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Environmental Epigenetics and Its Impacts on Disease Susceptibility: A Comprehensive Review

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Abstract: Environmental epigenetics, an emerging field, investigates the relationship between environmental factors and epigenetic changes, that defines an individual's disease vulnerability. This review highlights the associations among genetics, environment, and health. Environmental epigenetics significantly impacts disease susceptibility through mechanisms like non-coding RNAs, histone modifications, and DNA methylation, responding to external stimuli and dynamically interacting with genes. Lifelong epigenetic imprints, influenced by the prenatal environment, early experiences, diet, chemical exposures, and lifestyle, dictate health trajectories across the lifespan, elevating the risk of various illnesses, including cancer, cardiovascular, metabolic, and neurological conditions. Major findings demonstrate how antenatal environmental factors—like mother's diet, food, and stress level—shape fetal epigenetic programming and impact health consequences in the future. Furthermore, it has been demonstrated that environmental pollutants and dietary nutrients can modify epigenetic markers, highlighting the crucial role that lifestyle decisions have in reducing the risk of disease. Significantly, the notion that epigenetic alterations may be passed down through generations raises the possibility that environmental exposures may have an impact on health consequences for future generations. Environmental epigenetics revolutionizes our understanding of gene-environment interactions and their role in disease etiology. The study concludes by highlighting the revolutionary implications of environmental epigenetics for comprehending the etiology of disease and customizing public health approaches and by promoting the incorporation of both genetic and environmental components within public health frameworks. The knowledge acquired calls for an evolution of paradigms in medicine toward customized care utilizing epigenetic biomarkers and calls for more studies to improve therapies that lessen the harmful epigenetic consequences of exposure to the environment.

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1. Introduction

This comprehensive review's primary objective is to investigate how environmental influences impact epigenetic pathways, which in turn affects health results and illness susceptibility in successive generations future [1]. The goal of the study is to determine how environmental factors, including food, stress, and pollution, shape epigenetic alterations including DNA methylation, histone modifications, and non-coding RNA expression during the perinatal and lifetime stages of life. It also aims to investigate the possibility of epigenetic mark transmission over generations and clarify how these changes in the genome affect a person's vulnerability to a range of diseases, such as cancer and cardiovascular conditions [2]. This research postulates that environmental influences profoundly influence epigenetic mechanisms, which modify gene expression without modifying the DNA sequence and so impact susceptibility to disease. It claims that early environmental exposures significantly influence long-term results by determining health trajectories through epigenetic programming [3]. In addition, it emphasizes the complexity brought by the potential for transgenerational inheritance of epigenetic alterations and implies that dietary interventions can modify epigenetic patterns, providing a preventive approach to illness risk reduction [4]. This review's structure is intended to systematically explore these theories. Following a thorough explanation of the main ideas and scope in the introduction, the mechanisms of epigenetic alteration and the impact of environmental factors are covered in detail. The impact on disease susceptibility and the consequences of transgenerational epigenetic inheritance are examined in the following sections [5]. It also looks at how epigenetic biomarkers will function in customized medicine going forward. The results are summed up in the concluding remarks, which also address the findings' implications for future study, clinical practice, and public health policy. They support continued investigation and use of environmental epigenetics in public health policies [6].

The study of genetics is concerned with heritable variations in gene activity or function brought on by direct changes to the DNA sequence. These alterations include deletions, insertions, translocations, and point mutations [7]. However, epigenetics is a field of study targeted at understanding heritable modifications in gene activity or function that are unconnected to factors in the DNA sequence. Even while practically all of the cells in an organism share the same genetic composition, not all cell types express all of their genes simultaneously. In a broader sense, epigenetic mechanisms mediate the various gene expression profiles in different cells and organs of multicellular animal [8].

An area of genetics focused on studying the effects of environmental factors on the epigenome—the chemical alterations that modify gene expression without changing the DNA sequence—is commonly known as environmental epigenetics [9]. This developing field stresses the complex interaction between genetics and environment, offering insights into how environmental factors can affect human health and illness risk [4]. The idea highlights how our genetic makeup is dynamic and flexible, challenging the widespread belief that our DNA alone determines our biological fate. Additionally, the phrase "environmental epigenetics" has a limited definition that refers to the mechanism by which epigenetics showcases the variation in the environmental risks and severity [10]. Since there is no universally accepted and specific defining concept of environmental diseases, these review studies have chosen to concentrate on the external environmental factors involved. We also discuss the lifestyle factors affecting these diseases, e.g., Stress, abuse, addiction, alcoholism, and metabolic changes. We want instances that best convey the idea that over the course of time and space, complex mechanisms involved and the stages of development influence illness risk and health outcomes. Epigenetic changes, DNA methylation, Histone modifications, non-coding RNAs, and gene-environment interactions are main defining factors in environmental epigenetics [2].

2. Epigenetic Mechanisms

2.1. Mechanism shaping the epigenome

DNA methylation, modifications to histones, and the regulatory roles of microRNAs (miRNAs) are among the extensively studied epigenetic processes that impact a cell's epigenome. Together, these processes affect DNA accessibility, chromatin compaction, regulation of genome integrity and function, and maintenance of higher-order nuclear organization, impacting the health and susceptibility to disease of the cell or tissue [11, 12]. The addition of a methyl group to the 5′ position of the cytosine pyrimidine ring is referred to as "methylation of cytosines" or "the fifth base". Cytosine-guanine dinucleotides (CpGs1) are primarily affected. Typically, gene expression is inhibited by the excessive methylation of CpG islands in a gene's promoter [13]. According to Cusack et al. [14], the methyltransferases and histone deacetyltransferases, along with proteins and/or co-repressors that attach to methylation DNA, show a greater affinity for the methylated promoter area and a decreased affinity for transcription factors. DNA methyltransferases (DNMTs), such as DNMT1, DNMT3a, and DNMT3b, help to preserve the DNA methylation pattern during cell division throughout successive generations by facilitating de novo methylation [15]. The replication of the DNA methylation pattern between cell generations is facilitated by DNMTs, which mediate de novo methylation. The process of cytosine demethylation is not fully understood, as methylated DNA-binding proteins have a reduced affinity for CpG islands, which consist of dense concentrations of CpGs, or weak CpGs [16]. 5-hydroxymethyl cytosine (hmC1), a second modified cytosine base, has recently been discovered to exhibit high expression levels in bone marrow, brain, and embryonic cells [17]. It has been referred to as the sixth base [18]. The Ten Eleven Translocation (TET) enzyme family has been shown to be capable of converting mC into hmC, which may open up a channel for DNA demethylation and subsequent transcriptional activation [19]. The TETs are believed to be essential for preserving embryonic stem cells and establishing inner cell mass because of their high expression in these cells [20]. Furthermore, hmC may prevent methyl-binding proteins from binding to DNA, such as DNMT1 and methyl-binding domain proteins [21]; it is unclear how environmental factors affect how hmC and TET expression are regulated. Since the TET enzymes, like many other chromatin-modifying enzymes, are highly responsive to changes in the internal redox environment of the cell, it is thought that oxidative stress caused by environmental factors controls the level of DNA hydroxymethylation at specific gene promoters [22]. To properly understand how environmental factors

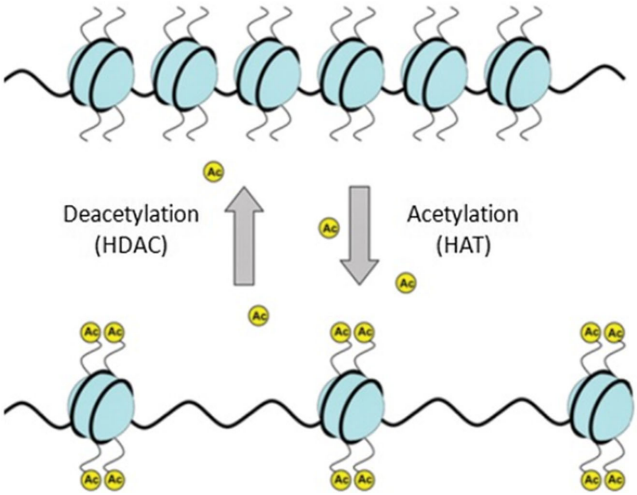

Figure 1. Histone acetylation and deacetylation

affect the distribution of hmC versus mC in gene promoters or regulatory elements, as well as the localization and activity of TETs in different cell types, unquestionably more research is required. Epigenetic reprogramming may be greatly impacted by these factors [23].

2.2. Histone modifications

The essential proteins called histones are in charge of putting DNA together into nucleosomes, which are the basic building blocks of chromatin. Certain enzymes, such as histone acetyltransferases (HATs), histone deacetylases (HDACs), methyltransferases, and demethylases, control this assembly process [24]. The N-terminal ends of histones include certain amino acids that are subject to various post-translational changes, including acetylation, methylation, phosphorylation, sumoylation, and ubiquitination. [25]. These alterations are essential for controlling transcription speed and the accessibility of histone-wrapped DNA for transcription. In addition to regulating gene transcription, histone changes also affect chromatin remodeling mechanisms, which control chromosomal replication, recombination, and higher-order organization. [26]. Histone modifications enable external signals to be translated into genomic processes at the cellular level by changing the structure of chromatin [26]. DNA methylation and histone modification together influence both short- and long-term changes in transcription pathways by modifying the architecture of chromatin [27].

In Figure 1 [28], HATs add acetyl groups (Ac) to histone tails, which opens up the nucleosome, allowing transcription factors to access DNA and initiate gene transcription. On the other hand, HDACs remove Ac groups from histone tails, resulting in chromatin adopting a closed conformation.

Methylation involves adding a methyl group (CH3) to lysine or arginine residues on histone tails, altering their function. Histone methyltransferases (HMTs) perform this modification on specific lysine or arginine residues. The amount of methylation can have activating or repressive effects on gene expression [29]. Depending on the particular histone residue and the circumstances, histone methylation can either promote or suppress gene expression. Methylation can take many different forms, including mono-, di-, and trimethylation, each of which may have distinct functional effects [30]. Complex regulatory networks can result from histone methylation's effect on other proteins' ability to bind, such as chromatin modifiers and transcription factors.

Histone methylation and acetylation, key players in chromatin remodeling, are illustrated in Figure 2 [31]. Heterochromatin, a condensed chromatin form, results from histone methylation, wherein methyl groups are added to histone core protein tails. Heterochromatin represses transcription by blocking the binding of transcriptional machinery to DNA. On the other hand, histone acetylation, leading to the formation of "euchromatin", a more relaxed chromatin state, occurs when Ac groups are added to lysine residues in histone N-terminal tails. Proteins and transcription factors can then bind to their DNA sites, initiating active transcription.

