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The Role of Epigenetic Modifications in Complex Human Diseases: A Review of Gene–Environment Interactions

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Abstract:

Epigenetics has emerged as a key field for understanding the interplay between genetic predisposition and environmental exposures in Human health. It is very unique because unlike with genetic mutations, epigenetics does not alter the genes themselves; rather it affects how the genes behave – whether they are turned on or off – offering us an amenable and reversible level of regulation. The induced alterations will act as molecular intermediaries of the gene-environment interactions that underlie susceptibility, course and phenotypic heterogeneity of complex human disorders. With increasing evidence suggesting that abnormal epigenetic changes are integrated into the development of cancer, cardiovascular diseases, neurological disorders, autoimmune diseases and metabolic syndromes. Nutrition, toxins, stress, and social determinants are environmental factors able to cause long-lasting epigenetic changes that can alter disease risk during the lifetime and even transgenerationally. This review summarizes our present knowledge on the mechanistic landscape underlying the epigenetic regulation process and its relevance in disease progression, as well as the possible use of precision/precision-like epigenetic therapies in practice, outlining the prospects and challenges to translating this understanding to precision medicine. Diet, toxins, stress and sociodemographic factors are the environmental aspects capable of producing persistent epigenetic modifications leading to change in disease risk both acutely throughout lifespan as well as intergenerationally. This review provides a general overview of the current mechanistic landscape of epigenetic regulation and how it relates to disease pathogenesis, as well as potential for precision/precision-like epigenetic therapies in clinical medicine, focusing on opportunities and challenges to implementing this understanding in practice.

Keywords: **miRNAs** (microRNAs), **lncRNAs** (long non-coding RNAs), **G×E** (gene-environment interaction), **CVDs** (cardiovascular diseases), **TSGs** (tumor suppressor genes), **DNMTs** (DNA methyltransferases),

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Introduction:

The intersection of two areas remarkably characterizes the dynamic scenario of human health and disease. Interplay between genetic map of a human being and his/her long-term surrounding environment (1). Last few generations, extensive records of human genomics have been made with gene diversity and its association with different diseases are used in documenting inborn predilections (2). However, it may be noted that people who develop a case of illness take action; Some genetic profiles with obvious large differences

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in the results of the disease can be very equally environmental factors that contribute greatly to the occurrence of a disease and its development, which highlights the deficiencies of the genetic approach (3). It is difficult to feel that the catalyzed development of Epigenetics as one of the most important areas of biomedical research, and provides a solid model to understand how the external factor can regulate gene expression without changing the core DNA sequence (4).

Epigenetics means that changes in gene expression have been studied and believed to have been assumed due to hereditary factors, defined as above, genetics that occur without genetic changes or deviations in the main DNA sequence (5). These adjustments act as a medium between parents and the child as a shield between their environment, related to the genome to make the changing environment compatible. They use gene activity to set conditions. However, compared to genetic mutation, this is epigenetic scars that are flexible and able to change their permanent impression of the code (6) in nature. Under the influence of countless environmental determinants, such as diet, personal lifestyle, contact with toxins, stress and even social life. It is this plasticity that combines epigenetics with the importance of epigenetic arbitration of exposure effects on environmental factors on the disease (7).The principle of gene environmental interaction (GxE) is prominent to understanding complex human diseases. Genetic sensitization does not yet provide any explanation for why a person develops a reaction that patients with cystic fibrosis have a genetic tendency for heavy breathing, but the more relevant question is why this person develops heavy breathing and not the brother. The environmental factors usually become triggers or modifiers, although they have an impact on the foundation of how a genetic predisposition is converted to disease and whether or not it is all. Epigenetic mechanisms have come to be considered as the molecular connection by which these GXE interactions are referred to as the modifications in the patterns of expression of genes and, finally, disease phenotypes (8). As an example, the effects of being exposed to some pollutants in the environment can be such that they cause certain epigenetic modifications that expose an individual to the risk of getting infected with cancer, without prior existing genetic mutations that are known factors for the same disease (9). On the same note, maternal nutrition or maternal stress in early life, as well, may provide long-term epigenetic modifications, which affect the vulnerability of a person to metabolic disorders or mental health conditions in the future.

The purpose of this review is to answer the question of the problems of epigenetics in the current state of knowledge, complex human diseases are modified, which emphasize their mechanisms for the mechanism of action. Jean-environment interactions are mediated by modifications. First, we will offer a dedication to the main forms of epigenetic changes, such as DNA methylation, histone modifications and non-coding RNA, and how they are necessary for gene regulation. Later, we will discuss evidence that combines these epigenetic changes with a series of complex conditions, including cardiovascular disease, nervous system disorders, autoimmune diseases and metabolic syndrome. A large part of this review will be dedicated to the spread of delicate mechanisms, where epigenetic changes can be brought by environmental factors, such as changes that pretend to be diseases and its development. Finally, we will discuss light over new treatment methods that work on epigenetic routes, challenges and future instructions in this rapidly growing part of the world.

1-Major Types of Epigenetic Modifications:

Epigenetics refers to various molecular processes that use genomic expression at one level that does not change the DNA code. Such changes are necessary in regular development, cell discrimination and tissue equipment that provide gene expression (10). They are also very active and

sensitive to the response to their surroundings, which makes them the major actors in moderating gene-environment interactions. The three significant formats of epigenetic changes are methylation of DNA, changes in histone, and non-coding RNA (11).

1-1-DNA Methylation:

One of the best-described epigenetic changes is DNA methylation, resembling the process of addition of a methyl group (CH_3) to the fifth atom of the cytosine base, mainly in CpG dinucleotides (a cytosine and a guanine nucleotide) (12). The CpG sites are commonly found to occur in clusters of sites referred to as CpG islands. They are found in the gene promoter regions (Figure 1). DNA methylation is usually linked to mammals. Regarding driver mutation, the gene silencing mechanism of HBsAg is the driver mutation. Heavy methylation of CpG islands in the promoter areas has been witnessed (13). They may cause a compacting of the chromatin that physically impedes transcription. The potential forces that inhibit DNA access by regulating gene expression are These factors hinder gene expression via restriction of the DNA access. Conversely, active genes are normally found to have unmethylated CpG islands in promoter regions for gene transcription (14).

