Epigenetic Modifications in Personalized Medicine: Advancing Targeted Therapies through Genomic Insights

Moushumi Afroza Mou [1*], Mimnu Tasnim [2]

Abstract

Background: Epigenetic modifications, such as non-coding RNA molecules, histone modifications, and DNA methylation, significantly impact an individual's health trajectory by regulating gene expression. Understanding these modifications offers unprecedented opportunities for precision medicine, allowing for more personalized healthcare strategies. Methods: This review explores the role of epigenetic changes in precision medicine, emphasizing the use of epigenetic biomarkers for disease diagnosis, prognosis, and treatment stratification. It examines their applications across various diseases, including cancer, neurodegenerative disorders, and cardiovascular conditions, and discusses the potential for tailoring interventions based on individual epigenetic profiles. Results: Epigenetic biomarkers have emerged as critical tools in precision medicine. For instance, specific DNA methylation patterns can distinguish between cancer subtypes and guide targeted therapies. Epigenetic signatures also enhance the prediction of medication responses and potential adverse effects, enabling more precise treatment strategies across diverse disease spectrums. Conclusion: Incorporating epigenetic data into precision medicine shifts healthcare away from a one-size-fits-all model toward individualized therapies. Although challenges such as standardization of methodologies and understanding the genetic-epigenetic interplay remain, the integration of epigenetic insights into clinical practice holds promise for revolutionizing personalized healthcare.

Keywords: Epigenetics, Precision Medicine, Dna Methylation, Histone Modifications, Personalized Healthcare.

Significance | This review discusses the understanding of epigenetic modifications for precise, personalized treatments, improving outcomes in cancers, neurodegenerative, and autoimmune diseases unresponsive to conventional therapies.

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1. Introduction

Epigenetic modifications are variations in gene expression that are not related to a gene's DNA sequence. These changes could be linked to any disease resulting from changes in an organism, including epigenetic carcinogenesis and inheritance. Multiple somatic cell divisions result in the transgenerational transmission of epigenetic modifications and/or information to daughter cells (Figure 1). The term "epigenome" refers to the modifications made to an organism's genome that result in altered gene expression and can be caused by a variety of chemical substances or biological species. Epigenetic changes can result from modifications to a biological system's internal and external environment, including oxidative and nitrosative stress and dietary adjustments (Heijmans et al,2018).The genotype of an organism is capable of displaying phenotypic variation brought about by the interaction of various environmental factors. This capacity is known as plasticity, and the most advantageous kind of plasticity happens during development to boost an organism's chances of surviving and procreating (Jirtle et al,2017). These basic epigenetic mechanisms (Figure 1) regulate changes in gene expression: chromatin remodeling, DNA

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methylation, histone modifications, and microRNAs that function as regulatory molecules.These mechanisms control gene expression and other biological functions related to homeostasis, allostasis, and disease. Human phenotypic variations resulting from epigenetic modifications have been linked to a number of diseases (Hirst et al,2019), including cancer (Jones et al,2017), neurodegenerative diseases like schizophrenia (Petronis et al,2014) and diseases of the skin and bones associated with autoimmune disorders (Richardson et al,2017). Consequently, treating patients whose diseases have epigenetic causes may not benefit from conventional therapies. Because of this, scientists are more likely to discover patient-specific therapies for these individuals also known as personalized or genomic medicines.

