressed, as predicted.[2] The common view of genetic determinism, over the past hundred years, relies on a simplistic conceptual scheme that there exist dominant and recessive genes, and that the combination of genes determines his or her revealed characteristic (phenotype).[3] There are many scientific reasons why possessing a specific gene (or set of genes) will not necessarily predict phenotype.[4] First, genes can come in different flavors or forms, called alleles. Second, there are many pleiotrophic and polygenic interactions[5] between the ~22,000 different genes that can influence how these genetic instructions present themselves in an individual. For example, in Ashkenazi Jews, the probability that a person who expresses specific gene mutations in BRCA genes will contract breast cancer in her lifetime is about 75%.[6] There are several reasons that the probability is not a 100%. There may be other genes that this person expresses that may mitigate the cancer risk. In addition, genes can be regulated by a variety of other processes, including epigenetics that can turn a gene on or turn off without changing

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1 One recognized exception to this is the fact that identical twins possess the same genes.

2 https://www.mechanobio.info/genome-regulation/; https://www.nature.com/scitable/topicpage/gene-expression-14121669.

3 TH Morgan, (1917), "The theory of the gene," *The American Naturalist*, 51, 513–544.

4 Ibid. 2.

5 Pleiotrophy is where one gene may affect many traits and polygeny is where many genes can affect one trait.

6 https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet; https://www.oncolink.org/risk-and-prevention/genetics-family-history/ashkenazi-jewish-heritage-and-genetic-risk.

the letters of the genetic code. These observations provide an important insight that genetics reflects a probability and not a destiny.

The second principle or traditional dogma of genetics is that only about 5% of our genetic code contains specific genes (i.e., set of instructions). The other 95% has sometimes been called "junk DNA" that contains DNA sequences that are similar to those seen in bacteria, viruses, and other organisms. We know that God does not create junk.[7] Over the past several years, scientists have been discovering that these non-encoding regions of our chromosomes can influence and regulate gene expression.[8] The third traditional dogma in genetics is that mitochondrial DNA represents a small amount of our genetic information, that mitochondrial DNA is not involved in personality traits or physical traits, and that mitochondrial DNA is maternally inherited. In all enucleated cells, genetic information is stored in two organelles, the nucleus and mitochondria. Conventional wisdom is that greater than 99% of the DNA contained in our chromosomes is located in the nucleus of the cell. In fact, a huge amount of DNA is found in another organelle called the mitochondria. Almost all human cells contain hundreds or thousands of mitochondria. Each mitochondrion contains a unique circular DNA with 37,000 base pairs (genetic letters). For example, the fertilized egg contains about 100,000 mitochondria and each mitochondrion contains at least two copies of mitochondrial DNA.[9] This means that the number of letters (nucleotides) in all mitochondrial DNA contained in each fertilized egg represents about **eight billion** letters [400,000 copies of mitochondrial DNA times 37,000 letters or nucleotides per mitochondrial DNA] compared with the **six billion** letters (3 billion base pairs) contained in the 46 chromosomes[10] of the nucleus of the fertilized egg. Mature human eggs (oocytes) with less

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7 See Rabbi Akiva's statement, "All that God does is for the good" (BT *Berakhot* 60a). See also Maimonides' *Introduction to the Mishna*, where he writes, "Anything that exists has of necessity a purpose for which it exists, for there is nothing that exists in vain." In *Moreh Nevukhim* (III, 25) Maimonides explains that purposeless acts cannot be attributed to God, based on the verse "And God saw everything that He had made, and, behold it was good" (Genesis 1:31).

8 https://ghr.nlm.nih.gov/primer/basics/noncodingdna.

9 Elnur Babayev, Emre Seli, *Oocyte mitochondrial function and reproduction*, published in final edited form as *Current opinion in obstetrics & gynecology*, 2015, 27.3: 175; Timothy Wai et al., "The role of mitochondrial DNA copy number in mammalian fertility," *Biology of reproduction*, 2010, 83.1: 52–62.