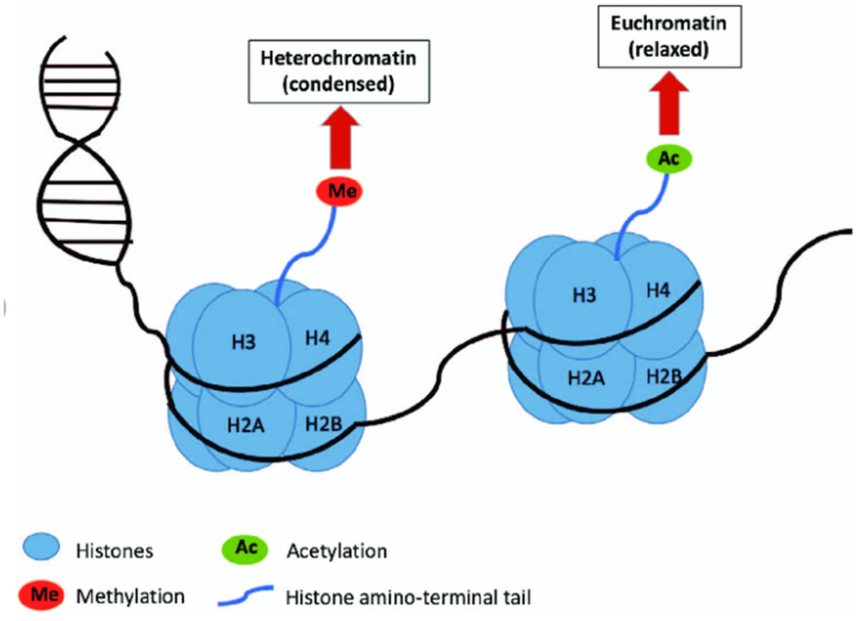

Figure 2. Histone methylation

During the procedure of histone phosphorylation, a phosphate group (PO4) is added to serine, threonine, or tyrosine residues on histone tails. Protein kinases are responsible for this alteration, which has an effect on the chromatin structure and gene expression. Histone phosphorylation frequently takes part in cellular signaling, which is linked to cellular reactions to environmental cues like stress or growth factors, and chromatin remodeling, in which phosphorylation can lead to structural alterations in chromatin that enhance the accessibility of the protein to transcription factors and other regulatory proteins [32]. Additionally, reversible dynamic regulation of histone phosphorylation that can be swiftly adjusted in response to shifting cellular circumstances also is present.

In Figure 3 [33], the key histone residues that are phosphorylated at various times during the cell cycle are depicted in the graphic, alongside the kinases and phosphatases involved in the process. The phosphorylation that occurs during mitosis, DNA transcription, DNA damage, and the spindle assembly checkpoint, respectively, are represented by the hues red, green, blue, and light purple. The necessary phosphatases are indicated in orange; PP1, PP2A, PP5, and PP6 refer to protein phosphatases 1, 2A, and 5, respectively. Histone H2AX is depicted in light green (A), while H2A and H2B are shown in dark green (B), purple (H2B), blue (H3 and H4), and pink (H4 and CENP-A). VRK represents vaccine-related protein kinases, ATM stands for ataxia telangiectasia mutated, and ATR denotes ataxia telangiectasia and Rad3-related protein. Phosphoribulokinase (PRK): Casein Kinase IICKII); Dlk, which stands for death-associated Protein (DAP)-like kinase; JAK, representing Janus kinase; and PKC, which stands for protein kinase C. Rarely do histone modifications work alone; instead, they frequently interact with one another to produce complex chromatin states. Interactions between various modifications, such as potential antagonistic or synergistic effects between acetylation and methylation, play a role in the epigenetic regulation of gene expression. Dysregulation of histone alterations has been associated with cancer, neurological issues, and metabolic diseases. The importance of histone modification in illness and treatment is known as this [34]. A molecular knowledge of these modifications has led to the development of specialized medications that affect histone modification patterns, opening up new therapeutic avenues. Acetylation, methylation, and phosphorylation are key histone modifications that play dynamic and intricate roles in controlling gene expression and chromatin structure. The epigenetic landscape is built on the complex interplay between these factors, which affects cellular identity, development, and disease susceptibility [35].

3. Environmental Factors Influencing Epigenetics

3.1. Prenatal environment

During the early phases of development, when the detailed blueprint for our existence is being created, the prenatal

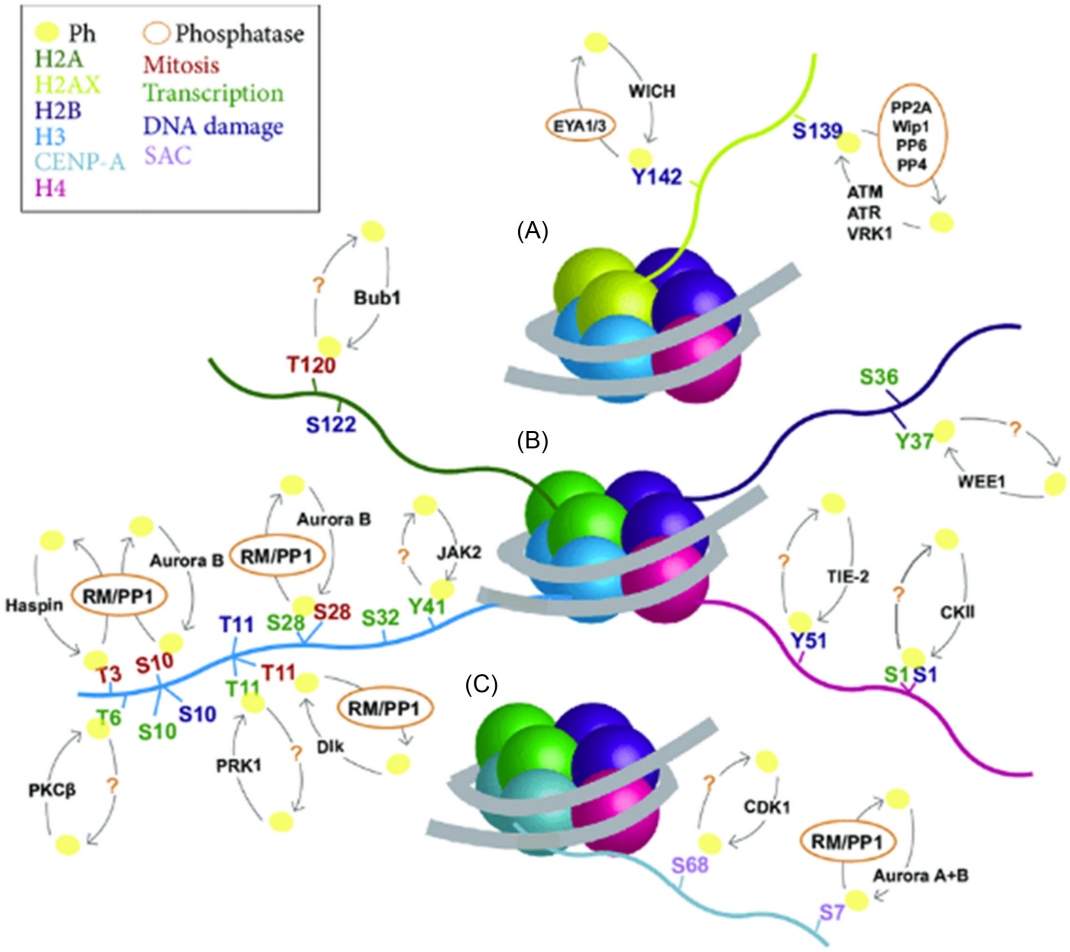

Figure 3. Histone phosphorylation regulation model

environment is crucial. Environmental variables interact intricately with our DNA at this period of life, affecting how our health and welfare evolve through the mastery of epigenetics [36]. The prenatal environment, which serves as a master carver, creates the epigenetic fingerprints on each of us. Epigenetics serves as a mediator between our genes and our environment, and this connection is especially important during the perinatal stage. The epigenetic composition of the fetus can be permanently changed by the maternal environment, which includes factors like nutrition, stress, and pollution exposure. These flaws can impact a person's immediate development as well as predispose them to a number of health issues later in life [37]. DNA methylation is one of the epigenetic changes brought on by the perinatal environment that has been studied the most. In a developing fetus, exposure to chemicals, stress levels, and maternal nutrition can alter DNA methylation patterns. These changes may have an effect on the expression of genes linked to development, growth, and the risk of developing certain diseases, including diabetes, obesity, and cardiovascular conditions [38]. The prenatal environment also influences the complex structure of chromatin, which consists of DNA and histone proteins. Maternally regulated histone modifications can affect gene accessibility, thereby influencing gene expression. These effects can have long-lasting impacts on various biological processes, such as immune response and brain development [38]. The subject of transgenerational epigenetic inheritance maybe even more exciting. The prenatal environment may cause epigenetic modifications that will affect subsequent generations and may have an effect on children's health and wellbeing [39]. This new information highlights the prenatal environment's long-lasting influence on the genetic heritage we pass on [40]. The ground-breaking theory known as Developmental Origins of Health and Disease postulates that early experiences, especially those had during pregnancy, may influence a person's later-life vulnerability to illness. During this period, epigenetic changes can train physiological responses that last a lifetime, affecting metabolic, cardiovascular, and even psychological health [41]. Understanding how the prenatal environment profoundly affects epigenetics has consequences for both health and policy. Prenatal nutritional therapies, stress management techniques, and limiting chemical exposures are all ways to protect fetal development and lower the likelihood of epigenetically induced health issues [42, 43].

3.2. Diet and nutrition

Early experiences, particularly those during pregnancy, can influence an adult's susceptibility to disease [44]. The Dutch Famine Birth Cohort, for example, was created as a result of the 1944–1945 Dutch Famine and has been used to study the impact of maternal fasting on the health and developmental outcomes of the postpartum period. According to Branje et al. [45], these effects have been linked to a higher risk of type II diabetes mellitus, cardiovascular disease (CVD), metabolic problems, and a decline in cognitive function as people age. The fact that many Dutch Famine babies were smaller than typical shows that the impacts can last a lifetime and impact not just our children but also those of future generations. Pregnancy risk appears to be most influenced during the first several months. The fetus appears to adapt epigenetically to malnutrition [46].

Grilo et al.'s study [47] examined the metabolic impacts of inadequate maternal nutrition on successive generations of human populations. Historical records suggest that the descendants of women who experienced famine or significant nutritional changes during pregnancy are more susceptible to health issues than those born under normal circumstances. Proposed molecular mechanisms of transgenerational inheritance highlight the methylation of gametes in both the paternal and maternal lines [48]. In fact, it is very likely that epigenetic change in the spermatozoan nucleus will lead to additional transmission down the paternal line. As examples of this paternal lineage-based transgenerational transmission, two historical cohorts are used. According to one research, female grandchildren (F2) of the paternal grandmother (F0) who were malnourished as children were more likely to die from CVD. In a more contemporary instance, grandkids whose fathers were fetuses and who went through starvation had higher BMIs than the average population [49]. Schellong et al. [50] examine the data demonstrating that dietary factors consumed by mothers and fathers can pass epigenetic information to offspring that alters the metabolic traits of mammals. It has been postulated that mitochondrial dysfunction and oxidative stress are two biological pathways for the prenatal origins of adult disease because they are among the first symptoms observed in children who are subjected to food restriction [51].