These patterns of DNA methylation are defined and stabilized by enzymes in a family of methyltransferases. The phenomena are catalyzed by DNMTs. The latter (DNMT3A and DNMT3B) are involved in the de- The transfer of methyl groups to new cytosines has occurred to form new patterns of methylation during development. NMT1 has gained popularity as DNA methyltransferase 1 (15). Maintenance methyltransferase, whose patterns of methylation are conserved, is replicated to be copied to the strands of the daughter during DNA replication, thereby maintaining epigenetic marks. The transfer of information between the cells. The aberrant methylation patterns, such as the aberrant DNA methylation patterns, the hypermethylation of the tumor suppressor genes, and the hypomethylation of the oncogenes, or repetitive components, can often be found in diverse diseases in human beings, especially cancer (16).

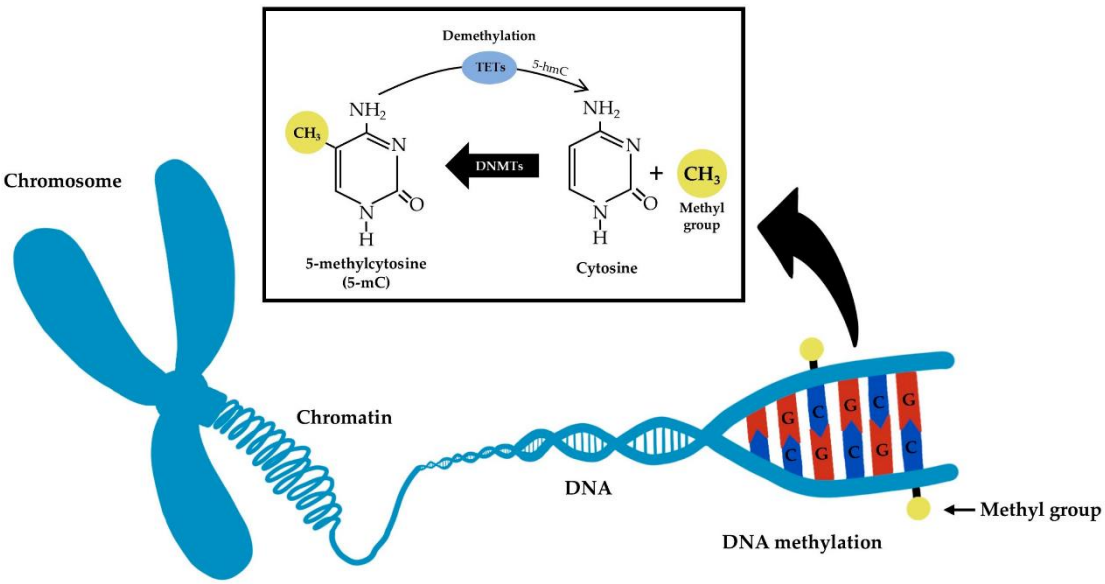

Fig.1: The mode of action of DNA methylation and its status in governing gene expression (addition of methyl groups to cytosine in DNA occurs through DNMTs, and removal (demethylation) occurs through TETs, which have a direct influence on gene activity). (14)

1-2-Histone Modifications:

A family of basic proteins, histones, is very important in the packaging of DNA structural groups known as nucleosomes, which build up chromatin. The N-terminal Histone tails undergo a great diversity of posttranslational modifications (PTMs) to include acetylation, methylation, phosphorylation, ubiquitination, and sumoylation. These alterations can change the charge and the structure of histones, which affects the availability of DNA to transcription factors, eventually regulating gene expression (17). The different histone modifications in combination form a transcription state of a gene that is determined by the so-called histone code. As an illustration, the example of a histone may be given. Acetylation by histone acetyltransferases (HATs), by and large, relaxes DNA, making it easier to transcribe because it is in the form of chromatin structure, enhancing the expression of genes. Figure 2. On the other hand, acetyl groups are stripped by histone deacetylases (HDACs) (18). One of the outcomes has been chromatin condensation and gene repression that are attributable to the formation of repressor groups—histone methylation. The histone methyltransferases (HMTs) catalyze this process, either turning on or shutting down a gene, depending on the particular lysine or arginine residue modified and the number of methyl groups added (19). As an example, methylation of H3K4 (lysine 4 on methylation of histone H3 is usually considered to be correlated with active transcription), and H3K9 methylation prevents transcription. H3K27 is associated with the silencing of genes. Altered patterns of modification of histones have been linked to many diseases, such as cancer, neurological disorders, and other cardiovascular diseases (20).

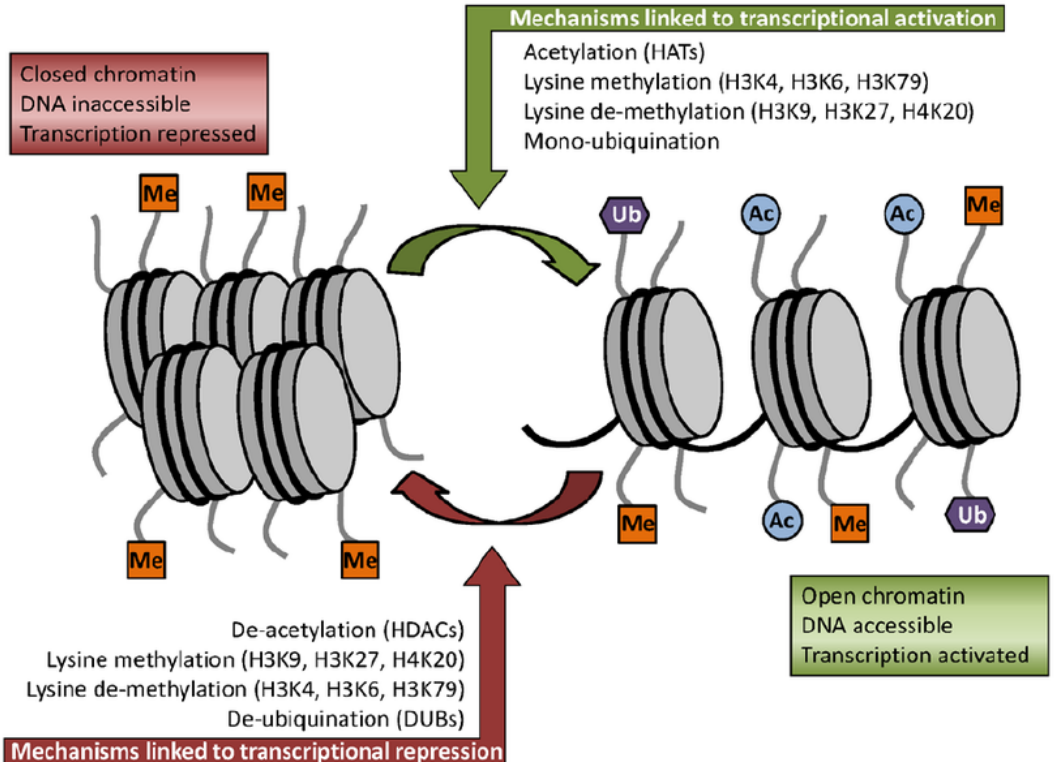

Fig. 2: Chroman activity on histone alterations and its effect on epigenetic changes (21)