10 https://ghr.nlm.nih.gov/primer/basics/dna.

than 50,000 copies of mitochondrial DNA tend to be infertile.[11] Regarding the point that mitochondrial DNA is not involved in personality traits or physical traits, there are also several peer-reviewed research studies that suggest that mitochondrial DNA regulates both personality traits and physical traits.[12] Secondly, the alleged dogma that mitochondria and mitochondrial DNA comes from our mothers has been recently challenged. In a paper published in the fall of 2018, scientists from China identified 17 individuals from three unrelated families in which their cells contained both paternal and maternal mitochondrial DNA.[13] At this point in time we do not know how common or rare paternal transmission DNA is. However, it is clear that paternal inheritance of mitochondrial DNA occurs in many species, including honey bees, chickens, mice, and sheep.[14] If paternal transmission of mitochondrial DNA is not a rare event, then there will be many medical / halakhic and scientific ramifications that need to be revisited that are beyond the scope of this article. One example is that the potential prevalence of paternal transmission could affect the recent recommendation by the *dayanim* of the Eretz Hemdah Institute for Advanced Jewish Studies in Jerusalem[15] to accept determination of Jewish status of immigrants to Israel from the former Soviet Union based on identifying unique mitochondrial genetic markers (haplotypes) found in almost all Ashkenazi Jews.

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11 Ibid.

12 Rebecca E. Anglin et al., "The psychiatric manifestations of mitochondrial disorders: a case and review of the literature," *The Journal of clinical psychiatry*, 2012, 73.4: 506–512; Chieko Kato et al., "Mitochondrial DNA polymorphisms and extraversion," *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 2004, 128.1: 76–79; Ann Gardner et al., "Alterations of mitochondrial function and correlations with personality traits in selected major depressive disorder patients," *Journal of affective disorders*, 2003, 76.1–3: 55–68; I. A. Pretty, D Sweet, "A look at forensic dentistry–Part 1: The role of teeth in the determination of human identity," *British dental journal*, 2001, 190.7: 359-. This article shows how obtaining teeth from a deceased victim can be used as a source of mitochondrial DNA to identify the deceased. Mark D. Shriver et al., "Ethnic-affiliation estimation by use of population-specific DNA markers," *American journal of human genetics*, 1997, 60.4: 957. This article shows how mitochondrial DNA determines ethnicity.

13 S Luo, CA Valencia, J Zhang, NC Lee, J Slone, B Gui, X Wang Z Li, S Dell, J Brown, SM Chen, "Biparental inheritance of mitochondrial DNA in humans," *Proceedings of the National Academy of Sciences*, 2018 Dec 18;115(51):13039–44; https://www.pnas.org/content/116/5/1475.long; https://www.pnas.org/content/116/6/1821.long.

14 Ibid.

15 Responsa, *Be-mareh Ha-bazak* Vol. 9, pp. 94–99.

The fourth alleged genetics dogma presented in every genetics textbook is that Gregory Mendel is the father of genetics. From a Torah perspective, one could propose that Yaakov Avinu is the true father of genetics. As you read the story how Yaakov acquired a herd of spotted sheep from Lavan, it is obvious that he understood the concepts of a dominant trait, a recessive trait and even epigenetics (how lifestyle can influence physical genetic traits) to mate non-spotted sheep to give birth to spotted sheep.

Section one: The Science of Gene Regulation and Epigenetics

As mentioned above, just because a person possesses a specific gene, it does not necessarily mean that the gene will be turned on to express a certain characteristic. There are various cellular processes that regulate whether a gene is active or inactive in expressing its genetic instructions. Specific genes can be controlled by other genes, proteins (transcription factors), different small RNA molecules, and epigenetics to regulate whether that gene or set of genes are turned on or off.[16] In general, all of these processes do not alter the letters of the genetic code (or DNA sequence). In other words, the DNA code is the hardware of inheritance and epigenetics is its software.

How does epigenetics work? Imagine you have a sentence in the text that reads "Nucleotides are the genetic letters of DNA." If you mask or cover this sentence with an opaque marker you will not be able to read the sentence. Once you erase the marker then the sentence is again readable. The marker does not erase the sentence; it just masks the reading of the sentence. Epigenetics are such markers that can mask or sometimes unmask genetic instructions.

On a basic level, epigenetics can be divided into three processes: a) histone-mediated methylation, b) histone-mediated acetylation, and c) methylation of specific DNA base pairs or nucleotides.[17] Specifically, in almost all human cells nuclear DNA is wrapped around proteins, called histones, and chemical modifications of these proteins affect whether a gene is transcribed (turned on or off). When the histone is methylated it generally increases its binding to a specific DNA region to prevent that gene from being read. When the histone is acetylated, it loosens the binding of the histone to the DNA gene and promotes the expression or reading of the gene. The third type of epigenetic mechanism is based on the capacity of cells to chemically tag the coded DNA base pair with a methyl

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16 Ibid #2; https://en.wikipedia.org/wiki/List_of_RNAs.

17 There are also epigenetic processes mediated by small RNAs that are beyond the scope of this article.

group. This methylation process is another way to mask or inactivate the set instructions encoded by that gene (see Figure 1). In all these epigenetic processes, the actual genetic code is never altered and continues to be inherited by offspring.