3.3. Chemical exposures

Chemical exposures, which are pervasive in our surroundings, have a significant impact on how delicately nature and nurture interact. By modifying the epigenome, the regulatory layer above our DNA, these environmental chemicals can enter our genes [52]. Chemicals can affect epigenetic markers like DNA methylation and histone modifications, which can disrupt gene expression patterns and have a variety of negative health impacts. The relationship between chemical exposure and epigenetics reveals an important facet of how our genetic makeup and environment interact to influence our health and vulnerability to disease.

Exposure to endocrine-disrupting chemicals (EDCs) during early life poses a significant risk as it has the ability to permanently modify the gene expression of both germline and somatic cells via epigenetic reprogramming, hence promoting transgenerational inheritance [53]. The xenoestrogen deoxygenase (DES) was widely utilized in the cattle and other animal industries, and it remains an EDC in many cultures. Mice exposed to DES early in life exhibit demethylation of the estrogen-responsive gene lactoferrin in the mouse uterus. The likelihood of getting uterine cancer rises as a result of this demethylation. BPA is an additional xenoestrogen with epigenetically active properties. When agouti mice were exposed to BPA during gestation, their progeny developed hypomethylated intracisternal a particle retrotransposon upstream of the agouti gene [46]. The epigenetic effects of a phytoestrogen may be counteracted by co-administration of a methyl donor. Furthermore, studies conducted by Yanning Li et al. [54] and Liang et al. [55] demonstrate that exposure to BPA during infancy can modify the DNA methylation patterns of important genes (Pde4d4, Nsbp1, and Hpcal1), which can result in notable transcriptional alterations linked to carcinogenic processes in the rat prostate. Moreover, it has been discovered that BPA exposure during pregnancy changes gene transcription by methylating particular gene promoters in the forebrain, which causes inappropriate behavior in the progeny [56]. Phytoestrogens cause endocrine disruption by acting as epigenome regulators. Their epigenetic roles in endocrine-related cancers have been studied most in-depth [57].

3.4. Epigenetic factors shown to trigger epigenetic event and affect disease state

Epigenetic changes related to exposure and/or illness have been demonstrated to be caused by environmental factors such as heavy

metals, endocrine disruptors, PAHs, infectious pathogens, outdoor pollutants, and indoor allergens [58]. Numerous investigations have demonstrated the presence of these connections in a wide range of complicated diseases, including lung diseases, cancer, obesity, stroke, CVD, and neurodegenerative disorders. Strong evidence also suggests that the severity and course of these disorders are influenced by early-life epigenetic reprogramming and subsequent epigenetic modifications made during adulthood, whether or not they occur before the disease or condition begins [59]. In this manner, certain epigenetic markers might function as exposure biomarkers or prognostic indicators of illness risk and progression, while other markers might offer fresh insights into the environmental factor's mode of action. Zhu et al. [60] suggest that a more profound comprehension of the mechanisms underlying these epigenetic alterations may facilitate the development of primary or secondary illness prevention strategies in the future and shed light on the etiology of environmental diseases.

3.5. Infectious pathogen

Numerous illnesses and disease states, such as type 2 diabetes, CVD, cancer, neurodegenerative diseases, immunodeficiency, aging, and asthma, are significantly impacted by inflammation and oxidative stress [61]. Chronic inflammation has been related to the methylation of cancer DNA and the production of certain miRNAs. After being exposed to many adverse environmental factors, inflammation and oxidative stress are common reactions that often act as indirect epigenetic modulators. According to Maiuri et al. [62], exposure to infectious pathogens, especially bacterial and viral ones, can cause oxidative stress and inflammation, which can alter host cells' or organs' epigenetic makeup [62]. In line with the aberrant DNA methylation patterns observed in gastric cancer, hypermethylation of particular CpG islands in the stomach mucosa has been linked to Helicobacter pylori infection, a significant risk factor for gastric cancer. Furthermore, it has been demonstrated that H. pylori causes DNA hypermethylation of RUNX3, a putative tumor suppressor gene, and the E-cadherin promoter, a protein involved in tumor invasion and metastasis. Numerous malignancies have been linked to viruses, and certain of their epigenetic regulation mechanisms have been identified. It has long been known that the hepatitis B virus and hepatocellular carcinoma are related and that there are several stages to this process, with the majority of the epigenetic modifications taking place in the early stages [63]. Numerous epigenetic modifications have been linked to the carcinogenesis caused by the hepatitis B virus X protein. These include the hypermethylation of p16[INK4a] DNA, which in turn causes the cyclin D1-cyclin-dependent kinase (CDK) 4/6-retinoblastoma protein (pRb)-E2F1 pathway to be activated transcriptionally, hence activating DNMT1 in HepG2 cells. In addition to cervical cancer, human papillomavirus has also been linked to cancers of the skin, head, and neck, as well as other organs [64]. Human papillomavirus has been associated with DNA hypermethylation for many years; this association may make it a useful cancer biomarker. Furthermore, DNMT1's enzymatic activity can be bound to and controlled by the human papillomavirus E7 protein. Additionally, it has been shown to interfere with the machinery involved in chromatin remodeling, including the acetyltransferase domain of pCAF, histone acetylase activity, and HDAC activity [64]. Epstein-Barr virus is associated with nasopharyngeal cancer, Burkitt lymphoma, Hodgkin disease, and lymphoproliferative malignancies. The Epstein-Barr virus exhibits epigenetic modifications such as DNA methylation, chromatin remodeling, and histone modification. Latent membrane protein 1, an oncoprotein of the Epstein-Barr virus, enhances the expression of DNMT1, DNMT3a, and DNMT3b. This results in a phenotype that is hypermethylated at the E-cadherin promoter, which is a feature of Helicobacter pylori [65].

4. Epigenetics and Disease Risk

4.1. Cancer

The unchecked development and spread of aberrant cells within the body characterizes the complex and multifaceted group of disorders known as cancer. Each year, it affects millions of people, making it the world's largest cause of disease and death. Cancer can affect almost every bodily part, including the blood, tissues, and organs [66]. Cancer develops as a result of genetic alterations that disrupt the regular regulatory mechanisms controlling cell division, growth, and death. These mutations can arise during an individual's lifespan as a result of exposure to many risk factors, including radiation, hazardous substances, tobacco smoke, certain infections, and unhealthy lifestyles [67]. Alternatively, these mutations might be inherited from parents. Disruption of normal cellular activities, often brought on by genetic mutations, is the pathogenic cause of cancer. Cancer is a dangerous and complicated illness. But the story of cancer is not just told by the deft manipulation of epigenetics; it is also written inside the sequence of DNA. DNA methylation stands out among the other epigenetic processes for its important function, particularly in the control of tumor suppressor genes. The fascinating subject of DNA methylation is examined in this essay, along with how it affects tumor suppressor gene regulation [68].

DNA methylation, which mostly happens at CpG dinucleotide sites, is the process of adding a methyl group to the cytosine base of DNA. As a molecular "silencer", this chemical alteration frequently suppresses the expression of genes. DNA methylation has two possible roles in relation to tumor suppressor genes: saboteur and defender. It can unintentionally quiet genes that support cancer while simultaneously inhibiting ones that prevent the development of tumors [69]. The genetic guardians of typical cellular growth and division are tumor suppressor genes. They control how the cell cycle develops, fix DNA damage, trigger apoptosis (planned cell death), and prevent angiogenesis (the creation of blood vessels to support tumor growth). Disruption of the delicate balance between cell growth and regulation occurs when tumor suppressor genes are altered or silenced. This disruption can lead to uncontrolled cell proliferation and the onset of cancer. Abnormal DNA methylation patterns can tip the balance in favor of cancer growth in the intricate interplay between DNA methylation and tumor suppressor genes [70].

This epigenetic silencing may act as a catalyst for the initiation, progression, and even dissemination of many cancers. Two prominent examples of DNA methylation-mediated suppression of tumor suppressor genes are the MLH1 gene, essential for DNA mismatch repair, and the CDKN2A gene, which encodes the p16INK4a protein that arrests cell cycle progression. Consequently, hypermethylation of these genes may increase the risk of melanoma and colorectal cancer [70]. DNA methylation, which also contributes to the genesis of cancer, silences tumor suppressor genes. Tumor suppressor gene activity is regulated by the delicate balance between methylation patterns, which is majorly influenced by hereditary and environmental factors. Understanding the complexities of this epigenetic conflict is crucial for unraveling the

complex pathways behind the emergence of cancer. Given the intricate relationship between DNA methylation and tumor suppressor genes, targeted therapy may be an option. DNMT inhibitors are epigenetic drugs that can rectify aberrant DNA methylation patterns, reactivating suppressed tumor suppressor genes and possibly reducing the progression of cancer [71].

As research into the precise targeting of epigenetic alterations advances, there is enormous potential for personalized and effective cancer treatments. The complex mechanism of cancer genesis is shown by the interaction of tumor suppressor genes and DNA methylation. Cancer-preventive genes may be activated or suppressed by epigenetic changes, disturbing the delicate balance of cellular growth and control [72]. We uncover new possibilities for therapeutic strategies that may fundamentally transform how we treat cancer as we delve further into the intricate epigenetic characteristics of cancer. These therapies aim to restore the balance of the cellular environment and fight cancer by reactivating tumor suppressor genes that have been silenced [73].

4.1.1. Histone modifications in oncogenesis

Apart from improper DNA methylation, recent research indicates that chromatin remodeling and abnormal histone modifications are also associated with cancer. The N-terminal "tails" of histones, extending from nucleosomes, the building blocks of chromatin, are often sites of histone modifications. Among these post-translational changes include acetylation, methylation, phosphorylation, and ubiquitination. Various modifications are possible at different amino acids in different histone tails due to their context. For example, lysines are acetylated, methylated, and ubiquitinated, while serine or threonine residues are phosphorylated [74]. The importance of these modification systems in development and their potential role in human cancers due to their dysregulation highlight the significance of histone changes. Histone proteins have become crucial carriers of epigenetic information, indicating that genetic code is not the sole source of regulatory information [29].

An increased interest in histone modifications has been brought about by recent discoveries and the identification of several histone-modifying agents and protein complexes. Under normal physiological settings, a variety of chromatin-modifying complexes affect DNA's accessibility to transcriptional and DNA repair machinery. Mutations in DNA repair genes, tumor suppressors, or oncogenes can alter these chromatin-based systems, which can cause oncogenic transformation, genomic instability, and cancer [75]. Two examples of the histone-modifying complexes are the HMTs, a class of enzymes that add methyl groups to multiple histone residues. These enzymes catalyze several reactions, including the synthesis of heterochromatin and the silencing of genes [76]. It is crucial to emphasize that aberrant activity of histone-modifying factors, as observed in human leukemia, can accelerate cancer growth by improperly regulating chromatin structure and function [77]. Oncogenesis is most likely to be initiated by aberrant epigenetic regulation of important cellular processes, specifically DNA repair and gene transcription. It is still unclear how histone modifications are changed in cancer, despite the explosive expansion of research into numerous types of epigenetic information in chromatin [78].