1-3-Non-coding RNAs:

Non-coding RNAs (ncRNAs) are a heterogeneous group of RNA molecules that are not translated and provide significant regulatory functions expressed in gene regulation at different levels, not only proteins but also epigenetic regulation (Figure 3). Epigenetic ncRNAs are the best-studied ncRNAs: microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) (22).

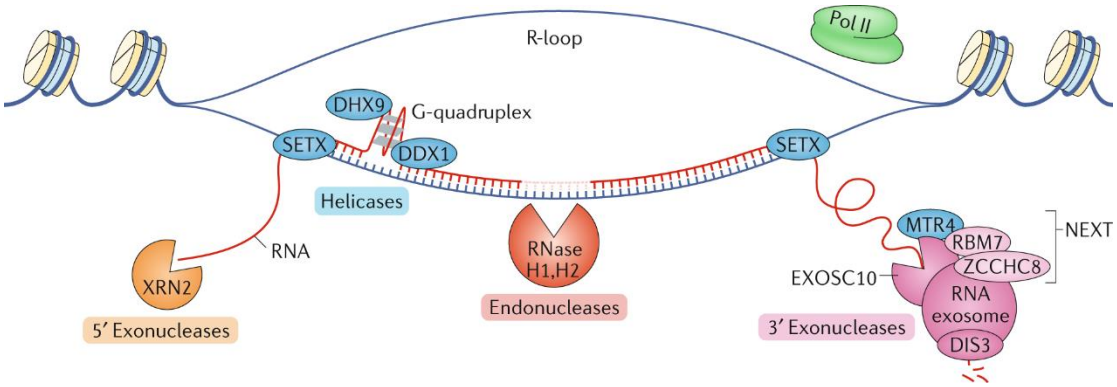

Fig. (3):- Transcription-associated RNA surveillance (23).

1-4-MicroRNAs (miRNAs):

They are short (about 20-22 nucleotides long), single-stranded RNA molecules that control gene expression after transcription by binding to complementary regions of target messenger RNAs (mRNAs), which results in repression or degradation of mRNA (24,25). Over and above their effects on mRNA, miRNAs also have an indirect effect on epigenetic changes because they trigger genes that encode epigenetic machines, e.g., DNMTs, HATs, HDACs, and HMTs. Dysregulation (26). Various disease conditions have been associated with the role of miRNA, such as cancer and cardiovascular diseases. Infectious diseases, neurodegenerative diseases, and immune system disorders are often caused by epigenetic landscape alterations (27).

1-5- Long Non-coding RNAs (lncRNAs):

This is a category of RNA molecules, more than 200 functionless nucleotides with little capacity to encode proteins. LncRNAs are extremely varied and modulate gene expression with different methods in their modes of action epigenetic mechanisms. They may serve as scaffolds, which congregate chromatin-modifying tags on enzymes to the genomic locations, and as landmarks, instructing the epigenetic engine to target genes; as decoys, sequestering epigenetic regulators; or as enhancers (28). Regulating gene expression, trans or cis. As an illustration (figure 4), the lncRNA XIST is involved in the process of regulating the induction of differentiation and plays a significant part in X chromosome inactivation by bringing in the polycomb repressive complex. The placement of 2 (PRC2) on the X chromosome, resulting in repressive histone changes and the inactivation of gene silencing. Dysregulated lncRNA has been suspected to participate in a variety of illnesses, including cancer, developmental disorders, and neurological diseases; the many roles are associated with the essence of a cell, and typical epigenetic control (29).

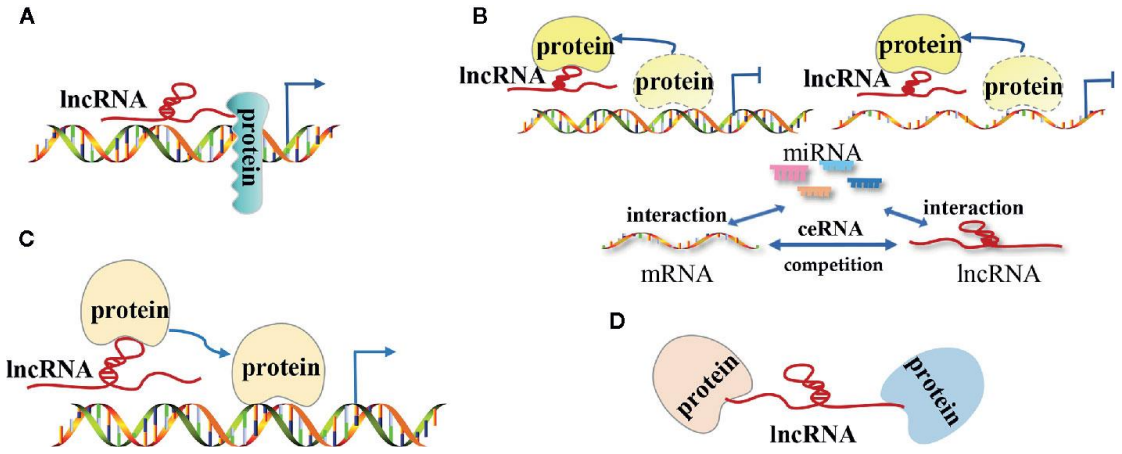

Fig.4:- The modes of action of long non-coding RNAs (lncRNAs) in tumors. (A) LncRNAs, as signal molecules, can be used alone or combined with some proteins (such as transcription factors) to mediate the transcription of downstream genes; (B) LncRNAs, as decoy molecules, bind to some functional protein molecules to block the protein molecules from regulating DNA and mRNA molecules, or bind to miRNA molecules competitively with mRNA molecules to block the inhibitory effect of miRNA on mRNA molecules; (C) LncRNAs, as guide molecules, carry some functional protein molecules and locate them in the target area to perform functions; (D) LncRNAs, as scaffold molecules, guide related different types of macromolecular complexes to assemble in the target area to work together (30).