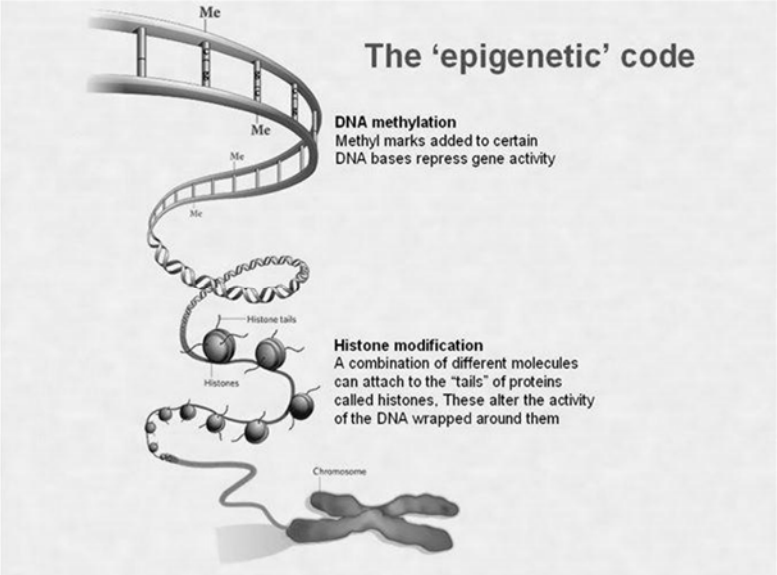

Figure 1

Two other important concepts of epigenetics need to be elucidated. First, the environment is a critical trigger of epigenetic modifications. Second, in many cases, epigenetic modifications can be passed down to children and even to grandchildren.

Understanding epigenetics underscores well-known biological processes, including cell differentiation,[18] genomic imprinting[19] and X chromosome inactivation.[20] One of the earliest studies on epigenetics was

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18 One essential function of epigenetic processes in multicellular organisms is orchestrating cell differentiation to turn on and off specific genes to direct stem cells to develop into organ-specific cells such as neurons, muscle cells, immune cells and skin cells.

19 All human beings inherit two copies of every autosomal gene, one copy from the mother and one from the father. Both copies are functional for the majority of these genes. However, in a small subset of genes, one copy is turned off in a parent-of-origin dependent manner and the other copy is allowed to function. The genes in this subset of our genome are called 'imprinted' because one copy of the gene was epigenetically marked or imprinted in either the egg or the sperm.

20 All female humans have two X chromosomes (one from the father and one

published by Waterland and his colleagues who showed that a mother mouse's diet during pregnancy influences the colors of her pups' coats via the methylation of a particular gene. This influence on coat color can present for several generations.[21]

Below we present a small number of examples to illustrate how diverse and widespread epigenetic processes can influence the physical and behavioral patterns of animals and human beings. While some people still believe epigenetics is only a theory, we now have technologies to biochemically identify the epigenetic markers on DNA. We also have technologies that can alter the epigenetic markers to turn genes on or off. These technologies provide concrete evidence that epigenetics is more than just a theory.

In the animal kingdom, one classic example of epigenetics is found in honey bees. A queen bee can lay many genetically identical larvae per day. If any particular bee larva of the identical genetic larvae laid is fed royal jelly (honey or royal jam that only the Queen bee makes) it will develop into a queen bee. However, if that same larva is fed regular honey it will develop into a worker bee.[22] Research has demonstrated that royal jelly produced from the queen and normal honey produced from worker bees each trigger different methylation sites on the bee larva's DNA that control the development of the larva into either a queen or a worker bee.

In human beings, each cell has the same unique genetic code all of which stem from the same zygote. Yet, the person who develops from this cell contains over 200 types of cells, which compose various bones and muscle tissues, as well as organs, such as the liver, brain, heart, etc. Why does a muscle cell look and function differently from a nerve cell if they both contain the same DNA or genetic information? The answer is that each cell or tissue type is characterized by its unique signature of

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from the mother) when only one is necessary for development. In all females, one X chromosome (either the maternally or paternally derived X) is randomly inactivated in an early embryonic cell, with fixed inactivation of that same X in all cells descended from that cell. The change that occurs with X inactivation is epigenetic: it is a heritable change in gene function without a change in the sequence of the DNA.

21 RA Waterland, RL Jirtle, "Transposable elements: targets for early nutritional effects on epigenetic gene regulation," *Molecular and cellular biology*, 2003 Aug 1;23(15):5293–300.