2. Epigenetic Modifications

DNA methylation is a significant factor contributing to disease development. DNA methylation regulates a number of biological processes, such as chromatin organization, imprinting, X-chromosome inactivation, gene expression, and others (Delgado-Morales et al,2017). The addition of a methyl group (-CH3) to cytosine is common in gene promoter regions with CpG islands, which make up 60% of the promoter region and contain large repetitive CpG dinucleotides (Andrieu et al,2016). Disease states, including cancer, have been linked to CpG dinucleotide(s) methylation (Zhang et al,2015). DNA methyltransferases (DNMTs), which are classified into five classes according to their distinct physiological and enzymatic roles, are the enzymes that methylate DNA (Gilbert et al,2013). Histone modifications (Wang et al,2019) are another instance of epigenetic modification. These modifications result from a variety of nuclear, enzyme-catalyzed processes, such as methylation and acetylation of arginine and lysine (Ziegler et al,2020) phosphorylation of threonine and serine, sumoylation of lysine, ubiquitination, and ADP-ribosylation (Thakore et al,2015). Numerous illnesses, including mental retardation, Parkinson's disease, and Angelman syndrome, have been linked to ubiquitination (table 1). Histone acetyltransferases (HATs) and histone deacetylases (HDACs) control the acetylation of histone proteins at different amino acid residues (Hilton et al,2015) (figure 1). Adenosyl methionine (AdoMet) transfers a methyl group to a histone, causing methylation. S-adenosylhomocysteine (AdoHcy) prevents DNMTs from working. AdoHcy hydrolase has the ability to hydrolyze AdoHcy into homocysteine and adenosine, which means it may be used as a therapeutic agent to treat epigenetic diseases. During the process of chromatin remodeling, energy-driven changes in nucleosome positioning and DNA-histone associations are mediated by catalytic ATPases (Tarjan et al,2019) (Table 1).

3. Genetic Testing/Screening

A medical test's clinical utility is determined by its impact on physician decisions and treatment options. A disease's signs and symptoms are used to make a diagnosis. These signs and symptoms can point to several different biological system disorders. Today, genetic testing or screening for mutations specific to a disease can determine the diagnosis and prognosis of any disorder. Through genomic studies, many molecular biomarkers associated with gene mutations can be found. Health care providers use the results of prognostic and diagnostic tests that use genomic data or DNA to diagnose illnesses or diseases, evaluate a patient's risk of developing a disease, determine the right dosage for a patient based on metabolic variations, and assess a patient's potential benefit from a specific medication intervention for managing an illness (Schuijers et al,2018).

Personalized medicine, on the other hand, uses each patient's unique genetic profile to predict disease, prevent disease through medical interventions, and make lifestyle and disease management decisions specific to their needs. Additionally, genetic screening is critical to a patient's treatment plan personalization (Stepper et al,2017).

4. Epigenetics and personalized/genomic medicine

A person's health and illness can be better understood by studying their genome and the information that goes along with it. The Human Genome Project (HGP) is now complete, making whole-genome DNA sequence data available. Patients for whom the success rate of managing their disease is very low and who are not responding as predicted to conventional medicines need to be treated with specific drugs. Patients are prescribed genomic or personalized medications following the collection of genomic data and related information, such as RNA, protein, and other metabolite levels, which are critical components in medical decision-making for personalized medicine (Zeitler et al,2019).

Precision in illness treatment and prediction can be achieved by the application of genomic methods, including transcriptomics, proteomics, metabolomics, and DNA sequence variation detection (Diesch et al,2016). These methods serve as helpful bridges between personalized medicine and epigenetics: The human genome sequence (genomics) comprises 10–15 million copy number variants (CNVs) and single nucleotide polymorphisms (SNPs); the proteome (proteomics) comprises about 100,000 specific protein products; the metabolome (metabolomics) is a metabolic profile of 1000–10,000 metabolites; and gene expression profiles (transcriptomics) comprise about 25,000 gene transcripts (Howell et al,2010).To accomplish personalized and genomic therapeutics, it is also essential to have access to information from an individual's genome sequence and the corresponding expressed biomarkers (Prebet et al,2014).

An individual's genetic origin may influence their susceptibility to a chronic illness, as conventional medication and therapies may not be helpful for them. Genomic applications can be used at several critical junctures during a patient's observation from a healthy state to a diseased state in order to customize the patient's medical care (Thottassery et al,2014).

5. Pharmacogenomics and personalized medicines

Pharmacogenomics is the study of biological factors associated with drug metabolism, such as drug transporters, the role of receptors, and enzymes that metabolize drugs and have polymorphisms that impact the drug response in different diseases (Ganesan et al,2019). These parameters are all controlled by epigenetic mechanisms.