4.1.2. Epigenetic biomarkers for cancer risk assessment

The range of cancer risk evaluations now includes factors other than only standard genetic markers because of the emergence of epigenetic biomarkers as powerful predictors of susceptibility. Epigenetics, which explores heritable changes in gene expression without alterations to the DNA sequence, provides new insights into the development of cancer [79]. Epigenetic modifications that are impacted by an individual's lifestyle and environment can offer important information for determining their risk of acquiring cancer. Epigenetic indicators for cancer risk assessment are also applicable beyond the lifetime of an individual. The transfer of epigenetic changes from one generation to the next is known as transgenerational epigenetic inheritance. [80]. These hereditary variations may affect a child's propensity for developing cancer. Intergenerational cancer risk can be viewed more comprehensively by comprehending transgenerational epigenetic patterns. Even though epigenetic biomarkers have great potential, challenges still exist. It can be challenging to evaluate epigenetic patterns because of their intricacy, which is influenced by both genetic and environmental variables [81]. To ensure accuracy and the ability to reliably duplicate results, standardized assessment techniques for epigenetic biomarkers must be developed. The assessment of cancer risk has a new frontier thanks to epigenetic biomarkers. Their capacity to recognize the impact of both heredity and environment offers a comprehensive understanding of a person's propensity to develop cancer [82]. As knowledge grows, incorporating epigenetic data into personalized medical tactics may alter approaches to cancer prevention, early diagnosis, and treatment, ushering in a time when therapies are more focused and efficient.

4.2. Cardiovascular diseases

Indeed, the intricate interplay between genetic predispositions and environmental influences in CVD has garnered increasing attention. Atherosclerosis, a chronic inflammatory disorder of the arteries, remains a primary culprit behind heart attacks and strokes. Although conventional risk factors such as high blood pressure, smoking, and high cholesterol have been extensively studied, recent studies highlight the important role that epigenetic variables play in the development and course of atherosclerosis [83]. grasp complex illnesses like atherosclerosis requires a grasp of epigenetics, which deals with heritable changes in gene expression that are impacted by environmental variables rather than changes in DNA sequence. Atherosclerosis-related epigenetic modifications can be influenced by a variety of environmental factors, including food, smoking, and pollution exposure [72]. Unhealthy diets high in sugar and saturated fats can change DNA methylation patterns, which can affect genes involved in inflammation and lipid metabolism. Exposure to cigarette smoke and air pollution can similarly induce epigenetic modifications that heighten the risk of atherosclerosis. These epigenetic changes may affect an individual's susceptibility to developing atherosclerosis and the spectrum of clinical outcomes observed in patients with CVD [73].

New paths for early identification, risk assessment, and therapeutic approaches are being made possible by epigenetic studies in atherosclerosis. Epigenetic biomarkers associated with atherosclerosis can provide details on disease susceptibility, facilitating the development of customized treatment and preventive strategies [74]. Epigenetic-based therapies, such as epigenetic inhibitors and activators, which show promise in altering the expression of genes associated with atherosclerosis, are providing novel strategies for treating CVD [75].

Research indicates that SIRT1 regulates the activation of endothelial nitric oxide synthase (eNOS), thereby preventing the formation of atherosclerotic plaques in ApoE/ mice. This inhibition of atherosclerosis is mediated by SIRT1. Conversely, HDAC3's deacetylation of eNOS K610 has been shown to accelerate atherosclerosis [76]. Inducible nitric oxide synthase

(iNOS) levels are also increased in atherosclerotic lesions.94 Atherosclerosis is promoted by nuclear factor-B (NF-B), which controls the expression of proinflammatory genes including Nos2 (the gene encoding iNOS) in endothelial cells.95 SIRT1 lowers NF-B activity by deacetylating P65 and severing the link between P300 and NF-B.96 Studies have shown that myocardial infarction and ischemia-reperfusion injury can be controlled by lysine acetylation. In the rat myocardium, overexpression of SIRT1 can lessen the effects of ischemia-reperfusion damage [77]. Forkhead box O3A (FOXO3A) is deacetylated by SIRT2 in renal ischemia-reperfusion damage, which encourages cell death. SIRT3 can reduce reperfusion injury and halt the opening of mitochondrial permeability transition pores, which results in cell death, by deacetylating cyclophilin D. The genesis and progression of atherosclerosis are not simply influenced by genetic predisposition or conventional risk factors; epigenetic mechanisms also play a significant role [78]. A new viewpoint on cardiovascular health is provided by epigenetic research, which opens the door to more individualized treatments and better control of atherosclerosis and its repercussions [79].

4.3. Neurological disorders

The primary cause of dementia is Alzheimer's disease (AD), a progressive neurodegenerative illness marked by an accumulation of the brain proteins tau phosphorylation and amyloid-beta (A-42). According to Valladares-Rodriguez et al. [84], these proteins contribute to the pathophysiology of the disease by forming intracellular tangles and extracellular plaques. These plaques and tangles are associated with neuronal death, apoptosis, dysregulation of microtubule assembly, and brain atrophy. It's interesting to note that about 5% of instances of AD with an early onset or family pattern can be explained by common genetic variants. This suggests that AD may have developed as a result of epigenetics [85]. Dysregulation of the APP gene is associated with the creation of amyloid plaques, which are essential to the development of AD. Differential methylation of 13 cytosine residues in the APP gene promoter region with aging has been found in post-mortem brain tissue from spontaneously dead persons [86].

Additionally, among patients older than, there was an almost 50% reduction in methylation at these cytosines. Variable methylation patterns are important in the pathophysiology of AD, as evidenced by the demonstration that elevated APP methylation in AD patients enhances APP production and the neurotoxic A42 aggregates [87]. The processing of APP requires the presence of two proteins, PS1 and BACE, whose dysregulation results in the aberrant A42 plaques that are hallmarks of AD. The methyl donor SAM is necessary for PS1 and BACE methylation, and AD is linked to a substantial reduction in SAM levels. Vitamin B12 and folate deficits cause dysregulation of PS1 and BACE in neuroblastoma cell lines, which can be corrected by SAM. Both β- and γ-secretase activity is decreased by SAM supplementation [88]. Improved spatial memory is seen in transgenic mice that overexpress human APP, show plaque deposition, and have normal levels of tau phosphorylation restored. A clinical research supporting these findings found that patients recently diagnosed with AD had lower plasma levels of SAM and greater amounts of SAM. The regulation of A-42 clearance by APOE is regarded to be a significant risk factor for late-onset AD, or LOAD. Because APOE has a non-classical (CpG-weak) promoter, it is difficult to regulate.

The APOE haplotypes 2–4 have been demonstrated to have distinct relationships with the risk of LOAD. Contrary to APOE3, APOE4 is associated with a higher risk of late-onset Alzheimer's disease (LOAD), albeit not all APOE4 carriers experience this condition, and many LOAD patients do not have the APOE4 allele [89]. Two APOE CpG sub-regions in the frontal lobes of patients with AD and Lewy body dementia showed considerable hypomethylation on post-mortem brain imaging. According to these results, the epigenetic regulation of LOAD may be influenced by methylation of the APOE promoter [90]. Histone acetylation is markedly reduced in AD-stricken human brains as well as AD transgenic mice. In AD transgenic mice, HDAC2 was shown to be increased, and learning and memory were improved by administering the HDAC2-specific inhibitor suberoylanilide hydroxamic acid (SAHA) [91]. Another HDAC inhibitor, sodium 4-phenylbutyrate (4-PBA), reduced the number of phosphorylated tau tangles and improved cognitive performance in transgenic mice with AD.

Additionally, HDAC6-deficient animals displayed enhanced memory and learning as well as resistance to the A42-induced modification of mitochondrial transport linked to amyloid disease [92]. It has been found that the majority of miRNAs are associated with AD control APP. Research in bioinformatics has identified numerous putative APP 3'UTR miRNA binding sites. It has been shown that miR-16 and miR-101 suppress APP and decrease the cytotoxicity of A in hippocampal neurons and PC12 cells. Numerous investigations have determined the function of miRNAs in the control of APP both in vivo and in vitro. In particular, it has been demonstrated that the miR-29 family, which includes miR-29a, miR-29b, and miR-29c, downregulates the 3'-UTR of the APP processor BACE1 in AD brains in both human and animal cell lines [93]. In vitro, inhibition of miR-29a and miR-29b increases Aβ production in human cells. When a miR-29c mimic was injected into the hippocampi of SAMP8 mice, Aβ levels were lowered and learning and memory were enhanced in comparison to untreated control animals.

4.3.1. Parkinson's disease

Over 600,000 Americans suffer from Parkinson's disease (PD), the second most common neurological condition. By 2040, this number is expected to quadruple. Degeneration of dopaminergic nigrostriatal connections from the striatum to the substantia nigra pars compacta is a characteristic of PD, which leads to motor deficits [94]. PD is characterized by aggregates of α-synuclein (α-syn), a synaptic protein, which leads to neurodegeneration. According to Zhang and Chew-Seng Tan [95], these aggregates cause dopaminergic neurons to die, which causes symptoms including tremors, stiffness, and non-motor symptoms like sadness and dementia. An amino acid precursor to neurotransmitters, levodopa (L-DOPA) is useful in treating PD motor symptoms. It does, however, have the potential to cause tardive dyskinesia, and similar medications are unsuccessful in treating the disorder's non-motor symptoms. PD in humans is thought to be caused by α-syn oligomerization and aggregation [95]. Although α-syn aggregation is known to be enhanced by phosphorylation and ubiquitination, the exact processes governing α-syn remain unclear. Hypomethylation of the CpG2 location (next to intron 1) in the α-syn gene has been found in the blood, putamen, and substantia nigra of PD patients. According to one explanation, this hypomethylation of the α-syn gene results in higher levels of α-syn, which is associated with the age at which PD first manifests [96]. The -syn promoter is less methylated in PD brain tissues, which may be explained by the discovery of 50% lower-than-normal DNMT1 levels. There is evidence that -syn sequesters DNMT1 in brain cells, causing the protein to hypomethylate itself

through a feed-forward mechanism. Therefore, the development and advancement of PD may be influenced by the epigenetic mechanisms that control the methylation of the α-syn promoter.

Numerous researches have connected the onset of PD to histone acetylation. Histone H3 binds to α-syn and becomes hypoacetylated in cells that overexpress α-syn. This result was reversed and cells were shielded against α-syn toxicity by treatment with sodium butyrate and SAHA, two HDAC inhibitors [97]. It has also been demonstrated that the H3 deacetylation inhibitors trichostatin A, SAHA, sodium butyrate, and valproic acid protect neuronal cells after treatment with MPTP, a neurotoxin that is absorbed by dopaminergic neurons and causes symptoms similar to Parkinsonism. H3 acetylation was observed to rise in an MPTP animal model of PD, although therapy with L-DOPA was able to reverse this effect. On the other hand, L-DOPA treatment was found to decrease H3 acetylation in PD models in primates [98]. Although the exact role that histone acetylation plays in PD pathogenesis is yet unknown, HDAC inhibitors may be able to shed light on the matter.