22 A Chittka, L Chittka, "Epigenetics of royalty," *PLoS biology*. 2010 Nov 2;8(11): e1000532; https://epigenie.com/bee-not-bee-queen-role-chromatin-structure-honey-bee-caste-determination/; Drone bees develop from the queen's unfertilized haploid eggs and each drone can produce 10 million male sperm cells, each genetically identical to the egg.

genes that are turned on or off. A muscle cell has a different set of hundreds of genes that are turned off or on, which are different from the set of genes turned on or off in a nerve cell or liver cell. Thus, during the embryological development from a fertilized egg into a child, the DNA in each cell and tissue is programed, via epigenetics, to turn into the appropriate cell type to generate a healthy child. What is really amazing is that when a sperm fertilizes and enters an egg, the egg must reprogram the sperm by removing almost all of its epigenetic markers to make all the genes of the fertilized egg and sperm available for embryological development.[23]

As mentioned above, an individual that has certain mutations can develop serious diseases but rarely do all of the people who possess these mutations develop the corresponding diseases. You would expect that these mutations result in 100% of the people developing these diseases, but they do not. The reason for less than 100% presentation of disease is that each individual has his or her own epigenetic markers that may inactivate those mutations that could cause the disease. Aside from the example of BRCA mutations, mentioned above, we know that there are individuals who have inherited the same genetic mutation from each parent (homozygous) that causes the child to develop Gaucher's disease. Yet, there is considerable heterogeneity in how this disease affects any patient. Not all children with this genetic predisposition will develop the symptoms for this disease. Some individuals will live their whole life symptom-free while others will develop serious symptoms at birth, during adolescence, or during their adult years.[24] When or if these symptoms develop is a function of their epigenetics that regulates gene expression.

One of the most important features of epigenetics is that it provides the mechanistic link of how environment and lifestyle can affect human health and behavior. The fact that epigenetics is inheritable is essential in understanding the ramifications of the lifestyle of a parent on the health of his or her child or grandchild.

For example, human diets including fruits, vegetables, olives, and chocolate have been shown to promote resilience against stress and reduce depression in the women and their children, via epigenetic mecha-

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23 M Teperek, K Miyamoto, "Nuclear reprogramming of sperm and somatic nuclei in eggs and oocytes," *Reproductive medicine and biology*, 2013 Oct 1;12(4):133–49.

24 Y Zhang, C Qin, L Yang, R Lu, X Zhao, G Nie, "A comparative genomics study of carbohydrate/glucose metabolic genes: from fish to mammals," *BMC genomics,* 2018 Dec;19(1):246.

nisms. Blueberries have been shown to epigenetically reduce environmentally induced or spontaneous DNA damage, thereby protecting humans against certain cancers and possibly even slowing aging. Moreover, individuals on specific diets have been shown to express epigenetic modifications on genes that regulate obesity.[25] Scientists have even discovered that limited fasting has concrete medical benefits, such as promoting longevity via epigenetic mechanisms, while uncontrolled dietary indulgence triggers different epigenetic mechanisms that shorten human lifespan. Epigenetics is also associated with longevity in general.[26] As a person ages, specific genes that encode for ribosomal proteins contain more and more epigenetic markers. Once these genes express a specific number or range of epigenetic markers, the person will die.[27]

Lifetime health of the parents at the time of conception is an important factor in producing healthy children.[28] Nicotine exposure in men during their reproductive years has been shown to lead to low sperm count in their sons,[29] and cognitive deficits in their children and even in

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25 P Kühnen, D Handke, RA Waterland, BJ Hennig, M Silver, AJ Fulford, P Dominguez-Salas, SE Moore, AM Prentice, J Spranger, A. Hinney, "Interindividual variation in DNA methylation at a putative POMC metastable epiallele is associated with obesity," *Cell metabolism,* 2016 Sep 13;24(3):502–9.; K Mochizuki, N Hariya, K Honma, T Goda, "Relationship between epigenetic regulation, dietary habits, and the developmental origins of health and disease theory," *Congenital anomalies,* 2017 Nov;57(6):184–90; MJ Heerwagen, MR Miller, LA Barbour, JE Friedman, "Maternal obesity and fetal metabolic programming: a fertile epigenetic soil," *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2010 Jul 14;299 (3): R711–22.

26 AW MacInnes, "The role of the ribosome in the regulation of longevity and lifespan extension," *Wiley Interdisciplinary Reviews*: *RNA,* 2016 Mar;7(2):198–212; https://www.inverse.com/article/53298-new-biological-clock-discovered-in-human-body; M Wang, B Lemos, "Ribosomal DNA harbors an evolutionarily conserved clock of biological aging," *Genome research,* 2019 Mar 1;29(3):325–33.