Pharmacogenomics aids in our comprehension of the concept of the exact and accurate medication for a given patient at the precise concentration and time. It also refutes the idea that "one drug fits all." A number of factors, including nutrition, age, body weight, sex, genetic behavior, infections, contraceptives, and organ function, are inescapable during the course of illness treatment and should be taken into account when analyzing multiple drug reactions. Furthermore, the therapy of a problem is highly focused by the integration of pertinent data linked to medical informatics and customized medications (Berdasco et al,2019).

Pharmacokinetics (PK) and pharmacodynamics (PD) are very helpful in understanding variable medication responses (conventional and/or tailored therapies). Quantitative assessments of drug exposure and effect are integrated by these two fields (Figure 2). Drug exposure and level monitoring are linked to pharmacokinetics data, which offer a platform for phenotypic marker analysis (epigenetic markers) relevant to personalized treatment (Ganesan et al,2016).

Drug metabolizing enzymes cytochrome P450 and glucuronyl transferase, which are encoded by polymorphic CYP450 family genes (Reddy et al,2016), as well as drug transporters, which are encoded by several hundred genes, are frequently associated to changes or mutations that cause variability in drug response.

Two significant CYP450 genes, CYP2D6 and CYP2C19, have 29 known variations that can be found using microarray technology (Halby et al,2017). These genes influence the metabolism of 25% of all prescribed medications.Furthermore, polymorphic genes also encode drug receptors (Cavenagh et al,2018), and mutations in receptors, including the receptor tyrosine kinases, have been connected to a number of malignancies and neurological illnesses (Halby et al,2017). For instance, trastuzumab is used to treat breast cancer over-expression of ErbB2 (v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2), leukemia patients' BCR/ABL fusion protein is highly sensitive to imatinib (Cavenagh et al,2018), and activating mutations of the epidermal growth factor receptor (EGFR) appear to be correlated with gefitinib responsiveness (O'Connor et al,2015).

With the application of personalized medicine, genotyping thus becomes crucial for researchers to comprehend disease, treatment, and medication effects. Future clinical research can make use of the knowledge gained from the experimental establishment of functional polymorphisms and genetic variability for well-studied genes.Variants in genes can impact mRNA processing, such as alternative splicing and mRNA stability, once they are translated into mRNA. About 35–59% of all human genes undergo alternative splicing, according to studies (Liu et al,2016). The catechol-O-methyltransferase gene (COMT) is a susceptibility gene for schizophrenia that has been shown to be downregulated in the postmortem brain tissues of patients, according to allelic expression analysis based on mRNA expression (Morera et al,2016).

Treatment outcomes for a number of conditions, including cancer and neurological diseases, are impacted by epigenetic modifications (Morera et al,2016). Patient-specific epigenetic and medication management data can be leveraged to personalize medical care.

Histological examination of tissues and/or cells is the basis for classifying cancer. Molecular biomarkers are employed in the treatment of leukemia and breast cancer, among other cancers. Furthermore, a number of malignancies, including hematological, colon, and early-stage breast cancers, can be identified and classified using the mRNA expression profiles discovered by microarray analysis (Stein et al,2018). Targeted therapy in the context of cancer is predicated on gene modifications in particular cellular pathways, which facilitate the use of genomic medicine (Eich et al,2020).

Targeted cancer therapy involves tumor cell-specific treatments including monoclonal antibodies and small molecule inhibitors that are less toxic in their mode of action. This therapeutic approach has created new opportunities for the treatment of cancer. Human malignancies involve a number of molecular targets and signaling pathways, including the PI3K/mTOR signaling (Chan-Penebre et al,2015), the FOXO-FOXM1 axis (Cochran et al,2019), and aurora kinases. For instance, by raising the Bax/Bcl-2 ratio, which causes apoptosis in acute myeloid leukemia with strong aurora-A expression, the small chemical VX-680 exhibits an inhibitory impact and triggers cell death in leukemic cells with a certain aurora expression profile (Piha-Paul et al,2020). Forkhead transcription factors, including FOXO and FOXM1, are essential for various biological processes such as angiogenesis, cell division, differentiation, apoptosis, DNA repair, and tissue homeostasis. The FOXO-FOXM1 axis regulates medication resistance and tumor development (Galiham et al,2016).

