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# Epigenetic modifications in schizophrenia: diagnostic and therapeutic implications

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**ABSTRACT**

**Introduction**: Schizophrenia is a complex psychiatric disorder influenced by both genetic and environmental factors. In recent years, epigenetic mechanisms have gained attention due to their role in gene expression regulation and diagnostic potential, offering the possibility of early detection and personalized diagnosis through molecular profiling. This paper focuses on recent advances in DNA methylation and histone modifications and referencing the most up-to-date evidence and emerging epigenetic targets significant for informing future diagnostic tools and personalized interventions.
**Objectives**: The present paper aims to map the key epigenetic changes observed in schizophrenia focusing on its implications in diagnosis as well as it's biomarkers relevance.
**Methodology**: ScienceDirect and Pubmed Databases were searched using the keywords Epigenetic, Neurological diseases and Schizophrenia, focusing on the last five years. Papers were selected on the basis of their abstract content discarding papers not relevant to the theme, focused on pharmaceutical sciences or specifically about other neurological diseases. References were managed using Zotero.
**Results**: Searches resulted in a total of 461 articles of which 32 were selected (three from Science Direct and 29 from Pubmed).
**Conclusion**: Epigenetic alterations play a critical role in schizophrenia. DNA methylation, of DISC1, BDNF, COMT and RELN genes, and histone modifications have been shown to contribute to the development and progression of schizophrenia, providing valuable clues for diagnosis and potential therapeutic targets.

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**INFORMAÇÃO DO ARTIGO**

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**RESUMO**

**Introdução**: A esquizofrenia é um transtorno psiquiátrico complexo influenciado por fatores genéticos e ambientais. Nos últimos anos, os mecanismos epigenéticos têm ganho destaque devido ao seu papel na regulação da expressão génica e ao seu potencial no diagnóstico, oferecendo a possibilidade de deteção precoce e diagnóstico personalizado por meio de perfis moleculares. Este artigo concentra-se nos avanços recentes na metilação do DNA e nas modificações das histonas e referindo as evidências mais recentes e os alvos epigenéticos emergentes relevantes para o desenvolvimento de futuras ferramentas de diagnóstico e intervenções personalizadas.
**Objetivos**: O presente artigo visa mapear as principais alterações epigenéticas observadas na esquizofrenia com foco nas suas implicações no diagnóstico, bem como na relevância dos seus biomarcadores.
**Metodologia**: As bases de dados ScienceDirect e Pubmed foram usadas utilizando as palavras-chave Epigenetic, Neurological diseases e Schizophrenia, com foco nos últimos cinco anos. Os artigos foram selecionados com base no conteúdo do resumo, descartando artigos não relevantes para o tema, focados em ciências farmacêuticas ou especificamente sobre outras doenças neurológicas. As referências foram geridas com o Zotero.
**Resultados**: As buscas resultaram em um total de 461 artigos, dos quais 32 foram selecionados (três da Science Direct e 29 da Pubmed).
**Conclusões**: As alterações epigenéticas desempenham um papel crítico na esquizofrenia. Foi demonstrado que a metilação dos genes DISC1, BDNF, COMT e RELN e modificações de histonas contribuem para o desenvolvimento e a progressão da esquizofrenia, fornecendo pistas valiosas para o diagnóstico e potenciais alvos terapêuticos.

## Introduction

Schizophrenia is a severe psychiatric disorder characterized by significant disturbances in thought processes, perception, and behavior. It is a chronic condition that affects approximately 1% of the global population.[1,2] Schizophrenia typically emerges in late adolescence or early adulthood, with symptoms that include hallucinations, delusions, disorganized speech and behavior, as well as impairments in cognitive and social functioning.

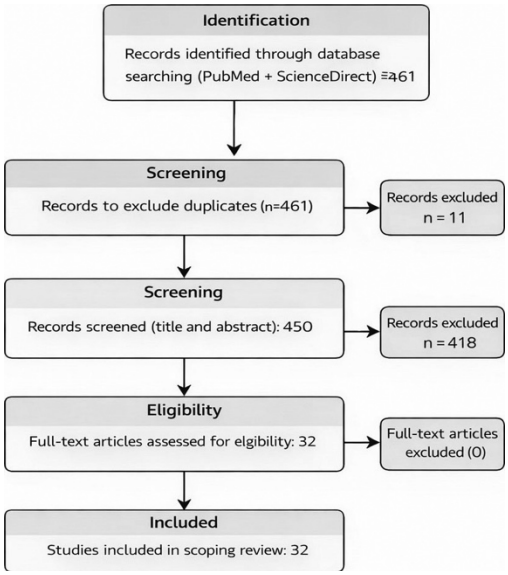


**Figure 1**. PRISMA ScR Flow Diagram

The etiology of schizophrenia is complex, involving an interplay between genetic, environmental, and neurobiological factors.[3,4] Research suggests that genetics plays a substantial role, with a heritable predisposition increasing the risk of developing the disorder, although environmental factors are also crucial. Exposure to variables such as viral infections, obstetric complications, and the use of psychoactive substances can heighten the likelihood of onset.