27 Ibid.

28 TP Fleming, AJ Watkins, MA Velazquez MA, JC Mathers, AM Prentice, J Stephenson, M Barker, R Saffery, CS Yajnik, JJ Eckert, MA Hanson, "Origins of lifetime health around the time of conception: causes and consequences," *The Lancet,* 2018 Apr 16.

29 J Axelsson, S Sabra, L Rylander, A Rignell-Hydbom, CH Lindh, A Giwercman, "Association between paternal smoking at the time of pregnancy and the semen quality in sons," *PloS one*. 2018 Nov 21;13(11):e0207221.

some of their grandchildren.[30] Other studies in mice show that paternal cigarette smoking may increase the risk of ADHD in their offspring.[31] Studies also have shown that nicotine use or smoking by pregnant women is associated with an increased risk of behavioral disorders in their children and even in subsequent generations.[32] What is really important is that vitamin C prevents epigenetic changes with maternal smoking.[33]

Scientists from Duke University have advised men to abstain from using cannabis (marijuana) for at least six months before trying to conceive a baby. They report that cannabis use is associated with extensive epigenetic changes in the genes of sperm. Many of these changes were associated with disorders in the growth and organ size of the fetus.[34] Since recent polls indicate that over 25% of males between 18 and 25 use cannabis in some form, which may only increase given the legalization of this drug spreading across the United States, the health impact of cannabis use on future generations may turn out to be significant.

Recent studies have also shown that the time of year when a baby is born can be a strong predictor of their risk of dying in young adulthood.[35]

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30 DM McCarthy, TJ Morgan Jr, SE Lowe, MJ Williamson, TJ Spencer, J Biederman, PG Bhide, "Nicotine exposure of male mice produces behavioral impairment in multiple generations of descendants," *PLoS biology,* 2018 Oct 16;16(10):e2006497.

31 https://medicalxpress.com/news/2019-02-maternal-pregnancy-adhd-offspring-three-fold.html

32 N Leybovitz-Haleluya, T Wainstock, D Landau, E. Sheiner, "Maternal smoking during pregnancy and the risk of pediatric cardiovascular diseases of the offspring: A population-based cohort study with up to 18-years of follow up," *Reproductive Toxicology,* 2018 Jun 1;78:69–74.

33 LE Shorey-Kendrick, CT McEvoy, B Ferguson, J Burchard, BS Park, L Gao, BH Vuylsteke, KF Milner, CD Morris, ER Spindel, "Vitamin C prevents offspring DNA methylation changes associated with maternal smoking in pregnancy," *American journal of respiratory and critical care medicine,* 2017 Sep 15;196(6):745–55.

34 SK Murphy, N Itchon-Ramos, Z Visco, Z Huang, C Grenier, R Schrott, K Acharya, MH Boudreau, TM Price, DJ Raburn, DL Corcoran, "Cannabinoid exposure and altered DNA methylation in rat and human sperm," *Epigenetics,* 2018 Dec 2;13(12):1208–21; https://www.genengnews.com/news/cannabis-use-linked-with-epigenetic-changes-to-sperm/.

35 SE Moore, TJ Cole, EM Poskitt, BJ Sonko, RG Whitehead, IA McGregor, AM Prentice, "Season of birth predicts mortality in rural Gambia," *Nature*, 1997 Jul;388(6641):434; RA Waterland, RL Jirtle, "Transposable elements: targets for early nutritional effects on epigenetic gene regulation," *Molecular and cellular biology,* 2003 Aug 1;23(15):5293–300; RA Waterland, R Kellermayer, E Laritsky, P Rayco-Solon, RA Harris, M Travisano, W Zhang, MS Torskaya, J Zhang, L

Such individual-specific epigenetic markings that occur early in development and continue to present in all tissues throughout the organism's lifetime are called metastable epialleles.[36] Thus, some epigenetic markers can affect many genes, not just one. The sages of the Talmud already discuss how the time when a person is born influences how that person's life may progress, yet they also recognize that such factors are not strictly determinative, especially for Israel.[37]

Metastable epialleles can show systemic (cross-tissue) inter-individual variation in methylation in the preimplantation embryo. These epigenetic modifications can stably be maintained in differentiated tissues, leading to inter-individual epigenetic variation that affects multiple cell types throughout the organism's lifetime. For example, a recent study in *Science Advances* identified 687 candidate metastable epialleles—and that list is likely to be incomplete.[38] The fact that environment can affect multiple genes may help explain how metastable epialleles are linked to various forms of human disease such as cancer and asthma.[39]

Sleep is another factor that can affect epigenetic markers and patterns. Lack of sleep has been linked to weight gain, a reduction of lean muscle mass and an increased risk of diabetes.[40] While the lack of sleep can trigger epigenetic pattern changes, we still do not have a clear idea of how many days of normal sleep are needed to reverse these epigenetic changes.

