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Cumulative Research into the Potential of Epigenetics in the Modern Medical Field

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Abstract

Several medical problems, such as Major Depressive Disorder, lupus, multiple sclerosis and Parkinson's are difficult to diagnose and treat due to subjective testing or symptom variation. MDD, currently, has no biological markers used for diagnosis and most diagnoses are subjective, focusing on textbook definitions of the DSM-5 and self-reported symptoms. The prolonged diagnosis process also prevents patients from being properly medicated, which can worsen their health. In terms of lupus, symptoms vary greatly from person-to-person and can change over time. The lack of consistency and similarities to other conditions, again, makes a successful diagnosis take a long time. Neurodegenerative diseases like Parkinson's and MS often have very subtle effects early on, making early diagnosis near impossible. By the time someone is diagnosed, serious nerve damage has already occurred and treatment is aimed at symptoms rather than prevention. The field of epigenetics is a relatively new emergence in biomedical science and has the potential to make diagnosis and prevention easier as it can provide a biological indicator that is more objective and there is less variation from person to person for certain medical problems. This paper summarized three main studies that investigated MDD, lupus, and neurological disorders, and their respective relationship with DNA methylation, offered a comparison of each one to other research, and analyzed future applications and limitations in the medical field for risk-identification, early diagnosis, and prevention, and treatment.

Keywords: Epigenetics, MDD, Neurodegenerative disorders, Lupus, Diagnosis and prevention

1. Introduction

Epigenetics is how heritable traits and environmental factors can affect how genes are expressed, turning them on and off (*Epigenetic Modification: Types, Functions, and Applications in Disease and Development*, 2025). The relationship between epigenetics and gene expression is similar to an analogy of a robot and a code. A person's genes are the code and the gene expression is the action that the code produces. In genetics, this could be the transcription and translation of a specific enzyme or protein. Epigenetics describes the factors that add to whether or not the gene gets coded based on the effects of environmental stimuli. This paper focuses on the effects of methylation, which is the presence of a specific molecule called methyl located at a spot on the gene called a CpG island (*Epigenetics, Health, and Disease*, 2025). In short, CpG islands are regions of highly concentrated cytosines on DNA that are usually located close to the start of the gene (*Epigenetic Modification: Types, Functions, and Applications in Disease and Development*, 2025). Epigenetic changes, caused by the addition or removal of a methyl group at specific places on the DNA helix, promote or inhibit transcription. Epigenetic changes can be inherited or can develop in response to severe trauma, stress, or can evolve from epigenetic changes in the parents (Grezenko et al., 2023). This paper discusses how certain epigenetic changes affect overall gene expression, mental states, and physical conditions, and applies these principles to future applications and areas that require more research.

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2. Background on Epigenetics

2.1 Introduction

This literature analysis is primarily based on three articles, which cover epigenetics and its relevance to conditions such as Major Depressive Disorder, neurodegenerative diseases, and lupus, respectively.

2.2 Epigenetics and MDD

Study Design

The first study in this paper–*Increased methylation of NR3C1 and SLC6A4 is associated with blunted cortisol reactivity to stress in major depression*, authored by Bakusic, Vrieze, Ghosh, and other contributors– is an observational study that ties into the psychopathological aspect of epigenetics; it explores how epigenetic changes to DNA affect transcription and can cause psychological responses (Bakusic et al., 2020).

The researchers involved in this study collected data from eighty depressed patients with confirmed MDD diagnoses and use of antidepressants before hospitalization. This study matched fifty-eight patients with control subjects by age and gender. The participants underwent multiple questionnaires and interviews to gain an insight on childhood trauma and personality. Then, each participant underwent a Trier Social Stress Test to see how their cortisol levels were affected when presented with a stressor.

Results and Analysis

After several thorough analyses of the data collected, the researchers discovered that there is a correlation between blunted cortisol reactivity, or an insufficient amount of cortisol produced in response to a stressor, and MDD. Additionally, there is a correlation between this blunted reactivity and hypermethylation at two gene sites: NR3C1 and SLC6A4.