4.4. Metabolic disorders

Nutrition, exercise, chemical exposures, behavior, and the microbiome are among the many genetic and environmental variables that interact to cause metabolic disease [99]. Interestingly, studies conducted on human and animal models have demonstrated that environmental exposures parents endure before, during, or after giving birth can affect the health of their children, possibly starting a family history of higher risk of illness [100]. With an emphasis on paternal lineage effects mediated by germ cells, we briefly examine the possible ways in which epigenetic mechanisms might contribute to metabolic disorders generated by environmental variables, both through direct exposure and throughout following generations [100]. Only approximately 5–10% of the risk for T2D is attributable to genetic factors, despite the fact that family history has been shown to be a significant role. The "missing heritability" phenomena may be explained by shared environmental exposures across family members, particularly in early life [101]. Based on the idea that adult diseases have developmental roots, a fetus can become resilient to similar postnatal exposures by adjusting to its environment during the prenatal stage. However, if the postnatal environment differs from the prenatal one, these adaptive responses may prove to be harmful [102]. For example, undernutrition during pregnancy may "train" the fetus to have a more efficient energy metabolism, reducing susceptibility to weight loss and increasing survival in the event of future nutritional shortages. Conversely, this genetic propensity may heighten vulnerability to obesity and weight gain in settings where high-calorie meals are widely available [103].

Scholars have been afforded the chance to investigate the ways in which wars and other humanitarian tragedies, such as socioeconomic instability, affect human societies through famine. The consequences on following generations are demonstrated by retrospective studies of human cohorts who were malnourished throughout pregnancy and the early postnatal period [104]. Understanding the Dutch "hunger winter" is helpful. This time, which was characterized by a severe famine in 1944–1945 due to the German blockade of the Netherlands, showed that maternal undernutrition during the famine was linked to increased body fat, hypertension, glucose intolerance, and mental health issues in the offspring as they grew older [105]. Regardless of nutritional considerations, low birth weight independently increases the risk of metabolic illnesses in adulthood [106]. David Barker pioneered the connection between low birth weight and the development of adult metabolic and CVDs [107]. These correlations have been confirmed by later research conducted in a variety of global populations, including the China Birth Weight Survey and the Helsinki Birth Cohort Study [108]. Events that parents experience before or at the time of conception may have an impact on the health of future generations [109]. For instance, prenatal exposure to famine in both maternal and paternal lines has been associated with elevated hyperglycemia in offspring, with effects being more prominent when both parents received prenatal exposure. Additionally, research conducted between 1890 and 1920 on people born in the northern Swedish province of Overkalix looked at the food that was available at different times of childhood. It is noteworthy that eating too much during a boy's slow-growing boyhood was linked to a higher risk of diabetes and cardiovascular illness in their grandchildren, suggesting that qualities may be passed down across generations.

5. Conclusion

In health and biology-related research, the relationship between environment, epigenetics, and disease risk has emerged as a cornerstone of understanding. This serves as a reminder that our genes do not operate in isolation, but instead interacts with the environment based on the epigenetic modifying factors. Firstly, the interdependence of environment, epigenetics, and disease risk cannot be understated. Our genes, while acting as the foundational code of life, are not immutable destinies. They act as responsive instruments, finely tuned to the environmental cues encountered throughout life. Epigenetic modifications, like tags on a roadmap, guide our genes' expression, directing them toward health or disease. The developmental origins of disease concept show that the environment's influence isn't confined to a singular moment but stretches across prenatal and postnatal stages of development, with potential implications cascading through generations. The ability to understand the mechanisms between environment, epigenetics, and disease risk opens doors to personalized interventions based on an individual's unique molecular structure. The prospect of analyzing epigenetic patterns to predict disease susceptibility and devise precise treatments is no longer a distant dream. Personalized medicine, by combining genetic and epigenetic insights, has capabilities of providing treatments and preventive measures that are as unique as our fingerprints. Conversely, the broader public health implications highlight the importance of creating environments conducive to health from early life. Strategies aimed at optimizing nutrition during developmental stages, reducing exposure to harmful pollutants, and mitigating stressors can potentially alleviate disease burdens on a larger scale.

Enhancing disease prevention, diagnosis, and treatment through the application of epigenetic mechanisms in clinical settings and public health policies presents new opportunities. Histone and DNA methylation are examples of epigenetic alterations that may be used to provide biomarkers for early disease identification and risk assessment. This would allow interventions to be more precisely targeted. By reversing aberrant gene expression patterns, medications that alter epigenetic states—also known as epigenetic therapy—have demonstrated promise in the treatment of cancer and other illnesses. Moreover, the integration of epigenetic information into public health initiatives could prove advantageous in addressing lifestyle and environmental factors that impact epigenetic modifications. This, in turn, could define policies that target the population's risk of disease. Healthcare systems can enhance patient outcomes through more individualized and efficient techniques by comprehending and utilizing the ideas of epigenetics, which would be a major advancement in the fields of public health and medicine.

In future research, the convergence of technological advancements, research methodologies, and interdisciplinary collaboration fuels the potential for transformative breakthroughs. Epigenome-wide association studies offer a promising approach to identifying specific epigenetic marks linked to disease risk, providing more understanding of the molecular mechanisms associated with a wide range of conditions, including cancer and neurodegenerative disorders. The single-cell epigenomics grants us the ability to examine the heterogeneity within tissues and organs, providing a better understanding of the cellular activities involved in disease development. The integration of big data, machine learning, and epigenetics further accelerates our understanding, enabling the extraction of patterns that would otherwise remain concealed. The continued relevance of environmental epigenetics is undeniable as we proceed in future research. Rapid urbanization, climate change, and evolving lifestyles create new environmental challenges that warrant exploration through the lens of epigenetics. The mechanisms involved in genetics, environment, and epigenetics are a dynamic conversation that adapts to societal shifts, making it an enduring field of inquiry. Additionally, the lessons learned from historical events, such as famines and crises, highlight the lasting impact of environmental factors on health, as we confront emerging health threats.

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Ethical Statement

This study does not contain any studies with human or animal subjects performed by any of the authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

Data Availability Statement

The data that support this work are available upon reasonable request to the corresponding author.

Author Contribution Statement

Taiwo Temitope Ogunjobi: Conceptualization, Investigation, Writing – Original Draft, Writing – Review & Editing. **Tolulope Judah Gbayisomore**: Investigation, Writing –Review & Editing. **Patrica Okwuchi Nneji**: Project administration. **Oluwatoyin Olabimpe Olofin**: Conceptualization, Methodology. **Emmanuel Niyi Olowe**: Validation, Formal analysis. **Chimaobi Divine Gigam-Ozuzu**: Validation, Formal analysis. **Jolayemi Ibidunni Afolabi**: Supervision. **Ngozi Benedette Okwuokei**: Resources. **Victor Abiodun Boluwaji**: Resources. **Taiwo Paul Ojeniran**: Visualization. **Ikenna Oluebube Ogini**: Visualization. **Seth Olorunmijuwonlo Adesope**: Methodology. Toheeb Damilola Yissa: Data Curation. **Cyril Arinze Eji**: Data Curation.

References

[1] Sebastiani, G., Andreu-Fernández, V., Herranz Barbero, A., Aldecoa-Bilbao, V., Miracle, X., Meler Barrabes, E., . . . , & García-Algar, O. (2020). Eating disorders during gestation: Implications for mother's health, fetal outcomes, and epigenetic changes. *Frontiers in Pediatrics*, *8*, 587. https://doi.org/10.3389/fped.2020.00587

[2] Smyth, L. J., Kilner, J., Nair, V., Liu, H., Brennan, E., Kerr, K., . . . , & McKnight, A. J. (2021). Assessment of differentially methylated loci in individuals with end-stage kidney disease attributed to diabetic kidney disease: An exploratory study. *Clinical Epigenetics*, *13*(1), 99. https://doi.org/10.1186/s13148-021-01081-x

[3] Hop, P. J., Luijk, R., Daxinger, L., Van Iterson, M., Dekkers, K. F., Jansen, R., . . . , & Heijmans, B. T. (2020). Genome-wide identification of genes regulating DNA methylation using genetic anchors for causal inference. *Genome Biology*, *21*, 1–24. https://doi.org/10.1186/s13059-020-02114-z

[4] Cimino, S., Cerniglia, L., Ballarotto, G., Marzilli, E., Pascale, E., D'Addario, C., . . . , & Tambelli, R. (2019). Children's DAT1 polymorphism moderates the relationship between parents' psychological profiles, children's DAT methylation, and their emotional/behavioral functioning in a normative sample. *International Journal of Environmental Research and Public Health*, *16*(14), 2567. https://doi.org/10.3390/ijerph16142567

[5] Czamara, D., Eraslan, G., Page, C. M., Lahti, J., Lahti-Pulkkinen, M., Hämäläinen, E., . . . , & Binder, E. B. (2019). Integrated analysis of environmental and genetic influences on cord blood DNA methylation in new-borns. *Nature Communications*, *10*(1), 2548. https://doi.org/10.1038/s41467-019-10461-0

[6] Kuźnicki, D., Meller, B., Arasimowicz-Jelonek, M., Braszewska-Zalewska, A., Drozda, A., & Floryszak-Wieczorek, J. (2019). BABA-induced DNA methylome adjustment to intergenerational defense priming in potato to Phytophthora infestans. *Frontiers in Plant Science*, *10*, 650. https://doi.org/10.3389/fpls.2019.00650

[7] Gorelick, A. N., Sánchez-Rivera, F. J., Cai, Y., Bielski, C. M., Biederstedt, E., Jonsson, P., . . . , & Taylor, B. S. (2020). Phase and context shape the function of composite oncogenic mutations. *Nature*, *582*(7810), 100–103. https://doi.org/10.1038/s41586-020-2315-8

[8] Glavaški, M., & Stankov, K. (2019). Epigenetics in disease etiopathogenesis. *Genetika*, *51*(3), 975–994. https://doi.org/10.2298/GENSR1903975G

[9] Skinner, M. K. (2023). Environmental epigenetics and climate change. *Environmental epigenetics*, *9*(1), 1–2. https://doi.org/10.1093/eep/dvac028

[10] Favé, M. J., Lamaze, F. C., Soave, D., Hodgkinson, A., Gauvin, H., Bruat, V., . . . , & Awadalla, P. (2018). Gene-by-environment interactions in urban populations modulate risk phenotypes. *Nature Communications*, *9*(1), 827. https://doi.org/10.1038/s41467-018-03202-2

[11] Buitrago, D., Labrador, M., Arcon, J. P., Lema, R., Flores, O., Esteve-Codina, A., . . . , & Orozco, M. (2021). Impact of DNA methylation on 3D genome structure. *Nature Communications*, *12*(1), 3243. https://doi.org/10.1038/s41467-021-23142-8