Regarding biological mechanisms, schizophrenia is frequently associated with alterations in dopamine levels in the brain,[5] particularly in regions such as the mesolimbic and mesocortical systems. Additionally, other neurochemical and structural abnormalities, including reduced brain volume and dysfunction in neural connectivity, have also been implicated in the pathogenesis of the disorder.

Epigenetic modifications have recently been recognized as significant contributors to the pathogenesis of schizophrenia. Epigenetics refers to changes in gene expression that do not involve alterations in the DNA sequence but can be inherited or induced by environmental factors. Key epigenetic mechanisms include DNA methylation, histone modification, and regulation by microRNAs, all of which can influence the expression of genes involved in brain development and function.[6] This article is focused particularly in DNA methylation and histone modifications.

## Methodology

A scoping review was conducted using the PubMed and ScienceDirect databases, targeting publications from the last five years (January 2020 to December 2024). The search was performed in January 2025 and included the keywords epigenetic, neurological diseases, and schizophrenia. To ensure methodological accuracy and transparency, the selection process adhered to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses in Scoping Reviews) guidelines (Figure 1).

Articles were initially screened by title and abstract, with exclusions applied to studies that were not relevant to the topic, addressed neurological disorders other than schizophrenia, or focused exclusively on pharmaceutical formulation, drug chemistry, or pharmacokinetics without evaluating epigenetic mechanisms. Pharmacological studies investigating epigenetic modulation or treatment-induced epigenetic changes were eligible for inclusion.

A total of 461 records were identified, of which 32 studies met the inclusion criteria and were analyzed in full (trhee from ScienceDirect and 29 from PubMed). No protocol was registered for this scoping review.

**Table 1**. Characteristics of studies included in the scoping review

| Author (Year) | Tissue | Epigenetic Mechanism | Target Genes | Main Findings |
|---|---|---|---|---|
| Abdolmaleky et al.,2024 | Brain | DNA Methylation | RELN,BDNF | Post-mortem epigenetic alterations |
| Casey et al., 2024 | Brain, Blood | Genetic/Epigenetic | Multiple | Genetic-epigenetic overlap |
| Alberry & Silveira,2023 | Brain | Epigenetic regulation | Multiple | Early life adversity eftects |
| Imamura et al.,2020 | Brain | Epigenetics | Multiple | Iwin study insights |
| Bilecki & Mackowiak, 2023 | Brain | DNA Methylation | Multiple | PFC dysregulation |
| Chen et al., 2021 | Brain, Blood | DNA Methylation | Multiple | Review of epigenetic findings |
| Chen et al., 2024 | Brain | Histone modification | H3K27 | Histone dysregulation |
| Magwai et al., 2021 | Blood | DNA Methylation | RELN, BDNF | Biomarker potential |
| Nohesara et al., 2024 | Brain | Epigenetic modulation | Multiple | Therapeutic targets |
| Huang et al., 2025 | Blood | Treatment-induced epigenetics | Multiple | Clinical trial outcomes |
| Domingos et al., 2022 | Animal models | DNA Methylation | Multiple | CBD epigenetic effects |
| Gardea-Resendez et al.,2020 | Brain/Blood | Epigenetic modulation | Multiple | Mood stabilizer effects |
| Khavari & Cairns, 2020 | Brain | DNA Methylation | Multiple | Biomarker exploration |
| Griffin et al., 2022 | Brain | Chromatin regulation | Multiple | Neurodevelop mental impact |
| Rasmi et al., 2023 | Brain | DNA Methylation | Multiple | Therapeutic implications |
| Vitorakis & Piperi, 2023 | Brain | Histone methylation | Multiple | Aging-related changes |
| Lin & Huang, 2020 | Brain | Epigenetic regulation | BDNF | Neurotrophic pathways |
| Richetto & Meyer, 2021 | Brain/Blood | DNA Methylation | Multiple | Environmental exposures |
| Smith et al.,2020 | Brain | Epigenetic changes | Multiple | Cannabis exposure |
| DeRosa et al., 2020 | Brain | Epigenetic regulation | Multiple | Environmental adversity |
| Wagh et al., 2021 | Blood | Gene expression | Multiple | Peripheral biomarkers |
| Miller, 2022 | Brain | Epigenetic loci | Multiple | Structured review |
| Wu et al., 2021 | Brain | Epigenetics | Multiple | Negative symptoms |
| Tan et al., 2023 | Brain | Epigenetic inheritance | Multiple | Paternal effects |
| Wawrzczak:Bargiela et al., 2023 | Brain | Epigenetic targets | Multiple | Therapeutic targets |
| Reichard & Zimmer-Bensch, 2021 | Brain | Epigenomic regulation | Multiple | Neurodevelopment |
| Xu et al., 2024 | Brain | DNA Methylation | Multiple | Brain development |
| Grigore et al., 2025 | Brain | Epigenetic biomarkers | Multiple | Cognitive decline |
| Rok-Bujko, 2022 | Brain | Drug-induced epigenetics | Multiple | Antipsychotic effects |
| Xie et al., 2024 | Brain | 5mC/5hmC | Genome-wide | Distinct methylation patterns |
| Zhou et al., 2021 | Blood | DNA Methylation | Multiple | Drug response |
| Postberg et al., 2024 | Brain | Epigenomic aging | Multiple | Aging processes |