6. Current Personalized Medicines

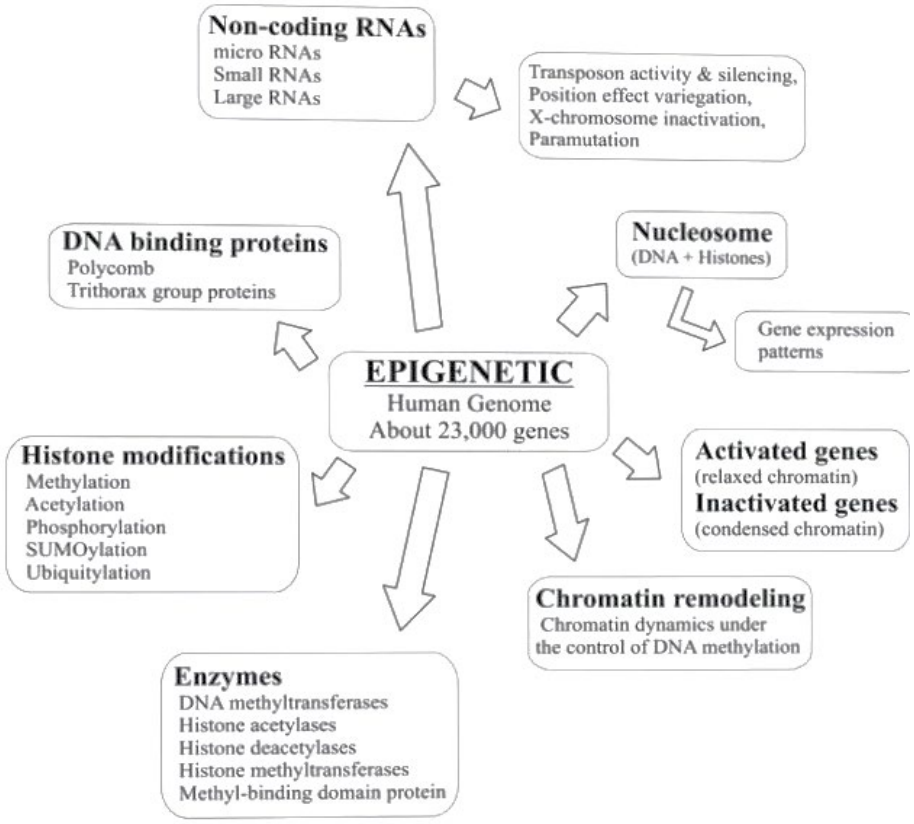

Figure 1. Epigenetic alterations in biological systems

Table 1. Multiple diseases related to ubiquitination

Gene	Encodes for	Disorder
Parkin	E3 ubiquitin ligase	Parkinson's disease (autosomal recess)
Uchl1	Ubiquitin C-terminal hydrolase (UCH-L1)	Parkinson's disease (autosomal recess)
E6-AP	Ubiquitin ligase E6-AP (UBE3A)	Angelman syndrome
Single point mutation in HUWE/Mule/ ARF-BP	Ubiquitin ligase HUWE/Mule/ ARFBP	Mental retardation, X-linked, syndromic Turner type (MRXST)
Ataxin-3	Deubiquitinating enzyme, ataxin-3	Familial amyotrophic lateral sclerosis, Machado-Joseph disease/ spinocerebellar ataxia type-3
Hippel Lindau vhl	E3-ubiquitin ligase	Pheochromocytoma (PCC
Cyld	Deubiquitinase CYLD	Turban tumor syndrome (cylindromatosis)
Aberrant expression/ mutations	E3 ubiquitin ligase/ deubiquitinating enzymes (DUBs)	Diverse types of cancer