[12] Rao, S., Chiu, T. P., Kribelbauer, J. F., Mann, R. S., Bussemaker, H. J., & Rohs, R. (2018). Systematic

prediction of DNA shape changes due to CpG methylation explains epigenetic effects on protein–DNA binding. *Epigenetics & Chromatin*, *11*, 1–11. https://doi.org/10.1186/s13072-018-0174-4

[13] Vanden Broeck, A., Cox, K., Brys, R., Castiglione, S., Cicatelli, A., Guarino, F., ..., & Vander Mijnsbrugge, K. (2018). Variability in DNA methylation and generational plasticity in the Lombardy poplar, a single genotype worldwide distributed since the eighteenth century. *Frontiers in Plant Science*, *9*, 1635. https://doi.org/10.3389/fpls.2018.01635

[14] Cusack, M., King, H. W., Spingardi, P., Kessler, B. M., Klose, R. J., & Kriaucionis, S. (2020). Distinct contributions of DNA methylation and histone acetylation to the genomic occupancy of transcription factors. *Genome Research*, *30*(10), 1393–1406. https://doi.org/10.1101/gr.257576.119

[15] Franzen, J., Georgomanolis, T., Selich, A., Kuo, C. C., Stöger, R., Brant, L., ..., & Wagner, W. (2021). DNA methylation changes during long-term in vitro cell culture are caused by epigenetic drift. *Communications Biology*, *4*(1), 598. https://doi.org/10.1038/s42003-021-02116-y

[16] Heindel, J. J., Blumberg, B., Cave, M., Machtinger, R., Mantovani, A., Mendez, M. A., ..., & Vom Saal, F. (2017). Metabolism disrupting chemicals and metabolic disorders. *Reproductive Toxicology*, *68*, 3–33. https://doi.org/10.1016/j.reprotox.2016.10.001

[17] Gordeeva, O., & Safandeev, V. (2021). 5-Hydroxytryptophan (5-HTP)-induced intracellular syndrome in mouse non-neural embryonic cells is associated with inhibited proliferation and cell death. *Neuropharmacology*, *195*, 107862. https://doi.org/10.1016/j.neuropharm.2019.107862

[18] Kozlenkov, A., Li, J., Apontes, P., Hurd, Y. L., Byne, W. M., Koonin, E. V., ..., & Dracheva, S. (2018). A unique role for DNA (hydroxy) methylation in epigenetic regulation of human inhibitory neurons. *Science Advances*, *4*(9), eaau6190. https://doi.org/10.1126/sciadv.aau6190

[19] Song, H., Chen, L., Liu, W., Xu, X., Zhou, Y., Zhu, J., ..., & Zhou, H. (2021). Depleting long noncoding RNA HOTAIR attenuates chronic myelocytic leukemia progression by binding to DNA methyltransferase 1 and inhibiting PTEN gene promoter methylation. *Cell Death & Disease*, *12*(5), 440. https://doi.org/10.1038/s41419-021-03637-4

[20] Mulholland, C. B., Nishiyama, A., Ryan, J., Nakamura, R., Yiğit, M., Glück, I. M., ..., & Leonhardt, H. (2020). Recent evolution of a TET-controlled and DPPA3/STELLA-driven pathway of passive DNA demethylation in mammals. *Nature Communications*, *11*(1), 5972. https://doi.org/10.1038/s41467-020-19603-1

[21] Madrid, A., Chopra, P., & Alisch, R. S. (2018). Species-specific 5 mC and 5 hmC genomic landscapes indicate epigenetic contribution to human brain evolution. *Frontiers in Molecular Neuroscience*, *11*, 39. https://doi.org/10.3389/fnmol.2018.00039

[22] Efimova, O. A., Koltsova, A. S., Krapivin, M. I., Tikhonov, A. V., & Pendina, A. A. (2020). Environmental epigenetics and genome flexibility: Focus on 5-hydroxymethylcytosine. *International Journal of Molecular Sciences*, *21*(9), 3223. https://doi.org/10.3390/ijms21093223

[23] Lorente-Pozo, S., Parra-Llorca, A., Núñez-Ramiro, A., Cernada, M., Hervás, D., Boronat, N., ..., & Vento, M. (2018). The oxygen load supplied during delivery room stabilization of preterm infants modifies the DNA methylation profile. *The Journal of Pediatrics*, *202*, 70–76. https://doi.org/10.1016/j.jpeds.2018.07.009

[24] Chen, H., Liu, X., Li, W., Peng, Y., & Nie, Z. (2019). Silver coordination complex amplified electrochemiluminescence sensor for sensitive detection of coenzyme A and histone acetyltransferase activity. *Biosensors and Bioelectronics*, *126*, 535–542. https://doi.org/10.1016/j.bios.2018.11.003

[25] Tan, L. M., Zhang, C. J., Hou, X. M., Shao, C. R., Lu, Y. J., Zhou, J. X., ..., & He, X. J. (2018). The PEAT protein complexes are required for histone deacetylation and heterochromatin silencing. *The EMBO Journal*, *37*(19), e98770. https://doi.org/10.15252/embj.201798770

[26] Ye, C., Sutter, B. M., Wang, Y., Kuang, Z., Zhao, X., Yu, Y., & Tu, B. P. (2019). Demethylation of the protein phosphatase PP2A promotes demethylation of histones to enable their function as a methyl group sink. *Molecular Cell*, *73*(6), 1115–1126. https://doi.org/10.1016/j.molcel.2019.01.012

[27] Mendoza, M., Egervari, G., Sidoli, S., Donahue, G., Alexander, D. C., Sen, P., ..., & Berger, S. L. (2022). Enzymatic transfer of acetate on histones from lysine reservoir sites to lysine activating sites. *Science Advances*, *8*(3), eabj5688. https://doi.org/10.1126/sciadv.abj5688

[28] Eslaminejad, M. B., Fani, N., & Shahhoseini, M. (2013). Epigenetic regulation of osteogenic and chondrogenic differentiation of mesenchymal stem cells in culture. *Cell Journal (Yakhteh)*, *15*(1), 1–10. https://www.celljournal.org/article_250141.html

[29] Martire, S., & Banaszynski, L. A. (2020). The roles of histone variants in fine-tuning chromatin organization and function. *Nature Reviews Molecular Cell Biology*, *21*(9), 522–541. https://doi.org/10.1038/s41580-020-0262-8

[30] Wong, W. K., Sørensen, A. E., Joglekar, M. V., Hardikar, A. A., & Dalgaard, L. T. (2018). Non-coding RNA in pancreas and β-cell development. *Non-coding RNA*, *4*(4), 41. https://doi.org/10.3390/ncrna4040041

[31] Kim, S., & Kaang, B. K. (2017). Epigenetic regulation and chromatin remodeling in learning and memory. *Experimental & Molecular Medicine*, *49*(1), e281. https://doi.org/10.1038/emm.2016.140

[32] Liu, B., Shyr, Y., Cai, J., & Liu, Q. (2019). Interplay between miRNAs and host genes and their role in cancer. *Briefings in Functional Genomics*, *18*(4), 255–266. https://doi.org/10.1093/bfgp/elz002

[33] Gil, R. S., & Vagnarelli, P. (2019). Protein phosphatases in chromatin structure and function. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*, *1866*(1), 90–101. https://doi.org/10.1016/j.bbamcr.2018.07.016

[34] Nadhan, R., Isidoro, C., Song, Y. S., & Dhanasekaran, D. N. (2022). Signaling by LncRNAs: Structure, cellular homeostasis, and disease pathology. *Cells*, *11*(16), 2517. https://doi.org/10.3390/cells11162517

[35] Chen, L. L. (2016). The biogenesis and emerging roles of circular RNAs. *Nature Reviews Molecular Cell Biology*, *17*(4), 205–211. https://doi.org/10.1038/nrm.2015.32

[36] You, C., He, W., Hang, R., Zhang, C., Cao, X., Guo, H., ..., & Mo, B. (2019). FIERY1 promotes microRNA accumulation by suppressing rRNA-derived small interfering RNAs in Arabidopsis. *Nature Communications*, *10*(1), 4424. https://doi.org/10.1038/s41467-019-12379-z

[37] Halgren, C., Nielsen, N. M., Nazaryan-Petersen, L., Silahtaroglu, A., Collins, R. L., Lowther, C., ..., & Bache, I. (2018). Risks and recommendations in prenatally detected de novo balanced chromosomal rearrangements from assessment of long-term outcomes. *The American Journal*

of Human Genetics, *102*(6), 1090–1103. https://doi.org/10.1016/j.ajhg.2018.04.005

[38] Tilley, S. K., Martin, E. M., Smeester, L., Joseph, R. M., Kuban, K. C., Heeren, T. C., . . . , & Fry, R. C. (2018). Placental CpG methylation of infants born extremely preterm predicts cognitive impairment later in life. *PloS One*, *13*(3), e0193271. https://doi.org/10.1371/journal.pone.0193271

[39] Siemelink, M. A., van der Laan, S. W., Haitjema, S., van Koeverden, I. D., Schaap, J., Wesseling, M., . . . , & Pasterkamp, G. (2018). Smoking is associated to DNA methylation in atherosclerotic carotid lesions. *Circulation: Genomic and Precision Medicine*, *11*(9), e002030. https://doi.org/10.1161/CIRCGEN.117.002030

[40] Rong, H., Lai, X., Mahmoudi, E., & Fang, H. (2019). Early-life exposure to the Chinese famine and risk of cognitive decline. *Journal of Clinical Medicine*, *8*(4), 484. https://doi.org/10.3390/jcm8040484

[41] Iqbal, M. S., Rahman, S., Haque, M. A., Bhuyan, M. J., Faruque, A. S. G., & Ahmed, T. (2019). Lower intakes of protein, carbohydrate, and energy are associated with increased global DNA methylation in 2-to 3-year-old urban slum children in Bangladesh. *Maternal & Child Nutrition*, *15*(3), e12815. https://doi.org/10.1111/mcn.12815

[42] Velazquez, M. A., Fleming, T. P., & Watkins, A. J. (2019). Periconceptional environment and the developmental origins of disease. *Journal of Endocrinology*, *242*(1), T33–T49. https://doi.org/10.1530/JOE-18-0676

[43] Nilsson, E., Klukovich, R., Sadler-Riggleman, I., Beck, D., Xie, Y., Yan, W., & Skinner, M. K. (2018). Environmental toxicant induced epigenetic transgenerational inheritance of ovarian pathology and granulosa cell epigenome and transcriptome alterations: Ancestral origins of polycystic ovarian syndrome and primary ovarian insufficiency. *Epigenetics*, *13*(8), 875–895. https://doi.org/10.1080/15592294.2018.1521223

[44] Xavier, M. J., Roman, S. D., Aitken, R. J., & Nixon, B. (2019). Transgenerational inheritance: How impacts to the epigenetic and genetic information of parents affect offspring health. *Human Reproduction Update*, *25*(5), 519–541. https://doi.org/10.1093/humupd/dmz017