The NR3C1 promoter region is the glucocorticoid receptor gene, and the SLC6A4 promoter region is the serotonin transporter gene, which plays a large role in the control of the stress response system. This study mainly explores the HPA axis and its effects, and how it relates to methylation at these sites (Bakusic et al., 2020). This axis includes the hypothalamus, pituitary gland, and the adrenal glands and allows the body to respond to stress. The cortisol triggers the hypothalamus to stop making the adrenocorticotropic hormone, which signals the end of a stress response. Frequent or intense stress can cause a dysfunction of the HPA axis (Cleveland Clinic, 2024).

Another notable finding of this study was the correlation between early life stress and depression later on in life. The control group had lower depression severity, a higher report of positive emotions than negative ones, lower anhedonia (or inability to experience joy), and lower neuroticism (emotional stability) in comparison to the MDD group (Bakusic et al., 2020; Cleveland Clinic, 2023; Cuncic, 2025). The control group had no depressive episodes, although roughly 20% of them reported an early life stress event. Roughly 33 people in the MDD group reported more than three episodes, and about 50% reported early life stress (Bakusic et al., 2020).

This study's findings make it plausible that the body's inability to appropriately react to a stressor likely plays a role in the patients' mental state and MDD condition. Therefore, it is also reasonable to infer that hypermethylation at these regions lead to the development of MDD, especially in patients with early life stress.

2.3 Epigenetics and Neurodegenerative Disorders

Study Design

The second study reviewed in this paper, The Effect of Epigenetic Aging on Neurodegenerative Diseases: A Mendelian Randomization Study by Fan, Liu, Lui, and colleagues, investigated the relationship between epigenetic aging and susceptibility to neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and Multiple Sclerosis (MS) (Fan et al., 2024).

The researchers used a bidirectional two-sample Mendelian randomization design, which uses genetic variants as instrumental variables to investigate potential causal relationships between biological traits and disease outcomes. A

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Mendelian Randomization design is the use of genetic variants as instrumental variables to infer causal relationships between an exposure and an outcome; bidirectional and two-sample means that they are analyzing how epigenetic age affects neurodegenerative diseases, and whether neurodegenerative diseases affect epigenetic age (*Bidirectional MR - Mendelian Randomization Dictionary*, n.d.; Hartwig et al., 2017). Publicly available genome-wide association study (GWAS) datasets were used to analyze several measures of epigenetic age (the biological age of your body measured through chemical modification to you DNA), including Hannum Age (epigenetic clock measuring intracellular and tissue aging), GrimAge (epigenetic clock measuring mortality risk, lifespan, and age-related chronic diseases) , and plasminogen activator inhibitor-1 (PAI-1) levels (a protein which plays a critical role in blood clotting), and their association with neurodegenerative diseases (Fan et al., 2024).

Results and Analysis

The results revealed several significant relationships between epigenetic aging markers and disease risk. Increased GrimAge was associated with reduced risk of Parkinson's disease, while increased Hannum Age was associated with greater risk of Multiple Sclerosis. Higher PAI-1 levels were also linked to an increased risk of Alzheimer's disease, however that association was much weaker perhaps as a result of the more indirect connection. Additionally, the study found that Alzheimer's disease may influence GrimAge and that Multiple Sclerosis may accelerate Hannum Age, suggesting a bidirectional relationship between disease progression and epigenetic aging.

These findings suggest that epigenetic age may serve as a useful biomarker for understanding neurodegenerative disease risk and progression. However, the researchers note that the study examined only a limited number of disease and epigenetic clocks, and the most participants were from European and North American populations, limiting the generalizability of the results. Additionally, the specific correlations between MD and lupus with certain genes and CpG islands, GrimAge and Hannum Age themselves can point to a wider variety of issues than just Parkinson's and Multiple Sclerosis, and is therefore a less reliable diagnostic tool (Fan et al., 2024).

2.4 Epigenetics and Lupus

Study Design

The third study reviewed in this paper, Genome-wide DNA Methylation Study Suggests Epigenetic Accessibility and Transcriptional Poising of Interferon-Regulated Genes in Naive CD4+ T Cells from Lupus Patients by Coit, Jeffries, Altorok, and colleagues, investigated the role of DNA methylation of CD4+T cells in systemic lupus erythematosus (lupus) (Coit et al., 2013).