2-Epigenetic Mechanisms in Complex Human Diseases:

The occurrence of epigenetic proto-germs, a trait of many complex human diseases, plays a major role in this induction, course, and different clinical expressions. These diseases are frequently the result of a combination of predisposition and environmental exposures mediated by epigenetic processes as intermediate steps. In this case, we investigate the role of epigenetic changes in some of the large groups of complex human diseases (31).

2-1-Cancer

The most widely researched disease about epigenetics is perhaps cancer. It is currently established that epigenetic changes, together with genetic alterations, are basic promoters of oncogenesis. Major cancer epigenetic alterations are the following:

DNA Hypomethylation: Global hypomethylation of the genome is a widespread phenomenon found in a lot of cancers. This may cause genomic instability, the process of activation of transposable elements (5), reactivation, and oncogenes, thereby adding to the growth of uncontrolled cell division and tumor growth and development (32).

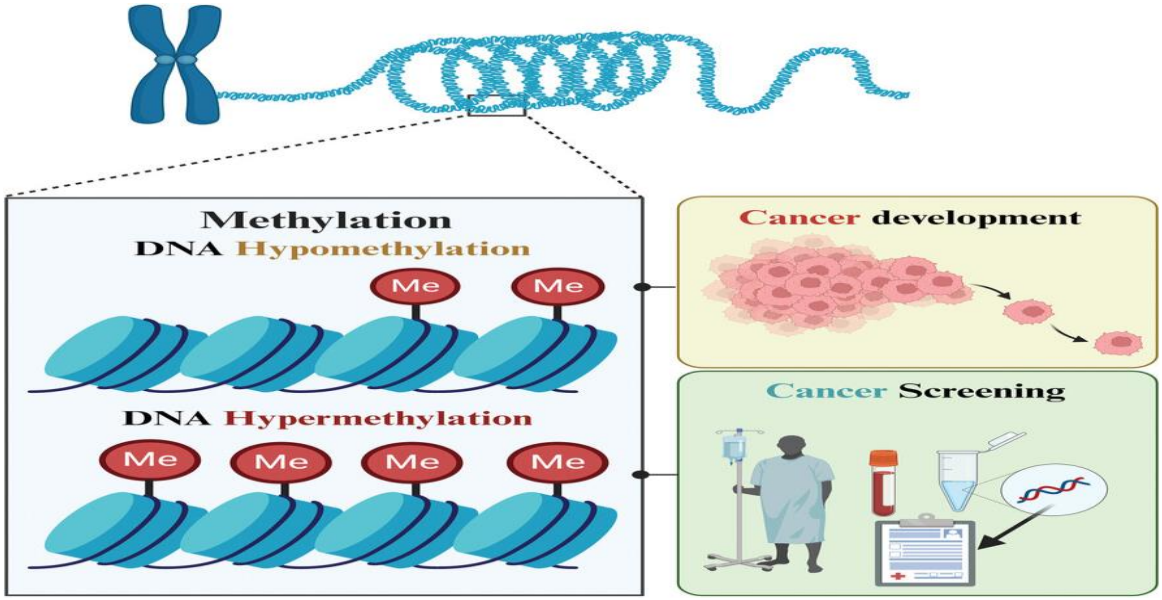

Fig. 5:- Epigenetic modifications have important roles in chromatin structure and gene expression (33).

DNA Hypermethylation: As opposed to that, hypermethylation of CpG islands in focal areas, KSilossi, half-located in the promoter regions of tumor suppressor genes (TSGs), is a vital process that was reported to silence them in cancer (34). These are exemplified by the hypermethylation of the RB1 gene in breast and ovarian cancer, retinoblastoma, and colorectal cancer, BRCA1, and MLH1, respectively. This silencing takes away important inhibitors to cell growth and cell division, promoting tumorigenesis (35).

Histone Modifications: Dysregulated acetylations and methylation of histones also occur frequently with cancer. As an example, heightened histone deacetylation (as a result of the repression of TSGs) can be induced by overexpression of HDACs (or by changes in other epigenetic modifiers such as DNA methylation). Histone methylation patterns (e.g., loss of H3K9me2/3 or H3K27me3) may contribute to oncogene activation and genomic instability (36).

Non-coding RNAs: Misexpression of lncRNAs and miRNAs participates in has a major contribution in the development of cancer. OncomiRs are oncogenic miRNAs (oncomiRs) that facilitate cell proliferation, survival, and metastasis by both TSGs or gene repression (37). Tumor-suppressor miRNAs can suppress these, but with apoptosis, they participate in it processes. The lncRNAs, in a similar vein, may either promote cancer or inhibit growth, similarly to oncogenes or tumor suppressors, respectively, adjusting epigenetic progress, chromatin organization, and controlling the level of gene expression involved in cancer hallmarks (38).

3-Cardiovascular Diseases (CVDs):

The most common causes of CVDs, such as atherosclerosis, hypertension, and heart failure, are the most common causes of mortality, morbidity, and deaths in countries all over the world (39,40). Mounting evidence indicates that epigenetic changes largely contribute to their pathogenesis and tend to be predetermined by environmental factors and lifestyles like diet, physical activities, and stress (41,42).

4- Neurological and Neurodegenerative Disorders:

Epigenetics plays an important role in the normal brain, neuronal activity, and psychological functions (43). Therefore, they have been involved in their improper broad array of neurological and neurodegenerative diseases, such as Alzheimer's (AD), Parkinson's (PD), autism (ASD), and schizophrenia (44). Risk factors, including prenatal stress and environmental exposures, remain active areas of research, in large part due to the relatively large number of studies conducted in high-income countries (HICs), where these risk factors might represent the most consistent risk factors. Brain spigenetics can be heavily affected by neurotoxin and diet (45).