Individuals who exercise improve their body and brain functions as well as the mental capacities of their future children. Epigenetic changes from regular exercise affect the sperm of men and significantly impact the

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Shen, MJ Manary, "Season of conception in rural Gambia affects DNA methylation at putative human metastable epialleles," *PLoS genetics,* 2010 Dec 23;6(12):e1001252; NJ Kessler, RA Waterland, AM Prentice, MJ Silver, "Establishment of environmentally sensitive DNA methylation states in the very early human embryo," *Science advances,* 2018 Jul 1, 4(7):eaat2624,Nat Commun, 5:3746.

36 P Dominguez-Salas, SE Moore, MS Baker, AW Bergen, SE Cox, RA Dyer, AJ Fulford, Y Guan, E Laritsky, MJ Silver, GE Swan, "Maternal nutrition at conception modulates DNA methylation of human metastable epialleles," *Nature communications,* 2014 Apr 29, 5:3746; NJ Kessler, RA Waterland, AM Prentice, MJ Silver, "Establishment of environmentally sensitive DNA methylation states in the very early human embryo," *Science advances,* 2018 Jul 1;4(7):eaat2624.

37 BT *Shabbat* 156a-b.

38 Ibid #34- Dominguez-Salas et al.

39 RA Harris, D Nagy-Szakal, R Kellermayer, "Human metastable epiallele candidates link to common disorders," *Epigenetics,* 2013 Feb 1;8(2):157–63.

40 https://www.genengnews.com/news/epigenetics-of-sleep-loss-linked-with-weight-gain-and-muscle-loss-in-humans/

mental fitness of their offspring.[41] Compared with the control group, the offspring of mice whose parents engaged in physical and mental exercise performed much better on the learning tests.[42] Additionally, these mice saw a boost in their synaptic plasticity in a region of the brain crucial to learning, the hippocampus. The greater the synaptic plasticity, the greater the ability of nerve cells to communicate with each other, which forms the cellular basis for learning. These studies are being substantiated in human beings as well.

Physical traits and susceptibility to disease are not the only processes regulated by epigenetics. Human behavior is also highly influenced by epigenetic processes. Epigenetics is of fundamental relevance to the social sciences in its complication of the nature-nurture dichotomy, as it demonstrates that environmental exposures can profoundly change social interactions and behaviors, even those that were previously seen as hard-wired in a person's genetics. In recent years, research has identified genetic variants triggered by negative environmental experiences during prenatal life, childhood and adolescence that strongly influence the development of long-lasting aggressive behavior and psychiatric disorders in adulthood.[43] Environmental factors also can have positive behavioral effects. Cuddling of babies can leave positive epigenetic traces on the babys' DNA to help them grow up to be calm adults.[44]

There is a rich literature on the role of epigenetics and the pregnant mother to imbue the fetus with certain predispositions.[45] The mother's emotion, such as fear, anger, love, and hope, can biochemically alter the genetic expression of the offspring. Epigenetic findings can provide scientific explanation for how R. Yochanan's practice to position himself so that he was the first male image women would see when they left the *mikvah* could be effective.[46] R. Yochanan explains that his motivation was

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41 https://www.askmen.com/sports/health/everyday-activities-that-may-be-impacting-your-fertility.html; E Benito, C Kerimoglu, B Ramachandran, T Pena-Centeno, G Jain, RM Stilling, MR Islam, V Capece, Q Zhou, D Edbauer, C Dean, "RNA-dependent intergenerational inheritance of enhanced synaptic plasticity after environmental enrichment," *Cell reports,* 2018 Apr 10;23(2):546–54.

42 Ibid.

43 S Palumbo, V Mariotti, C Iofrida, S Pellegrini, "Genes and aggressive behavior: epigenetic mechanisms underlying individual susceptibility to aversive environments," *Frontiers in behavioral neuroscience,* 2018;12.

44 https://www.whatisepigenetics.com/cuddling-can-leave-positive-epigenetic-traces-babys-dna/.

45 JA Russell, PJ Brunton, "Giving a good start to a new life via maternal brain allostatic adaptations in pregnancy," *Frontiers in neuroendocrinology,* 2019 Feb 22.