The study compared 18 female lupus patients with 18 matched control subjects. Researchers isolated naive CD4+T cells from blood samples and analyzed DNA methylation and gene expression patterns to determine whether epigenetic changes could contribute to lupus susceptibility and disease development (Coit et al., 2013).

Results and Analysis

The researchers identified 86 differentially methylated CpG sites in lupus patients, with most showing hypomethylation. Many of the affected genes were involved in interferon signaling, and immune pathway known to play a major role in lupus, Notably, 21 of 35 hypomethylated genes were interferon-regulated genes, suggesting that epigenetic changes may prime immune cells for abnormal activation (Coit et al., 2013).

Although these genes were hypomethylated in naive CD4+T cells, they were not overexpressed until the cells matured in total CD4+T cells suggesting that the epigenetic changes occur before symptoms develop and may prepare immune cells for later overexpression. The results support the idea that DNA methylation contributed to lupus susceptibility and may help explain how immune dysfunction develops in affected individuals (Coit et al., 2013).

3. Methodology

3.1 Collecting Sources

This review was conducted using peer-reviewed scientific literature obtained through databases including

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PubMed, Google Scholar, Frontiers, and journal publisher databases. When first searching for research, our keywords were “epigenetics”, “neurodegenerative”, “autoimmune”, and “mental disorders”. We then narrowed our search to “methylation–hypo and hyper–”, “Parkinson’s disease”, “Multiple Sclerosis”, “Alzheimer's disease”, and “Major Depressive Disorder”. Sources were selected based on relevance to DNA methylation, date–-only considering those published in the last 20 years, making them a more accurate representation of modern capabilities and issues—methodological quality, and relevance to potential medical applications. The remaining experiments were fewer than ideal, but were then selected based on concrete correlation, more easily understood research with possible simplification, and the results potential to be used in diagnosis and prevention, of course considering source reliability throughout. When narrowing down to the chosen disorder and diseases, each was picked for its difficulty in diagnosis, prominence and importance in the modern day, strong correlation to genetics, and its encompassing of a certain medical field. MDD is a prominent issue in the mental medical field; PD, AD, and MS together encompass diseases in the neurological medical field; and lupus, which attacks all body systems, encompasses autoimmune diseases.

4. Comparative Discussion

The medical field is constantly progressing, seeking new and improved methods to advance medicine. One such new field is epigenetics, and as more research is done, its importance becomes increasingly apparent, as it influences physical and mental health. Without epigenetics, even different cell types, such as muscle and nerve cells, would not exist, and biological life as we know it would be impossible. However, with the development of medicine comes the need for it. Approximately 7.2 million Americans struggle with Alzheimer’s alone, disregarding other neurodegenerative diseases; 8% of Americans suffer from autoimmune diseases, and roughly 13.1 million adolescents and adults struggle with depression, with numbers only increasing (Alzheimer’s Association, 2025; National Institute of Health, n.d.; Brody & Hughes, 2025). Beyond their growing numbers, each of these disorders is either hard to diagnose, prevent, or treat, if not all three. Neurodegenerative diseases all have very limited prevention and treatment, and they can be mistaken for one another or dismissed as normal aging. Autoimmune diseases also overlap in symptoms, present differently from person to person, and are initially brushed off as a regular sickness; the treatment process is also long and complex, and can only manage the disease. Finally, major depressive disorder is notoriously difficult in all three, as it is often not taken seriously and not diagnosed. Prevention is difficult as causes are both environmental and genetic, and treatment is very individual and can even worsen the mental health of the patient. Therefore, the value of epigenetics, which shows a significant connection with such disorders, becomes more apparent as scientists’ understanding grows and new possibilities appear. Epigenetics offers a previously unavailable diagnostic path, based on analysis of methylation patterns at key genes and CpG islands. The data and results from all three main articles suggest that epigenetics may serve as an early biomarker for diagnosis, risk assessment, and preventive treatments in clinical medicine.