2-5- Metabolic Disorders:

Metabolic behavior such as type 2 diabetes (T2D), obesity and non-alcoholic fat disease (NAFFLD) is metabolic and includes liver disease (NAFFLD), which contains a large lifestyle and environmental effects (46,47). Epignant changes act as a molecular contact between such environmental conditions and metabolic dysfunction (48).

3- Gene-Environment Interactions and Epigenetic Mediation:

The term "gene environment interaction" (G XE) believes that the effect of a genetic factor is affected by the environmental factor. Either the phenotypical version is replaced through environmental risk, or vice versa (49). Epigenetics are identified as the most important molecular-tantic mechanisms that mediate such interactions, which definitely change signs of the environment, even though they are reversible, changes in gene expression. This section extends how different environmental factors work in epignant scars, thus disseminating G XE ratio of complex human deformity (50).

3-1- Environmental Toxicants and Pollutants:

A major risk factor is in contact with environmental toxins and pollutants and many diseases, and negative effects often feel by using epigenetic changes. Heavy metals (e.g. arsenic, cadmium, lead), air pollution (e.g. particle-shaped material, polycyclic aromatic hydrocarbons) and endocrine-disrupting chemicals EDCs famous epigenetic interferers are there (51).

3-2- Diet and Nutrition:

Environmental factors include dietary components, which can have a major impact on epigenomas, to regulate the possibility of the occurrence of the disease. The nutrients offer substrates so they can modify directly or indirectly the activity of epigenetic enzymes. Such a region, referred to as nutritional epigenetics, which is quickly growing, plays a part (52).

3-3- Stress and Psychological Trauma:

Psychological stress and traumatic events, especially in childhood, may result in the development of conditions such as permanent epigenetic alterations that affect the predisposition of a person to mental health disorders and other stress-related illnesses. Highly vulnerable to the brain are epigenetic adaptations to stress, such as those of the genes in neuroplasticity, stress, and neurotransmission (53).

3-4- Infectious Agents:

The host genome can be manipulated by viruses and bacteria, which are infectious agents, to enable their replication and maintenance, and such epigenetic alterations can also add to the pathogenesis of the diseases (54).

Discussion

Epigenetic changes define the onset, course and clinical variability of diseases in detailed human patterns of disease. Epigenetic modifications now play a role epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNA regulation, providing an active and reversible level of gene regulation that is in contrast to gene mutations, which result in permanent change of the DNA sequence. These modifications provide a mechanistic pathway mediating variability in disease response among individuals with the same genetic predisposition by serving as molecular links between genetic susceptibility and environmental

exposure (55). DNA methylation is an important epigenetic mechanism, which is made on a large scale, the cancer process is very related to abnormal methylation of DNA patterns, such as total hypomethylation and hypermethylation of genes, pushing the tumor. For example, it has been found that hypermethylation of BRCA1 and MLH1 promoters explains a lot about the occurrence of breast, ovarian, and colon cancer, making the two genes quiet and releasing cell division control (56). In addition, the hypomethylation of the entire genome leads to activation of oncogenes and the instability of the genome, which increases carcinogenesis (57). The importance of changes in these methylation lies in the fact that they not only cause damage, but can also serve as a biomarker for early cancer diagnosis (58).

One more important epigenetic mechanism is the change in histone; the changes in acetylation and methylation patterns that are dysregulated cause the accessibility of chromatin and transcriptional activity. As an instance, elevated histone deacetylase (HDAC) activity has been linked to the repression of the transcription of tumor suppressor genes in several types of cancer. On a similar basis, a relationship has been found between the activation of oncogenes and the instability of the genome and the disappearance of repressive histone markers such as H3K9me3 or H3K27me3 (59). The information provided in the latest studies indicates that therapeutic targeting of histone modifiers, for example, histone methyltransferase inhibitors and HDAC inhibitors, may be effective against cancer, especially when combined with immunotherapeutic approaches (60).

Non-coding RNAs (ncRNAs), mainly long non-coding RNAs (lncRNAs), and microRNAs (miRNAs), significantly contribute to the epigenetic regulatory landscape. The tumor-suppressor miRNAs antagonize, while oncomiRs, which represent a subclass of oncogenic miRNAs, inhibit the tumor suppressor genes and stimulate cancer cell proliferation. In addition, the changes in chromatin structure and epigenetic silencing in cancer and neurodevelopmental diseases are coincident with the dysregulated lncRNAs such as HOTAIR and XIST (60). These findings underpin the concept that ncRNAs could serve as therapeutic targets as well as diagnostic biomarkers.

Along with cancer, changes in epigenetics have also been recognized as a major factor in the development of neurodegenerative, metabolic, and cardiovascular conditions. Cardiovascular disorders have been confirmed as atherosclerosis and hypertension—two diseases that are still largely dependent on diet and lifestyle—were linked to DNA methylation of endothelial genes and histone changes in vascular smooth muscle cells (61). Precisely, nutrient factors affect the activity of epigenetic enzymes in metabolic disorders such as type 2 diabetes and obesity, which lead to lipid metabolism and insulin sensitivity changes (62). The concept of nutritional epigenetics has become quite popular with its practice as a possible strategy for the prevention of diseases (63).

The epigenetic mechanisms are the mainstay of neuronal development, synaptic plasticity, and memory formation in the nervous system. There are several studies that provide the evidence of the relationship between histone changes and methylation of the DNA in genes with neuropsychiatric disorders such as schizophrenia, autism spectrum disorders, Parkinson's disease, and Alzheimer's disease (62).

For instance, DNA methylation-associated epigenetic clocks are presently considered as likely indicators for the early recognition of neurodegenerative disorders and the aging process of the brain (63). The findings of the study reveal that epigenetic changes play a core role in the diseases' pathophysiology and are not only responsible for their symptoms.

One major element is the reversibility of epigenetic regulation which places it above epigenetic mutations in the category of not being reversible. Because of this characteristic, the development of epigenetic drugs has been made more rapid. While the research is still ongoing for their combination with immune checkpoint inhibitors in solid tumors, the use of DNMT inhibitors (like azacitidine) that are approved and thus activated along with HDAC inhibitors that act like vorinostat is currently the basis of clinical practice in hematological malignancies (64). Exercise has also been identified as a good histone acetylation and DNA methylationchanger that could be a support to the idea of non-pharmacological methods of epigenetic therapy (64).