46 *Nedarim* 20a: *Midrash, Bereishit Rabba* 71:5.

that, since he was so handsome, gazing upon him before conception would lead women to have more beautiful children. His reasoning, and the potential explanation for its efficacy, could also explain how Yaakov's sheep that grazed upon the "rods of fresh aspen that were peeled" and became excited [at the sight of the rods][47] gave birth to spotted sheep.

One of the most important aspects of epigenetics is that changes in life-style may alter the deleterious epigenetics effects. For example, exercise, dietary changes and even surgery-induced weight loss can reverse the ill effects of non-nutritious diets that alter the health and fertility of men's sperm.[48]

In summary, our fate or genetic destiny is not locked in our genes. The environment or life-style of human beings can affect either a specific gene or a family of genes via epigenetic modifications. Scientists are just now beginning to track how various life styles or diets influence our genome. In the future, when diagnosing human disease, we will need to include analysis of the patient's genes, genetic mutations and epigenetic patterns. Obtaining this information with family history of disease will open the door to a new phase of maintaining optimal human health, disease treatment, and longevity.

Halakha and Epigenetics

In general, medical halakhic rulings are driven by our understanding of science and medicine. As medical and scientific knowledge expands, the application of halakha to new areas will expand and our understanding of how the halakha should apply to areas where our understanding was previously lacking may change. An example of this may be seen in the previous debate over maternity in cases of gestational surrogacy. There has been a strong consensus among Israeli *poskim* that in cases of surrogacy, the genetic mother should be considered the actual mother of the child. This is based on the understanding that children's physiological development is based on their DNA and that the role of the woman gestating a fetus was understood as simply providing the proper environment for healthy fetal development. However, scientists have now shown not only that the surrogate's stem cells traverse the placenta and implant into the fetus' tissue but also that the environment of the womb created by the surrogate (both through her lifestyle behaviors and through the production of hormones) affects the genetic expression of the fetus' DNA. The fact that the gestating mother and her lifestyle impacts, via epigenetics, the health and future phenotype (both physiological and behavioral) of the fetus, as well as of subsequent generations, enriches our understanding

47 See Hirsch, Genesis 30:37–40.

48 JAMA, 2017;317(20):2049-2051. doi:10.1001/jama.2017.1566.

of the unique and important role that pregnancy has on fetal development. These observations create a biological link between gestational motherhood and the fetus she is carrying, thereby supporting a reading of the Talmud and *poskim* that views the surrogate mother as the halakhic mother.[49]

Spiritual Epigenetics and Metastable Epialleles

One of the most difficult modern problems we face today is how to reconcile our genetic behavioral predispositions with our actions and how both might affect the fate of our children. Equally important is the question of how we can understand our obligation to fulfill commandments in the face of strong genetic determinants, which can give rise to the justification that we cannot control our own behavior. Understanding the nuance and variability of our "genetic destiny" underscores many stories in *Bereshit*, including the story of Kayin and Hevel. Even before Kayin kills Hevel, God warns Kayin that even if human beings have genetic predispositions to perform undesirable behaviors, God also provided humans with the power to control their genetics,[50] ואתה תמשל בו.

Could this power to control our genetic predisposition to sin be related to the spiritual effects of lifestyle (i.e., mitzvot) and epigenetics?

The science of epigenetics can serve to explain many of the lessons of the Jewish tradition related to the power of mitzvot to refine people.[51] For example, Maimonides writes in *Hilkhot De'ot* that people who sin have a spiritual ailment and should seek the advice of the wise who will "heal" their character traits of the soul.[52] He also discusses how the repetition of positive conduct will lead a person to acquire character traits (virtues) that embody the positive values that such conduct demonstrates.[53] Likewise, a person who habituates himself to regularly perform undesirable conduct will acquire those faults associated with such conduct. This idea is further supported by *Sefer HaḤinuch* who exemplifies the concept when he writes, "If a king forcefully appointed [a righteous man] to an evil vocation, then, in truth, if his entire occupation…will be that vocation, at some point in time he will turn from righteousness."[54]

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49 Loike and Tendler, "Becoming a Surrogate for an Infertile Jewish Couple," *Journal of halakha and Contemporary Society*, 66:5–21, 2013.

50 Genesis 4:7.

51 *Midrash Rabbah*, Genesis 44:1.

52 *Hilkhot De'ot* 2:1.

53 *Hilkhot De'ot* 1:7.

54 *Mitzvah* 16.