Both the lupus and MDD studies present findings supporting the use of methylation patterns at specific genomic biomarkers for disease detection. In the MDD study, hypermethylation at NR3C1 and SLC6A4 was associated with blunted cortisol reactivity and MDD. Although the relationship is correlational rather than causal, NR3C1 and SLC6A4 CpG islands could potentially serve as biomarkers in epigenetic testing to assess whether a patient has MDD. Likewise, the lupus study found hypomethylation of interferon-regulated CpG islands and naive CD4+ T cells, which are associated with heightened immune activity; these features could serve as early biomarkers of the condition.

However, beyond identifying existing diseases, these biomarkers may allow earlier detection than is currently possible. One study suggests that methylation patterns collected through blood or urine can indicate diseases before symptoms appear (BiologyInsights Team, 2025). Clinical researchers have already adopted DNA methylation as an early biomarker due to its chemical stability and established detection methodologies (Iyer et al., 2026). This is particularly significant for diagnostically difficult disorders such as lupus, MDD, and general neurodegeneration, and can be vital to provide early care. Epigenetic analysis has also already proven to be valuable in conditions such as diabetes and CVD (Song & Li, 2025). The distinction between purely genetic and epigenetic biomarkers is especially essential for conditions such as MDD, as epigenetics accounts for how the environment affects the body, and MDD is a condition greatly influenced by outside stressors. Traditional genetic biomarkers may identify inherited risk, but

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epigenetic markers provide information on how environmental stressors have influenced the inherited gene and exacerbated the disorder.

There are still limitations to this, however, as demonstrated in the neurodegenerative study. Although there was a correlation between certain types of epigenetic methylation, the epigenetic clocks themselves can point to a multitude of other issues, not just neurodegeneration. Furthermore, not only can abnormal epigenetic age point to other diseases and issues, but it can also point to different neurodegenerative disorders, not just one. The Frontiers review similarly noted that epigenetic modifications are highly dynamic and tissue-specific, meaning that methylation patterns observed in blood or saliva may not perfectly represent changes occurring in the brain, immune system, or other affected sites. This presents a challenge when developing universal biomarkers because the same epigenetic alteration may have different implications depending on the tissue. It is important that this type of research continues to be studied because of the relative youth of the field and various discrepancies among studies. The NR3C1 region has mixed results in the scientific community on whether or not it is a reputable biomarker. While the MDD study explained in this article says yes, other recent research reports no correlation between the two (Czarny et al., 2021). It is possible that this discrepancy exists due to the other factors that each study examines, like early life stress in the study discussed in this article, further proving the need for more extensive research.

Furthermore, the results of all three studies suggest that epigenetic testing can help to identify individuals who are at increased risk of developing these issues. In the MDD study, a relationship between patients who developed MDD, experienced early life stress, and had altered methylation patterns was observed. This correlation could be the benchmark for extensive epigenetic testing because certain gene promoters can serve as biomarkers for mental conditions such as MDD. If an at-risk individual also displays hypermethylation at one of the acknowledged sites, it can be an indicator that the person may be developing or already has MDD, which can expedite their treatment and get them help before symptoms significantly progress.

Because environmental stressors and changes can affect gene expression and methylation, this kind of epigenetic testing should be performed over a person's life, as their diet, physical health, location, and experiences change and possibly affect the development of MDD. DNA methylation is catalyzed by a group of enzymes called DNA methyltransferases (DNMTs). These enzymes are responsible for adding a methyl group to cytosine at the fifth position of the carbon ring, which can prevent gene expression. DNMT3a and 3b establish new methylation patterns in response to environmental stimuli, which is why a person's test results can change over time (Garg et al., 2023, Iyer et al., 2026). Unlike genetic information, which remains largely constant throughout life, epigenetic information is dynamic and potentially reversible.