[45] Branje, S., Geeraerts, S., de Zeeuw, E. L., Oerlemans, A. M., Koopman-Verhoeff, M. E., Schulz, S., . . . , & Boomsma, D. I. (2020). Intergenerational transmission: Theoretical and methodological issues and an introduction to four Dutch cohorts. *Developmental Cognitive Neuroscience*, *45*, 100835. https://doi.org/10.1016/j.dcn.2020.100835

[46] Li, Y. (2018). Epigenetic mechanisms link maternal diets and gut microbiome to obesity in the offspring. *Frontiers in Genetics*, *9*, 342. https://doi.org/10.3389/fgene.2018.00342

[47] Grilo, L. F., Tocantins, C., Diniz, M. S., Gomes, R. M., Oliveira, P. J., Matafome, P., & Pereira, S. P. (2021). Metabolic disease programming: From mitochondria to epigenetics, glucocorticoid signalling and beyond. *European Journal of Clinical Investigation*, *51*(10), e13625. https://doi.org/10.1111/eci.13625

[48] Matsumoto, M., Saito, A., Okada, C., Okada, E., Tajima, R., & Takimoto, H. (2021). Consumption of meals prepared away from home is associated with inadequacy of dietary fiber, vitamin C and mineral intake among Japanese adults: Analysis from the 2015 National Health and Nutrition Survey. *Nutrition Journal*, *20*, 1–13. https://doi.org/10.1186/s12937-021-00693-6

[49] Yu, R., Wang, X., & Moazed, D. (2018). Epigenetic inheritance mediated by coupling of RNAi and histone H3K9 methylation. *Nature*, *558*(7711), 615–619. https://doi.org/10.1038/s41586-018-0239-3

[50] Schellong, K., Melchior, K., Ziska, T., Rancourt, R. C., Henrich, W., & Plagemann, A. (2020). Maternal but not paternal high-fat diet (HFD) exposure at conception predisposes for 'diabesity' in offspring generations. *International Journal of Environmental Research and Public Health*, *17*(12), 4229. https://doi.org/10.3390/ijerph17124229

[51] Bell, J. T., Tsai, P. C., Yang, T. P., Pidsley, R., Nisbet, J., Glass, D., . . . , & Deloukas, P. (2012). Epigenome-wide scans identify differentially methylated regions for age and age-related phenotypes in a healthy ageing population. *PLoS Genetics*, *8*(4), e1002629. https://doi.org/10.1371/journal.pgen.1002629

[52] Zgheib, E., Kim, M. J., Jornod, F., Bernal, K., Tomkiewicz, C., Bortoli, S., . . . , & Audouze, K. (2021). Identification of non-validated endocrine disrupting chemical characterization methods by screening of the literature using artificial intelligence and by database exploration. *Environment International*, *154*, 106574. https://doi.org/10.1016/j.envint.2021.106574

[53] Lei, L., & Desai, S. (2021). Male out-migration and the health of left-behind wives in India: The roles of remittances, household responsibilities, and autonomy. *Social Science & Medicine*, *280*, 113982. https://doi.org/10.1016/j.socscimed.2021.113982

[54] Li, Y., Chen, F., Wei, A., Bi, F., Zhu, X., Yin, S., . . . , & Cao, W. (2019). Klotho recovery by genistein via promoter histone acetylation and DNA demethylation mitigates renal fibrosis in mice. *Journal of Molecular Medicine*, *97*, 541–552. https://doi.org/10.1007/s00109-019-01759-z

[55] Liang, Y. S., Qi, W. T., Guo, W., Wang, C. L., Hu, Z. B., & Li, A. K. (2018). Genistein and daidzein induce apoptosis of colon cancer cells by inhibiting the accumulation of lipid droplets. *Food & Nutrition Research, 62*. https://doi.org/10.29219/fnr.v62.1384

[56] Zhou, X., Jiao, D., Dou, M., Chen, J., Li, Z., Li, Y., . . . , & Han, X. (2019). Association of glutathione-S-transferase p1 gene promoter methylation and the incidence of prostate cancer: A systematic review and meta-analysis. *Journal of Cancer Research and Clinical Oncology*, *145*, 1939–1948. https://doi.org/10.1007/s00432-019-02962-8

[57] Nieminen, T. T., Walker, C. J., Olkinuora, A., Genutis, L. K., O'Malley, M., Wakely, P. E., . . . , & De La Chapelle, A. (2020). Thyroid carcinomas that occur in familial adenomatous polyposis patients recurrently harbor somatic variants in APC, BRAF, and KTM2D. *Thyroid*, *30*(3), 380–388. https://doi.org/10.1089/thy.2019.0561

[58] Alvarado-Cruz, I., Alegría-Torres, J. A., Montes-Castro, N., Jiménez-Garza, O., & Quintanilla-Vega, B. (2018). Environmental epigenetic changes, as risk factors for the development of diseases in children: A systematic review. *Annals of Global Health*, *84*(2), 212–224. https://doi.org/10.29024/aogh.909

[59] Sidorkiewicz, I., Czerniecki, J., Jarząbek, K., Zbucka-Krętowska, M., & Wołczyński, S. (2018). Cellular, transcriptomic and methylome effects of individual and combined exposure to BPA, BPF, BPS on mouse spermatocyte GC-2 cell line. *Toxicology and Applied Pharmacology*, *359*, 1–11. https://doi.org/10.1016/j.taap.2018.09.006

[60] Zhu, L., Yuan, C., Wang, M., Liu, Y., Wang, Z., & Seif, M. M. (2020). Bisphenol A-associated alterations in DNA and

histone methylation affects semen quality in rare minnow Gobiocypris rarus. *Aquatic Toxicology*, *226*, 105580. https://doi.org/10.1016/j.aquatox.2020.105580

[61] Liu, X., Du, H., Chen, D., Yuan, H., Chen, W., Jia, W., ..., & Gao, L. (2019). Cyclophilin D deficiency protects against the development of mitochondrial ROS and cellular inflammation in aorta. *Biochemical and Biophysical Research Communications*, *508*(4), 1202–1208. https://doi.org/10.1016/j.bbrc.2018.12.064

[62] Maiuri, A. R., Savant, S. S., Podicheti, R., Rusch, D. B., & O'Hagan, H. M. (2019). DNA methyltransferase inhibition reduces inflammation-induced colon tumorigenesis. *Epigenetics*, *14*(12), 1209–1223. https://doi.org/10.1080/15592294.2019.1634986

[63] Pandey, S., Jha, H. C., Shukla, S. K., Shirley, M. K., & Robertson, E. S. (2018). Epigenetic regulation of tumor suppressors by Helicobacter pylori enhances EBV-induced proliferation of gastric epithelial cells. *MBio*, *9*(2), 10-1128. https://doi.org/10.1128/mbio.00649-18

[64] Shi, F., Zhou, M., Shang, L., Du, Q., Li, Y., Xie, L., ..., & Cao, Y. (2019). EBV (LMP1)-induced metabolic reprogramming inhibits necroptosis through the hypermethylation of the RIP3 promoter. *Theranostics*, *9*(9), 2424–2438. https://doi.org/10.7150/thno.30941

[65] Cao, Y., Xie, L., Shi, F., Tang, M., Li, Y., Hu, J., ..., & Bode, A. M. (2021). Targeting the signaling in Epstein–Barr virus-associated diseases: Mechanism, regulation, and clinical study. *Signal Transduction and Targeted Therapy*, *6*(1), 15. https://doi.org/10.1038/s41392-020-00376-4

[66] Saquib, M., Agnihotri, P., Monu, & Biswas, S. (2021). Exogenous miRNA: A perspective role as therapeutic in rheumatoid arthritis. *Current Rheumatology Reports*, *23*(6), 43. https://doi.org/10.1007/s11926-021-01009-7

[67] Müller, M., Bird, T. G., & Nault, J. C. (2020). The landscape of gene mutations in cirrhosis and hepatocellular carcinoma. *Journal of Hepatology*, *72*(5), 990–1002. https://doi.org/10.1016/j.jhep.2020.01.019

[68] Hoang, P. H., & Landi, M. T. (2022). DNA methylation in lung cancer: Mechanisms and associations with histological subtypes, molecular alterations, and major epidemiological factors. *Cancers*, *14*(4), 961. https://doi.org/10.3390/cancers14040961

[69] Mishra, M., & Kowluru, R. A. (2019). DNA methylation—A potential source of mitochondria DNA base mismatch in the development of diabetic retinopathy. *Molecular Neurobiology*, *56*(1), 88–101. https://doi.org/10.1007/s12035-018-1086-9

[70] Bond, C. E., Liu, C., Kawamata, F., McKeone, D. M., Fernando, W., Jamieson, S., ..., & Whitehall, V. L. (2018). Oncogenic BRAF mutation induces DNA methylation changes in a murine model for human serrated colorectal neoplasia. *Epigenetics*, *13*(1), 40–48. https://doi.org/10.1080/15592294.2017.1411446

[71] Jung, H., Kim, H. S., Kim, J. Y., Sun, J. M., Ahn, J. S., Ahn, M. J., ..., & Choi, J. K. (2019). DNA methylation loss promotes immune evasion of tumours with high mutation and copy number load. *Nature Communications*, *10*(1), 4278. https://doi.org/10.1038/s41467-019-12159-9

[72] Mohammad, H. P., Barbash, O., & Creasy, C. L. (2019). Targeting epigenetic modifications in cancer therapy: Erasing the roadmap to cancer. *Nature Medicine*, *25*(3), 403–418. https://doi.org/10.1038/s41591-019-0376-8

[73] Romani, M., Pistillo, M. P., & Banelli, B. (2018). Epigenetic targeting of glioblastoma. *Frontiers in Oncology*, *8*, 448. https://doi.org/10.3389/fonc.2018.00448

[74] Alpha-Bazin, B., Gorlas, A., Lagorce, A., Joulié, D., Boyer, J. B., Dutertre, M., ..., & Armengaud, J. (2021). Lysine-specific acetylated proteome from the archaeon Thermococcus gammatolerans reveals the presence of acetylated histones. *Journal of Proteomics*, *232*, 104044. https://doi.org/10.1016/j.jprot.2020.104044

[75] Sulkowski, P. L., Oeck, S., Dow, J., Economos, N. G., Mirfakhraie, L., Liu, Y., ..., & Glazer, P. M. (2020). Oncometabolites suppress DNA repair by disrupting local chromatin signalling. *Nature*, *582*(7813), 586–591. https://doi.org/10.1038/s41586-020-2363-0

[76] Komar, D., & Juszczynski, P. (2020). Rebelled epigenome: Histone H3S10 phosphorylation and H3S10 kinases in cancer biology and therapy. *Clinical Epigenetics*, *12*, 1–14. https://doi.org/10.1186/s13148-020-00941-2

[77] Gomes, A. P., Ilter, D., Low, V., Rosenzweig, A., Shen, Z. J., Schild, T., ..., & Blenis, J. (2019). Dynamic incorporation of histone H3 variants into chromatin is essential for acquisition of aggressive traits and metastatic colonization. *Cancer Cell*, *36*(4), 402–417. https://doi.org/10.1016/j.ccell.2019.08.006