It is possible that scientific research will be able to show us how the engagement in a lifestyle of *chesed* can generate global epigenetic modifications that can affect many genes that normally control unethical behavior. Knowing that even temporary engagement in certain types of behavior can lead to lasting epigenetic changes, research might also show how Maimonides' suggestion in *Hilkhot Teshuva* to engage in many mitzvot and specifically *tzedakah* or *ḥesed* between *Rosh Hashanah* and *Yom Kippur* can alter our personality via epigenetics.[55] Similarly, the *mitzvoth* of the *nazir*[56] and Malbim's interpretation of *Kidoshim te'hihu*[57] that engagement in specific *mitzvot* will raise the level of a person's *kedusha*[58] may be mediated by both spiritual and molecular process (i.e., epigenetics).

We still need to investigate which *mitzvot* will influence which evil genetic traits, but the Talmud already gives several examples with which to begin our investigation. For example, the Talmud states that if a person has a genetic predisposition to killing, he should become a mohel; it is possible that acting as a mohel will epigenetically suppress the killing genes.[59]

Halakhic Challenges Associated with Epigenetics

One of the major halakhic ramifications of our broadened understanding of epigenetics is the importance for rabbinical leaders to devote time to understand emerging biotechnologies. Epigenetics is a difficult scientific discipline to fully understand even for scientists. There are many unanswered questions. For rabbinical decisors who must deal with the halakhic ramifications of epigenetics it is imperative that they spend significant time trying to master the underlying science. For example, Rabbi Shlomo Zalman Auerbach spent months learning about the physics of electricity before writing his teshuva on the use of electricity on Shabbat. Rabbi Moshe Feinstein consulted with many transplantation physicians and visited the ICU at Downstate and Beth Israel Hospital to observe comatose patients and how physicians clinically determine brain stem death before issuing a *psak* on the halakhic determination of death. In this regard, there should be classes for rabbis that present the scientific background on new technologies such as epigenetics, gene editing and CRISPR. While CRISPR is now becoming a household word for gene editing, few if any rabbis know what it stands for and how it works. In reality CRISPR is an

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55 *Hilkhot Teshuva* 3:4.

56 Numbers 6:2–21: Nachmanidies, Numbers 6:14 s.v. *ve-ta'am.*

57 Lev. 19:2.

58 Malbim, Lev 19:2.

59 BT *Shabbat* 156a. See also the introduction to the third *ḥelek* of the *Mishnah Berura* (Introduction to *Hilkhot Shabbat*).

abbreviation for "clustered regularly interspaced short palindromic repeats." In lay terms CRISPR are unique DNA sequences not normally found in bacteria. However, when a bacterium has survived a viral infection it encodes part of the viral DNA nucleotides as a memory signal to protect it from further viral infections.

Another significant halakhic ramification for epigenetics is based on the principle that epigenetics can be inherited. Thus, a pregnant woman who is not careful about her diet or exercise regimen not only will impact the health of her child but also may affect the health of her grandchildren. This translates to a moral imperative that pregnant women, and men interested in fathering children must maintain a healthy lifestyle to provide the best epigenetics for their future children. While halakha allows a person to engage in dangerous lifestyles, e.g., becoming a policeman or fireman, this is permitted only when it affects the individual. Once a lifestyle affects others such as future children, halakha would consider the effects of one's lifestyle on others.

Conclusions

One of the basic tenets of Judaism is the capacity of human beings to control their behavior since everyone has the potential to become a righteous individual. In this article we propose that there might be a molecular/cellular understanding, based on epigenetics, of how a lifestyle devoted to doing *mitzvot* can enhance this capacity to control behavior. The Talmud discusses the obligation to train your child with ethical reproof.[60] This discussion is immediately followed by a discussion about teaching your child Torah. The Talmud continues with the statement "I [*Hashem*] created the evil inclination and I created the *Torah* as its antidote. If you are engaged in Torah study you will not be given over into the hand of the evil inclination, as it is stated: 'If you do well, shall it not be lifted up?'" The verse quoted is that which relates God's advice to Kayin before he struck and killed his brother Hevel, ואתה תמשל בו, 'yet you can be its [the evil inclination's] master.'

Why is Torah the antidote? Because one essential goal of learning Torah is to enhance observance of the *mitzvot* and the performance of *ḥesed*. With new understandings in epigenetics, we can now discover how Torah observance provides the mechanism of control and change both spiritually and epigenetically to enable human beings to become righteous. [61]

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60 BT *Kiddushin* 30.

61 *Nefesh Ha-Ḥayyim* (*Sha'ar* 3* ch. 1 s.v. *ve-gam*): Gr"a (Mishlei 25:21) writes that even learning *shelo lishma* helps combat the *yetzer hara*.