The lupus study provides particularly strong evidence of risk identification because the researchers observed DNA hypomethylation before the corresponding increase in gene expression. This finding suggests that epigenetic alterations may occur earlier than observable and detectable anomalies such as immune overactivity. Rather than serving solely as markers of existing disease, methylation changes may represent the earliest measurable indication of disease progression. Likewise, the neurodegeneration study pointed to an inverse relation between GrimAge and Parkinson's risk and a direct relation between Hannum Age and Multiple Sclerosis Risk. Such a correlation will allow scientists to steadily track the epigenetic ages of people with a history of such disorders, and therefore identify risk before significant degradation. Together, these studies suggest that traceable epigenetic changes occur before clinical symptoms.

However, for epigenetic testing to become a practical clinical tool, sample collection must be accessible and cost-effective. More research should be conducted to collect samples from a variety of physical locations to determine which is the most accurate and best for diagnosis. The kind of care needed may determine the kinds of samples collected. The MDD study collected saliva and blood samples, which is what this supporting article suggests for mental health-related diagnoses (Song & Li, 2025). Both of these were relatively easy to come by and should be much less expensive in comparison to tissue samples from the brain or other invasive collection sites. This should make this kind of diagnosis available to many people by keeping costs lower and limiting the invasiveness of these diagnoses.

Epigenetic biomarkers may also contribute significantly to disease prevention. Across all three studies, researchers identified certain CpG islands, promoter regions, or epigenetic age markers that correlated with disease risk or diagnosis. As these biomarkers become better understood, they may allow clinicians to identify individuals at

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risk for early intervention before irreparable damage. The lupus study is particularly noteworthy because epigenetic changes preceded the overactivity of mature CD4+T cells. This suggests that preventative interventions could potentially be implemented before the disease becomes active. The earlier a person can be diagnosed or labeled "at risk," the sooner treatment and preventative care can be administered to reduce risk and delay progression.

Many preventative measures would not necessarily involve medication. Epigenetic changes are so massively influenced by environmental factors, changes to the patient's environment and habits, such as diet, stressors, location, job, etc., are easily the first possible step. Lifestyle modifications may help reduce harmful methylation patterns and promote beneficial ones. Research has already demonstrated that healthy dietary patterns can contribute to epigenetic modification (BiologyInsights Team, 2025). Consequently, epigenetic testing can provide physicians and patients with actionable information long before symptoms appear, shifting health care towards prevention rather than reaction.

Once an individual is identified as "at risk" or begins developing symptoms, continued monitoring becomes vital to track epigenetic changes and guide clinical decision-making. However, methylation levels should not be interpreted as direct measures of disease severity. In the MDD study, methylation patterns differed among the depressed subjects, but there was no correlation between symptom severity and methylation levels. This distinction is important as abnormal methylation levels do not necessarily indicate that immediate pharmacological treatment is necessary. Instead, early detection provides time for clinicians and patients to monitor symptoms, develop intervention plans, and implement preventative strategies.

Unfortunately, preventative pharmacological therapies remain limited for many diseases. Currently, the closest there is to "prevention medication" is lighter anti-depressants (SSRIs) for the beginnings of mental distress before the extremity of MDD, and Donanemab and Lecanemab for very early Alzheimer's (Hansen et al., 2008). However, true preventative medication remains rare. This does, however, offer an opportunity for epigenetics and prevention treatments to grow together as fields. If both are further researched, early identification before symptoms and subsequent prevention could potentially save many lives and raise the standards of those at risk of disease.

Recent advances in epigenetic therapy further demonstrate the clinical potential of this field, most notably with epigenetic drugs, or "epi-drugs," which have been approved by the FDA. Currently, there are ten different types of epi-drugs. These therapies function by reversing abnormal epigenetic patterns and restoring typical gene expression, unlike typical genetic mutations, which are often stagnant and irreversible (Iyer et al., 2026). The implications of this reversibility can be seen across all three studies. In lupus, future therapies may be able to target and reverse the hypomethylation of naive CD4+T cells and potentially reduce the abnormal immune activation associated with the disease. For MDD, treatments that modify stress-related methylation patterns could address the biological side of depression, which, paired with therapy, could lead to consistent improvement in patients. Likewise, as the correlation between neurodegenerative disease and epigenetics continues, the future may hold more specific treatments of certain CpG islands rather than just epigenetic age.