It is, however, still a big distance before the epigenetic findings can be assimilated into precision medicine. The conversion of epigenetic marks into reliable biomarkers is hindered by tissue heterogeneity, interindividual variability, and the context-dependent nature of these marks. On top of that, most of the epigenetic research is conducted in rich countries which lead to the question of whether the results can be generalized to different genetic and environmental contexts (65). These issues can only be resolved and the translational gap closed by large-scale, multi-omics strategies and equitable global research initiatives.

Conclusion:

The turning point in the scope of epigenetic adjustments is the redefinition of the idea of complicated human diseases, whereby it's been found that genetic factors do not comprehensively represent the disorder risk or its diversity in the effects of medical practice. Epigenetics offers an indirect contact between the surroundings and the genome through incorporating lifelong exposures into heritable alterations of gene expression. Pathogenic aberrant epigenetic landscape, possibly through hypermethylation of DNA tumor suppressor genes, imbalance of histone modifications, or deregulation in non-coding RNAs, is emerging as one of the causes of pathogenesis in many disease situations. Notably, their reversibility gives them the advantage of the never-before-seen therapeutic possibility of crops of epigenetic drugs and lifestyle-modifying interventions to target these regulatory pathways. The innovations in the future will be related to the optimization of mapping, decoding, and tunable silencing of epigenetic marks by almost tissue- and time-specific control. Finally, implementing epigenomic profiling in the clinical context may allow predictive diagnostics, personalized strategies of prevention, and precision treatment, highlighting a paradigm-shifting progress toward defining such a notion as personalized medicine in the full sense of this word.

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References:

1- Suleiman, F. M. S. (2025). The role of epigenetics in disease mechanisms: understanding gene-environment interactions. *Eurasian Journal of Theoretical and Applied Sciences (EJTAS)*, 57-71.

2- Alemu, R., Sharew, N. T., Arsano, Y. Y., Ahmed, M., Tekola-Ayele, F., Mersha, T. B., & Amare, A. T. (2025). Multi-omics approaches for understanding gene-environment interactions in noncommunicable diseases: techniques, translation, and equity issues. *Human Genomics*, *19*(1), 8.

3- Khan, Z., Messiri, N. E., Iqbal, E., Hassan, H., Tanweer, M. S., Sadia, S. R., ... & Zaidi, M. (2025). On the role of epigenetic modifications of HPA axis in posttraumatic stress disorder and resilience. Journal of neurophysiology, 133(3), 742-759

4- Nienaber-Rousseau, C. (2025). Understanding and applying gene–environment interactions: a guide for nutrition professionals with an

emphasis on integration in African research settings. *Nutrition Reviews*, *83*(2), e443-e463.

5- Milic, J., Vucurovic, M., Jovic, D., Stankovic, V., Grego, E., Jankovic, S., & Sapic, R. (2025). Exploring the Potential of Precision Medicine in Neuropsychiatry: A Commentary on New Insights for Tailored Treatments Based on Genetic, Environmental, and Lifestyle Factors. *Genes*, *16*(4), 371.

6- Jayaraman, S., Eswaran, A., Priya Veeraraghavan, V., Fazal, M., Al-Rahbi, A., & Sirasanagandla, S. R. (2025). Implications of petrochemical exposure and epigenetic alterations on human health. *Frontiers in Toxicology*, *7*, 1542871.

7- Addissouky, T. A., El Tantawy El Sayed, I., & Wang, Y. (2025). Epigenetic factors in posttraumatic stress disorder resilience and susceptibility. Egyptian Journal of Medical Human Genetics, 26(1), 50

8- Im, H., Song, Y., Kim, J. K., Park, D. K., Kim, D. S., Kim, H., & Shin, J. O. (2025). Molecular regulation of palatogenesis and clefting: an integrative analysis of genetic, epigenetic networks, and environmental interactions. International journal of molecular sciences, 26(3), 1382.

9- Jensen, P. (2025). From nature to nurture–How genes and environment interact to shape behaviour. Applied Animal Behaviour Science, 285, 106582

10- Billah, M. M., Guo, C., Mizuno, K., Nakachi, Y., Bundo, M., & Iwamoto, K. (2025). DNA methylation studies in mouse models of depression: a systematic review. Epigenomics, 1-13

11- Suleiman, F. M. S. (2025). The role of epigenetics in disease mechanisms: understanding gene-environment interactions. Eurasian Journal of Theoretical and Applied Sciences (EJTAS), 57-71

12- Herrera-Luis, E., Benke, K., Volk, H., Ladd-Acosta, C., & Wojcik, G. L. (2024). Gene–environment interactions in human health. Nature Reviews Genetics, 25(11), 768-784

13- Motsinger-Reif, A. A., Reif, D. M., Akhtari, F. S., House, J. S., Campbell, C. R., Messier, K. P., ... & Woychik, R. (2024). Gene-environment interactions within a precision environmental health framework. Cell Genomics, 4

14- Mittal, R., Camick, N., Lemos, J. R., & Hirani, K. (2024). Gene-environment interaction in the pathophysiology of type 1 diabetes. Frontiers in Endocrinology, 15, 1335435**.**

15- Chen, X., Xu, H., Shu, X., & Song, C. X. (2025). Mapping epigenetic modifications by sequencing technologies. *Cell Death & Differentiation*, *32*(1), 56-65.

16- Khan, Z., Messiri, N. E., Iqbal, E., Hassan, H., Tanweer, M. S., Sadia, S. R., ... & Zaidi, M. (2025). On the role of epigenetic modifications of HPA axis in posttraumatic stress disorder and resilience. *Journal of neurophysiology*, *133*(3), 742-759.

17- Zheng, X., Liu, X., Guo, Y., Lv, Y., Lin, C., Wang, D., ... & Hu, X. (2025). Physical exercise and epigenetic modifications in skeletal muscle, brain, and heart. *Epigenetics & Chromatin*, *18*(1), 12.

18- El Omari, N., Bakrim, S., Bakha, M., Balahbib, A., Bouyahya, A., Ardianto, C., ... & Ser, H. L. (2025). DNA methylation: its role and interaction with epigenetic modifications in cancer. *Progress In Microbes & Molecular Biology*, *8*(1).

19- Obeagu, E. I. (2025). Epigenetic modifications and immune responses in HIV-infected infants: a narrative review. *Annals of Medicine and Surgery*, *87*(6), 3381-3387.