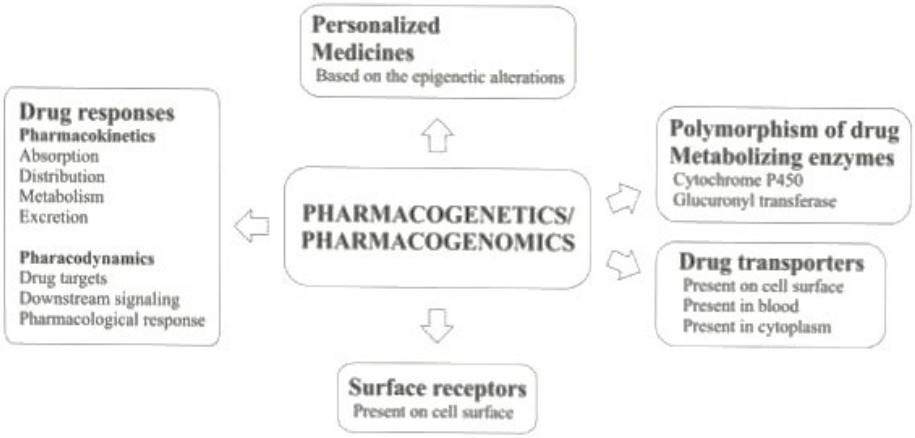

Figure 2. Roles of pharmacogenomics and pharmacogenetics in disease treatment and personalized medicine

Table 2. Treatments and diagnostics of some selected personalized (genomic) medicine drugs.

Treatment	Genetic test/biomarker	Description
Mivacurium	Cholinesterase gene	Used for anesthesia adjunct, metabolized by plasma cholinesterase
Divalproex	ornithine transcarbamylase deficiency (OTC)	Used in bipolar disorder, in patients with urea cycle disorders (UCD); OTC
Trastuzumab, Lapatinib	Human epidermal growth factor receptor-2 (HER2)/neu receptor	Patients with metastatic breast cancer
Warfarin	Cytochrome P450 (CYP2C9)	Used in cardiovascular diseases (CVD), patients with CYP2C9*2 and CYP2C9* 3 alleles
Atorvastatin	LDLR	Used in cardiovascular diseases (CVD), homozygous familial hypercholesterolemia and heterozygous
Irinotecan	UGTIA1	Used in colon cancer, homozygous condition for UGTIA1*28
Cetuximab, Panitumumab	EGFR expression	Used in colon cancer
Carbamazepine	HLA-B*1502	Used in epilepsy and bipolar disorder
Abacavir	HLA-B*5701	Used in human immunodeficiency syndrome (HIV)
Mercaptopurine,Thioguanine, azathioprine	Thiopurine S methyltransferase (TPMT) test	Used in leukaemia

Conventional cancer therapies are not effective for certain individuals with late-stage non-small cell lung cancer (NSCLC) due to rearrangements in the anaplastic lymphoma kinase (ALK) gene (table 2).

Crizotinib (Xalkori®), an anti-cancer drug that inhibits ROS1 and ALK, is used for the 5% of patients who respond due to a chromosomal rearrangement that causes a gene fusion (ALK and EML4, echinoderm microtubuleassociated protein-like 4) that leads to carcinogenesis (Lui et al,2018).

Approximately 1,600 molecular diagnostic tests that target various disorders are available; these tests are advised for a number of diseases that may be addressed through personalized medicine (Okada et al,2017). Studies have revealed that variations in the genes encoding drug targets, transporters, and metabolizing enzymes such cytochrome P450 and glucuronyl transferase are the reason why many patients do not respond to first-line therapy (Geen et al,2018).