Of course, epi-drugs are far from universal cures. In MDD, the underlying trauma and stress that led to abnormal methylation do not disappear with drugs, and neurodegenerative disorders still lack clearly defined disease-specific epigenetic targets, making broad treatment with epi-drugs potentially dangerous. It also remains to be seen whether the epigenetic modification produced remains stable over time, or whether the body simply returns to previous methylation patterns. Despite these limitations, the existence of FDA-approved epigenetic drugs demonstrates that epigenetic research has already moved beyond theory and into clinical application. Although substantial research is still necessary, the findings in the three studies collectively suggest that epigenetics may transform medicine through early diagnosis, improved risk assessment, targeted prevention, and novel therapeutic strategies.

5. Limitations

Although the reviewed studies demonstrate promising applications of epigenetics in medicine, several limitations remain. Firstly, this review examined only MDD, lupus, and neurodegenerative disease, which, although they provide insights into different medical practices, cannot represent the full range of diseases influenced by epigenetics. As mentioned earlier, there is much evidence for epigenetics' role in diabetes and cardiovascular disease, which was not discussed much in this paper. Additionally, each study had its own methodological limitations. The MDD study was

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largely an observational design, identifying a significant association between DNA methylation and depression, but did not establish causation. Although the neurodegenerative study used Mendelian randomization to strengthen causal inference, it examined only three neurodegenerative diseases, and the participants were largely European and North American. Likewise, the lupus study also had a small sample size of entirely female participants, limiting its generalizability.

The field of epigenetics itself also presents several challenges. DNA methylation patterns are constantly changing with age and environment; as such, methylation changes observed in blood and saliva may not represent changes occurring in the affected organs, such as the brain in neurodegenerative disease, and immune tissues in lupus. Furthermore, while several studies have identified potential biomarkers, they are still not universally accepted to reliably diagnose disease. Conflicting findings, such as the evidence surrounding the MR3C1 methylation in MDD, continues to emphasize the need for larger, more diverse, and longitudinal studies.

Finally, although epigenetic therapies through epi-drugs have become FDA-approved and have entered clinical medicine, the disorder examined in this review still lacks validated therapeutic targets. Additional research is imperative to determine the long-term stability, safety, and effectiveness of manipulating epigenetic modifications before these approaches may become clinical practice. Consequently, current evidence supports epigenetics as a promising area of research rather than an established diagnostic or therapeutic tool.

6. Conclusion

Epigenetics has established itself as a promising medical field by providing insight into how environmental factors influence gene expression without influencing the underlying DNA sequence. The studies reviewed in this paper demonstrate that DNA methylation plays an important role in MDD, lupus, and neurodegenerative disease through related biological mechanisms. Across all three disorders, disease-associated methylation changes were identified before or during measurable clinical symptoms, highlighting the potential of epigenetic biomarkers for risk assessment, early detection, and disease monitoring.

Although each study examined different diseases and employed different methods, they all provide evidence towards the influence of epigenetics over disease susceptibility and progression. The most notable evidence from the neurodegenerative MR study, which provides causal inference between epigenetic aging and disease risk, while the lupus study demonstrated that methylation may precede clinical symptoms. The MDD study illustrated how environmental stressors produce measurable epigenetic changes that correspond with illness. Together, the studies represent the potential of early biomarkers and diagnosis by providing objective biological information alongside clinical information.

However, current evidence remains insufficient for widespread clinical implementation. DNA methylation is highly tissue-specific and influenced by the environment and biological factors, meaning that many proposed biomarkers require further research to validate before their implementation in patient-care. Likewise, while epi-drugs have been FDA-approved and demonstrate epigenetics potential in clinical treatment, further research is imperative to identifying disease-specific targets and establishing the long-term safety and effectiveness of the drugs.

As epigenetic technologies continue to improve, future research may transform medicine from a largely reaction-focused system to one emphasizing prediction, prevention, and personalized care. Although many questions remain unanswered, the evidence reviewed in this paper suggests that epigenetics has significant potential in the medical field for accurate and early diagnosis, preventative interventions, and even targeted therapies across a wide-range of medical conditions.

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