20- Colapietra, F., Della Monica, P., Di Napoli, R., França Vieira e Silva, F., Settembre, G., Marino, M. M., ... & Di Domenico, M. (2025). Epigenetic Modifications as Novel Biomarkers for Diagnosis, Prognosis, and Therapeutic Targeting in Thyroid, Pancreas, and Lung Neuroendocrine Tumors. *Journal of Clinical Medicine*, *14*(8), 2622.

21- Zheng, H., Hua, Y., Yang, S., Liu, V., Huang, N., Li, J., ... & Liu, Q. (2025). Epigenetic modification and tumor immunity: Unraveling the interplay with the tumor microenvironment and its therapeutic vulnerability and implications. *Cancer Letters*, 217587.

22- Serafini, G., Guglielmo, R., Escelsior, A., Amerio, A., Aguglia, A., & Amore, M. (2025). Early-life adversities and epigenetic modifications: the impact on brain development, synaptic function, and stress response. *Biological Psychiatry Global Open Science*, 100560.

23- Nair, L., Chung, H., & Basu, U. (2020). Regulation of long non-coding RNAs and genome dynamics by the RNA surveillance machinery. *Nature reviews Molecular cell biology*, *21*(3), 123-136.

24- Li, W., Luo, P., Chen, Q., Cheng, L., Gan, L., Zhang, F., ... & Qian, B. (2025). Epigenetic modifications in bladder cancer: crosstalk between DNA methylation and miRNAs. *Frontiers in Immunology*, *16*, 1518144.

25- Yameny, A. miRNA-122 from Laboratory biomarker to the treatment of HCV. *Journal of Bioscience and Applied Research*, 2017; 3(4): 145-151. doi: 10.21608/jbaar.2017.125861

26- Aloisi, M., & Poma, A. M. G. (2025). Epigenetic Modifications and Gene Expression Alterations in Plants Exposed to Nanomaterials and Nanoplastics: The Role of MicroRNAs, lncRNAs and DNA Methylation. *Environments*, *12*(7), 234.

27- Pan, J., Chen, S., Chen, X., Song, Y., & Cheng, H. (2025). Histone modifications and DNA methylation in psoriasis: a cellular perspective. *Clinical Reviews in Allergy & Immunology*, *68*(1), 6.

28- Bhootra, S., Jill, N., Shanmugam, G., Rakshit, S., & Sarkar, K. (2023). DNA methylation and cancer: transcriptional regulation, prognostic, and therapeutic perspective. *Medical oncology*, *40*(2), 71.

29- Chen, L., Li, X., Liu, H., He, F., Li, M., Long, R., ... & Yang, Q. (2025). Comprehensive analysis of epigenetic modifications in alfalfa under cadmium stress. *Journal of Hazardous Materials*, *482*, 136545.

30- Hsieh, H. H., Kuo, M. Z., Chen, I. A., Lin, C. J., Hsu, V., Huangfu, W. C., & Wu, T. Y. (2025). Epigenetic modifications as novel therapeutic strategies of Cancer chemoprevention by phytochemicals. *Pharmaceutical Research*, *42*(1), 69-78.

31- Zheng, H., Hua, Y., Yang, S., Liu, V., Huang, N., Li, J., ... & Liu, Q. (2025). Epigenetic modification and tumor immunity: Unraveling the interplay with the tumor microenvironment and its therapeutic vulnerability and implications. *Cancer Letters*, 217587.

32- Goodrich, J. M., Furlong, M. A., Urwin, D. J., Gabriel, J., Hughes, J., Jung, A. M., ... & Burgess, J. L. (2025). Epigenetic Modifications Associated With Wildland–Urban Interface (WUI) Firefighting. *Environmental and molecular mutagenesis*, *66*(1-2), 22-33.

33- Dogan, F., & Forsyth, N. R. *Telomerase regulation: a role for epigenetics. Cancers 2021; 13: 1213*.

34- Kaimala, S., Yassin, L. K., Hamad, M. I., Allouh, M. Z., Sampath, P., AlKaabi, J., ... & Emerald, B. S. (2025). Epigenetic crossroads in metabolic and cardiovascular health: the role of DNA methylation in type 2 diabetes and cardiovascular diseases. *Cardiovascular diabetology*, *24*(1), 231.

35- Li, L., Chen, R., Zhang, H., Li, J., Huang, H., Weng, J., ... & Xie, J. (2024). The epigenetic modification of DNA methylation in neurological diseases. *Frontiers in Immunology*, *15*, 1401962.

36- Zhang, J., Tian, Z., Qin, C., & Momeni, M. R. (2024). The effects of exercise on epigenetic modifications: focus on DNA methylation, histone modifications and non-coding RNAs. *Human Cell*, *37*(4), 887-903.

37- Bogan, S. N., & Yi, S. V. (2024). Potential role of DNA methylation as a driver of plastic responses to the environment across cells, organisms, and populations. *Genome biology and evolution*, *16*(2), evae022.

38- Aloisi, M., & Poma, A. M. G. (2025). Epigenetic Modifications and Gene Expression Alterations in Plants Exposed to Nanomaterials and Nanoplastics: The Role of MicroRNAs, lncRNAs and DNA Methylation. *Environments*, *12*(7), 234.

39- Aloisi, M., & Poma, A. M. G. (2025). Epigenetic Modifications and Gene Expression Alterations in Plants Exposed to Nanomaterials and Nanoplastics: The Role of MicroRNAs, lncRNAs and DNA Methylation. *Environments*, *12*(7), 234.

40- Pan, J., Chen, S., Chen, X., Song, Y., & Cheng, H. (2025). Histone modifications and DNA methylation in psoriasis: a cellular perspective. *Clinical Reviews in Allergy & Immunology*, *68*(1), 6.

41- Socha, M. W., Flis, W., & Wartęga, M. (2024). Epigenetic genome modifications during pregnancy: the impact of essential nutritional supplements on DNA methylation. *Nutrients*, *16*(5), 678.

42- Sonar, S., Nyahatkar, S., Kalele, K., & Adhikari, M. D. (2024). Role of DNA methylation in cancer development and its clinical applications. *Clinical and Translational Discovery*, *4*(1), e279.