[78] Ford, B. R., Vignali, P. D. A., Rittenhouse, N. L., Scharping, N. E., Peralta, R., Lontos, K., ..., & Poholek, A. C. (2022). Tumor microenvironmental signals reshape chromatin landscapes to limit the functional potential of exhausted T cells. *Science Immunology*, *7*(74). https://doi.org/10.1126/sciimmunol.abj9123

[79] Farooqi, A. A., Fayyaz, S., Poltronieri, P., Calin, G., & Mallardo, M. (2022). Epigenetic deregulation in cancer: Enzyme players and non-coding RNAs. *Seminars in Cancer Biology*, *83*, 197–207. https://doi.org/10.1016/j.semcancer.2020.07.013

[80] Maamar, M. B., Nilsson, E., Thorson, J. L. M., Beck, D., & Skinner, M. K. (2021). Transgenerational disease specific epigenetic sperm biomarkers after ancestral exposure to dioxin. *Environmental Research*, *192*, 110279. https://doi.org/10.1016/j.envres.2020.110279

[81] Belli, M., & Tabocchini, M. A. (2020). Ionizing radiation-induced epigenetic modifications and their relevance to radiation protection. *International Journal of Molecular Sciences*, *21*(17), 5993. https://doi.org/10.3390/ijms21175993

[82] Yamashita, S., Kishino, T., Takahashi, T., Shimazu, T., Charvat, H., Kakugawa, Y., ..., & Ushijima, T. (2018). Genetic and epigenetic alterations in normal tissues have differential impacts on cancer risk among tissues. *Proceedings of the National Academy of Sciences*, *115*(6), 1328–1333. https://doi.org/10.1073/pnas.1717340115

[83] Jiang, W., Agrawal, D. K., & Boosani, C. S. (2020). Non-coding RNAs as epigenetic gene regulators in cardiovascular diseases. In J. Xiao (Ed.), *Non-coding RNAs in cardiovascular diseases* (pp. 133–148). Springer. https://doi.org/10.1007/978-981-15-1671-9_7

[84] Valladares-Rodriguez, S., Fernández-Iglesias, M. J., Anido-Rifón, L., Facal, D., Rivas-Costa, C., & Pérez-Rodríguez, R. (2019). Touchscreen games to detect cognitive impairment in senior adults. A user-interaction pilot study. *International Journal of Medical Informatics*, *127*, 52–62. https://doi.org/10.1016/j.ijmedinf.2019.04.012

[85] Xiao, X., Liu, X., & Jiao, B. (2020). Epigenetics: Recent advances and its role in the treatment of Alzheimer's disease. *Frontiers in Neurology*, *11*, 538301. https://doi.org/10.3389/fneur.2020.538301

[86] Mecocci, P., Baroni, M., Senin, U., & Boccardi, V. (2018). Brain aging and late-onset Alzheimer's disease: A matter of increased amyloid or reduced energy? *Journal of*

Alzheimer's Disease, *64*(s1), S397–S404. https://doi.org/10.3233/jad-179903

[87] Pai, M. C., Kuo, Y. M., Wang, I. F., Chiang, P. M., & Tsai, K. J. (2019). The role of methylated circulating nucleic acids as a potential biomarker in Alzheimer's disease. *Molecular Neurobiology*, *56*, 2440–2449. https://doi.org/10.1007/s12035-018-1229-z

[88] Wan, X., Ma, B., Wang, X., Guo, C., Sun, J., Cui, J., & Li, L. (2020). S-Adenosylmethionine alleviates amyloid-β-induced neural injury by enhancing trans-sulfuration pathway activity in astrocytes. *Journal of Alzheimer's Disease*, *76*(3), 981–995. https://doi.org/10.3233/jad-200103

[89] Sánchez-Juan, P., Moreno, S., de Rojas, I., Hernández, I., Valero, S., Alegret, M., . . . , & Ruiz, A. (2019). The MAPT H1 haplotype is a risk factor for Alzheimer's disease in APOE ε4 non-carriers. *Frontiers in Aging Neuroscience*, *11*, 327. https://doi.org/10.3389/fnagi.2019.00327

[90] Kulminski, A. M., Huang, J., Wang, J., He, L., Loika, Y., & Culminskaya, I. (2018). Apolipoprotein E region molecular signatures of Alzheimer's disease. *Aging Cell*, *17*(4), e12779. https://doi.org/10.1111/acel.12779

[91] Lillico, R., Zhou, T., Khorshid Ahmad, T., Stesco, N., Gozda, K., Truong, J., . . . , & Namaka, M. (2018). Increased post-translational lysine acetylation of myelin basic protein is associated with peak neurological disability in a mouse experimental autoimmune encephalomyelitis model of multiple sclerosis. *Journal of Proteome Research*, *17*(1), 55–62. https://doi.org/10.1021/acs.jproteome.7b00270

[92] Oh, S. J., Lee, H. J., Jeong, Y. J., Nam, K. R., Kang, K. J., Han, S. J., . . . , & Choi, J. Y. (2020). Evaluation of the neuroprotective effect of taurine in Alzheimer's disease using functional molecular imaging. *Scientific Reports*, *10*(1), 15551. https://doi.org/10.1038/s41598-020-72755-4

[93] Ooi, C. Y., Carter, D. R., Liu, B., Mayoh, C., Beckers, A., Lalwani, A., . . . , & Marshall, G. M. (2018). Network modeling of microRNA–mRNA interactions in neuroblastoma tumorigenesis identifies miR-204 as a direct inhibitor of MYCN. *Cancer Research*, *78*(12), 3122–3134. https://doi.org/10.1158/0008-5472.CAN-17-3034

[94] Haque, A., Samantaray, S., Knaryan, V. H., Capone, M., Hossain, A., Matzelle, D., . . . , & Banik, N. L. (2020). Calpain mediated expansion of CD4+ cytotoxic T cells in rodent models of Parkinson's disease. *Experimental Neurology*, *330*, 113315. https://doi.org/10.1016/j.expneurol.2020.113315

[95] Zhang, J., & Tan, L. C. S. (2016). Revisiting the medical management of Parkinson's disease: Levodopa versus dopamine agonist. *Current Neuropharmacology*, *14*(4), 356–363. http://dx.doi.org/10.2174/1570159X14666151208114634

[96] Hansen, C., Angot, E., Bergström, A. L., Steiner, J. A., Pieri, L., Paul, G., . . . , & Brundin, P. (2011). α-Synuclein propagates from mouse brain to grafted dopaminergic neurons and seeds aggregation in cultured human cells. *The Journal of Clinical Investigation*, *121*(2), 715–725. https://doi.org/10.1172/jci43366

[97] Lee, J. Y., Kim, H., Jo, A., Khang, R., Park, C. H., Park, S. J., . . . , & Shin, J. H. (2021). α-Synuclein A53T binds to transcriptional adapter 2-alpha and blocks histone H3 acetylation. *International Journal of Molecular Sciences*, *22*(10), 5392. https://doi.org/10.3390/ijms22105392

[98] Blesa, J., Juri, C., Collantes, M., Peñuelas, I., Prieto, E., Iglesias, E., . . . , & Obeso, J. A. (2010). Progression of dopaminergic depletion in a model of MPTP-induced Parkinsonism in non-human primates. An 18F-DOPA and 11C-DTBZ PET study. *Neurobiology of Disease*, *38*(3), 456–463. https://doi.org/10.1016/j.nbd.2010.03.006

[99] Jeon, J. Y., Ha, K. H., & Kim, D. J. (2015). New risk factors for obesity and diabetes: Environmental chemicals. *Journal of Diabetes Investigation*, *6*(2), 109–111. https://doi.org/10.1111/jdi.12318

[100] Montrose, L., Padmanabhan, V., Goodrich, J. M., Domino, S. E., Treadwell, M. C., Meeker, J. D., . . . , & Dolinoy, D. C. (2018). Maternal levels of endocrine disrupting chemicals in the first trimester of pregnancy are associated with infant cord blood DNA methylation. *Epigenetics*, *13*(3), 301–309. https://doi.org/10.1080/15592294.2018.1448680

[101] Pitchika, A., Jolink, M., Winkler, C., Hummel, S., Hummel, N., Krumsiek, J., . . . , & Beyerlein, A. (2018). Associations of maternal type 1 diabetes with childhood adiposity and metabolic health in the offspring: A prospective cohort study. *Diabetologia*, *61*, 2319–2332. https://doi.org/10.1007/s00125-018-4688-x

[102] Ponsonby, A. L., Symeonides, C., Saffery, R., Mueller, J. F., O'Hely, M., Sly, P. D., . . . , & Vuillermin, P. (2020). Prenatal phthalate exposure, oxidative stress-related genetic vulnerability and early life neurodevelopment: A birth cohort study. *Neurotoxicology*, *80*, 20–28. https://doi.org/10.1016/j.neuro.2020.05.006

[103] Hu, Z., Tylavsky, F. A., Han, J. C., Kocak, M., Fowke, J. H., Davis, R. L., . . . , & Zhao, Q. (2019). Maternal metabolic factors during pregnancy predict early childhood growth trajectories and obesity risk: The CANDLE Study. *International Journal of Obesity*, *43*(10), 1914–1922. https://doi.org/10.1038/s41366-019-0326-z

[104] Dong, Y., Bennett, K., Jan, C., Dong, B., Zou, Z., Hu, P., . . . , & Ma, J. (2019). Subnational variation of stunting, wasting and malnutrition in Chinese primary-school children between 2010 and 2014: Urban–rural disparity. *Public Health Nutrition*, *22*(11), 2043–2054. https://doi.org/10.1017/s1368980019000235

[105] Stickley, A., & Leinsalu, M. (2018). Childhood hunger and depressive symptoms in adulthood: Findings from a population-based study. *Journal of Affective Disorders*, *226*, 332–338. https://doi.org/10.1016/j.jad.2017.09.013

[106] Gillberg, L., Rönn, T., Jørgensen, S. W., Perfilyev, A., Hjort, L., Nilsson, E., . . . , & Ling, C. (2019). Fasting unmasks differential fat and muscle transcriptional regulation of metabolic gene sets in low versus normal birth weight men. *EBioMedicine*, *47*, 341–351. https://doi.org/10.1016/j.ebiom.2019.08.017

[107] Sperling, J., & Nilsson, P. M. (2020). Does early life programming influence arterial stiffness and central hemodynamics in adulthood? *Journal of Hypertension*, *38*(3), 481–488. https://doi.org/10.1097/hjh.0000000000002292

[108] Scifres, C. M. (2021). Short-and long-term outcomes associated with large for gestational age birth weight. *Obstetrics and Gynecology Clinics of North America*, *48*(2), 325–337. https://doi.org/10.1016/j.ogc.2021.02.005

[109] Ficks, C. A., Lahey, B. B., & Waldman, I. D. (2013). Does low birth weight share common genetic or environmental risk with childhood disruptive disorders? *Journal of Abnormal Psychology*, *122*(3), 842–853. https://psycnet.apa.org/doi/10.1037/a0033079

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