Molecular diagnostics for a variety of cancer types are available to help doctors better manage their patients' conditions and raise their chances of survival (Table 2). Melanoma patients, for instance, are categorized according to the outcomes of the BRAF genetic test. Additionally, ALK and BRAF mutations can be detected in non-small cell lung tumors, which is helpful for focusing on these gene alterations while undergoing molecular therapy (Nunez et al,2021). The rates of genetic mutations that cause carcinogenesis vary amongst malignancies; melanoma has the highest rate of genetic alterations (73%), followed by thyroid cancer (56%). Lung cancer (41%), gynecological cancers (31%), gastrointestinal cancers (25%), and both ovarian and head and neck cancers (21%), rank second and third, respectively, in driver mutation prevalence [68]. For instance, compared to the 13% risk for all females, women with mutations in the BRCA1 or BRCA2 genes have a 36–85% likelihood of acquiring breast cancer (Morel et al,2020).

Human epidermal growth factor receptor 2 (HER2) is a cell surface protein that is overexpressed in about 30% of breast cancer cases; patients with this overexpression are not responsive to standard therapy (table 2). However, when used in conjunction with chemotherapy, the antibody medication trastuzumab can reduce the recurrence of HER2-positive tumors by 52%, a response that is larger than that of chemotherapy alone (Halby et al,2017).. It is advised that only patients with a normal KRAS gene be treated with cetuximab (Erbitux®) and panitumumab (Vectibix®) in conjunction with chemotherapy, even though these medications may be used to treat patients with metastatic colon cancer that have a KRAS mutation (Piha-Paul et al,2020).

7. Future Recommendations

Advances in epigenetic research are ushering in a new era of understanding the complicated regulatory processes that control gene expression. Scholars are exploring the intricacies of epigenetic alterations, like DNA methylation and histone changes, to elucidate their functions in molding cellular identity and reacting to external stimuli. The identification of epigenetic markers has accelerated with the introduction of high-throughput sequencing methods, yielding a comprehensive map of the epigenome (Smith et al., 2020).

As researchers investigate the possibility of targeting particular epigenetic alterations to cure diseases, this enhanced understanding opens doors to new treatment paths. Clinical studies for diseases like cancer are already seeing progress with epigenetic medications, also referred to as epigenetic modifiers (Johnson et al., 2022). A level of accuracy and specificity never before seen in medicine is made possible by the capacity to alter gene expression at the epigenetic level.

Healthcare is changing concurrently with the increasing importance of epigenetics in customized therapy (Brown & Miller, 2019). There is a shift toward customizing medical interventions based on this individualized information since it is recognized that each person has a distinct genetic and epigenetic composition that influences how they respond to treatments. Precision medicine is increasingly reliant on epigenetic profiling to help clinicians tailor treatment plans to individual patients.

Epigenetics in personalized medicine has potential applications in oncology and neurology, among other medical specialties (Lee et al., 2023). The identification of biomarkers that predict illness risk, progression, and response to particular therapies is made possible by an understanding of an individual's epigenetic imprint. This strategy represents a major advancement toward more patient-centric and effective healthcare by improving therapeutic efficacy and minimizing side effects.In essence, the future of epigenetic research is inextricably linked to the progress of personalized medicine, with the potential for a paradigm change in how we approach and tailor healthcare interventions to each individual's unique needs.

8. Conclusion

Plasticity is the capacity of a given genotype to impart a range of phenotypes in the presence of various environmental variables. Fundamental epigenetic mechanisms, including as DNA methylation, histone modifications, chromatin remodeling, and microRNAs that function as regulatory agents, regulate changes in gene expression. To detect phenotypic or epigenetic changes in biological systems, a variety of methods are employed.

Patients with epigenetic modifications and the problems they are connected with do not respond to traditional therapy, and such environmental influences can cause a variety of disorders. As a result, medications employed in personalized medicine can be utilized to treat various conditions according to a person's unique

genetic profile. The FDA has authorized a large number of the medications used in customized medicine.

Author contributions

M.A.M. and M.T. both contributed significantly to the manuscript. M.A.M. conceptualized and designed the study, coordinated the research activities, and drafted the manuscript. M.T. participated in data collection, analysis, and critical revision of the manuscript for intellectual content. Both authors read and approved the final manuscript.

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Competing financial interests

The authors have no conflict of interest.

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