43- Zhu, D., Zeng, S., Su, C., Li, J., Xuan, Y., Lin, Y., ... & Fan, Q. (2024). The interaction between DNA methylation and tumor immune microenvironment: from the laboratory to clinical applications. *Clinical Epigenetics*, *16*(1), 24.

44- Conole, E. L., Robertson, J. A., Smith, H. M., Cox, S. R., & Marioni, R. E. (2025). Epigenetic clocks and DNA methylation biomarkers of brain health and disease. *Nature Reviews Neurology*, 1-11.

45- Myrou, A., Barmpagiannos, K., Ioakimidou, A., & Savopoulos, C. (2025). Molecular Biomarkers in Neurological Diseases: Advances in Diagnosis and Prognosis. *International Journal of Molecular Sciences*, *26*(5), 2231

46- Xu, J., Lu, J., Kuang, T., Wang, D., Dong, Z., Chen, M., ... & Qin, Z. (2025). The Role of Methylation in Neurodegenerative Diseases: Insights From a Bibliometric Study. *Brain and Behavior*, *15*(8), e70732.

47- Yameny, A. Diabetes Mellitus: A Comprehensive Review of Types, Pathophysiology, Complications, and Standards of Care in Diabetes 2025. *Journal of Medical and Life Science*, 2025; 7(1): 134-141. doi: 10.21608/jmals.2025.424001

48- LaFlamme, C. W., Karimi, K., Rastin, C., Almanza Fuerte, E. P., Allan, T., Russ-Hall, S. J., ... & Mefford, H. C. (2025). SCN1A pathogenic

variants do not have a distinctive blood-derived DNA methylation signature. *Epilepsia*, *66*(4), e66-e72.

49- Nagamatsu, S. T., Navarrete, F., & Garcia-Gutierrez, M. S. (2025). Methylation in the human brain. *Frontiers in Genetics*, *16*, 1589816.

50- Chen, L., Liu, Q., Li, J., Zhang, Y., Yang, C., & Zhao, Y. (2025). Peripheral blood ABCG1 gene DNA methylation: mediating the relationship between dietary intake of methyl donor nutrients and stroke risk. *Nutrition Research*, *133*, 54-63.

51- Harvey, J., Imm, J., Kouhsar, M., Smith, A. R., Creese, B., Smith, R. G., ... & Lunnon, K. (2025). Interrogating DNA methylation associated with Lewy body pathology in a cross brain-region and multi-cohort study. *medRxiv*.

52- Bergmann, P. E., Madrid, A., Papale, L. A., Clark, L. R., Asthana, S., Johnson, S. C., ... & Alisch, R. S. (2025). Sex-Specific Differential DNA Methylation in Mild Cognitive Impairment and Alzheimer's Disease. *bioRxiv*, 2025-05.

53- Welsh, H., Batalha, C. M., Li, W., Souza-Pinto, N. C., Duarte, Y. A., Naslavsky, M. S., & Parra, E. J. (2025). Age-related changes in DNA methylation in a sample of elderly Brazilians. *Clinical Epigenetics*, *17*(1), 17.

54- Xia, Q., Zhao, Y., Dong, H., Mao, Q., Zhu, L., Xia, J., ... & Xin, Z. (2024). Progress in the study of molecular mechanisms of intervertebral disc degeneration. *Biomedicine & Pharmacotherapy*, *174*, 116593.

55- Mechanic, L. E., & Hutter, C. M. (2015). Gene-environment interactions in human health. In *Environmental epigenetics* (pp. 229-249). London: Springer London.

56- Klupczyńska, E. A. (2023). DNA methylation in cancer epigenetics. In *Epigenetics-Regulation and New Perspectives*. IntechOpen.

57- Sonar, S., et al. (2024). Role of DNA methylation in cancer development and its clinical applications. Clinical and Translational Discovery, 4(1), e279.

58- Clay, M. R., Pinto, E. M., Cline, C., Tran, Q. T., Lin, T., Dyer, M. A., ... & Ribeiro, R. C. (2019). DNA methylation profiling reveals prognostically significant groups in pediatric adrenocortical tumors: a report from the International Pediatric Adrenocortical Tumor Registry. *JCO Precision Oncology*, *3*, 1-21.57- Pan, J., et al. (2025). Histone modifications and DNA methylation in psoriasis: a cellular perspective. Clinical Reviews in Allergy & Immunology, 68(1), 6–17.

59- Yang, Y., & Wang, Y. (2021). Role of epigenetic regulation in plasticity of tumor immune microenvironment. *Frontiers in Immunology*, *12*, 640369.

60- Shivakumar, M., Lee, Y., Bang, L., Garg, T., Sohn, K. A., & Kim, D. (2017). Identification of epigenetic interactions between miRNA and DNA methylation associated with gene expression as potential prognostic markers in bladder cancer. *BMC medical genomics*, *10*(Suppl 1), 30.60- Kaimala, S., et al. (2025). Epigenetic crossroads in metabolic and cardiovascular health. Cardiovascular Diabetology, 24(1), 231.

61- Rasmi, Y., Shokati, A., Hassan, A., Aziz, S. G. G., Bastani, S., Jalali, L., ... & Alipour, S. (2023). The role of DNA methylation in progression of neurological disorders and neurodegenerative diseases as well as the prospect of using DNA methylation inhibitors as therapeutic agents for such disorders. *IBRO Neuroscience Reports*, *14*, 28-37.

62- Xie, J., Xie, L., Wei, H., Li, X. J., & Lin, L. (2023). Dynamic regulation of DNA methylation and brain functions. *Biology*, *12*(2), 152.

63- Shireby, G. L., Davies, J. P., Francis, P. T., Burrage, J., Walker, E. M., Neilson, G. W., ... & Mill, J. (2020). Recalibrating the epigenetic clock: implications for assessing biological age in the human cortex. *Brain*, *143*(12), 3763-3775.

64- Plaza-Diaz, J., Izquierdo, D., Torres-Martos, Á., Baig, A. T., Aguilera, C. M., & Ruiz-Ojeda, F. J. (2022). Impact of physical activity and exercise on the epigenome in skeletal muscle and effects on systemic metabolism. *Biomedicines*, *10*(1), 126.

65- San-Cristobal, R., de Toro-Martin, J., & Vohl, M. C. (2022). Appraisal of gene-environment interactions in GWAS for evidence-based precision nutrition implementation. *Current Nutrition Reports*, *11*(4), 563-573.