The data extraction and exclusion criteria were performed and set by one author, later sought the second author's opinion. Any disagreements between reviewers were resolved through discussion and consensus. A formal risk-of-bias or methodological quality assessment was not performed (Table 1).

## Results

### *DNA methylation*

DNA methylation is one of the primary epigenetic mechanisms associated with schizophrenia. This process involves the addition of a methyl group ($CH_3$) to a cytosine residue in the DNA, typically within gene promoter regions.

Methylation inhibits gene transcription, thereby silencing gene expression. In simple terms, DNA methylation regulates when, where, and how genes are activated or silenced.

Studies have shown that abnormal methylation patterns are present in several genes critical to brain development and cognitive function.[7-9] One such gene is DISC1 (Disrupted in Schizophrenia 1), which is implicated in neurogenesis and synaptic plasticity. Aberrant methylation of DISC1 may lead to dysfunction in neuronal circuits, contributing to the psychotic symptoms observed in schizophrenia.[9,10]

Additionally, the BDNF gene (Brain-Derived Neurotrophic Factor), which is involved in neuroplasticity and central nervous system function, also exhibits altered methylation in individuals with schizophrenia[10,11,12]. These modifications can affect BDNF expression and contribute to cognitive deficits. These findings suggest that DNA methylation plays a crucial role in regulating genes implicated in schizophrenia. Likewise, genes such as COMT and RELN are epigenetically dysregulated in schizophrenia and may represent promising candidates for further investigation as diagnostic or therapeutic biomarkers.[12,13]

## *Histone modification*

Histones are essential proteins that assist in compacting DNA within the cell nucleus. They form structures known as nucleosomes, which consists of a histone core wrapped with DNA, enabling its organization and regulation. Histones can undergo various post-translational modifications, including acetylation, methylation, and phosphorylation. These modifications influence chromatin structure which ultimately influences gene activity. Since multiple histone residues can undergo different modifications, and gene expression depends on their combined effects, the link between histone modifications and gene expression is extremely complex. Still, acetylation and methylation play a critical role in regulating transcription. In general, histone acetylation increases DNA accessibility and promotes gene expression, while methylation is commonly associated with transcriptional repression.[7,9] Alterations in histone modification patterns have been implicated in several neuropsychiatric disorders, including schizophrenia. Some studies suggest that these mechanisms affect brain regions involved in emotional and cognitive processing - areas commonly disrupted in schizophrenia. These modifications may impact neuronal plasticity, memory, and behavior, all of which are altered in patients with schizophrenia.[10,13-15] For instance, HDAC inhibitors such as sulforaphane have demonstrated the capacity to modulate histone acetylation and improve symptoms in schizophrenia models.[10]

## *Clinical and diagnostic implications*

Schizophrenia is a complex disorder resulting from the interaction between genetic and environmental factors. Although advances in molecular genetics have provided significant insights into disease susceptibility, early and accurate diagnosis remains a challenge. In recent years, the investigation of epigenetic alterations has opened new perspectives for both the understanding and diagnosis of schizophrenia. Epigenetic changes, such as DNA methylation and histone modifications,[6] emerged as promising biomarkers for the disorder. These modifications are particularly relevant because they can be influenced by environmental triggers, potentially serving as a mechanistic link between genetic predisposition and external factors that contribute to the onset of schizophrenia[9,12,16]. Moreover, these epigenetic alterations may occur prior to the clinical manifestation of symptoms, which raises the possibility of detecting biological markers before the disease becomes fully symptomatic. Consequently, the identification of specific epigenetic patterns holds potential not only for improving our understanding of disease pathophysiology but also for enabling earlier diagnosis and better identification of individuals at risk.[9,16]

Methylation: Aberrant DNA methylation can be relatively easily assessed in biological samples such as blood or saliva. Studies focusing on specific genomic regions, such as the DISC1 and BDNF genes, have shown that abnormal methylation patterns are associated with an increased risk for schizophrenia. These patterns may potentially be used to identify at-risk individuals before the onset of overt psychiatric symptoms.[10,17] Furthermore, research suggests that DNA methylation may be related to treatment response, making these epigenetic changes even more relevant for clinical practice. Schizophrenia patients may exhibit different therapeutic responses depending on their epigenetic profiles, indicating that methylation analysis could help predict treatment efficacy.[10,12,18,19]

Histone Modification: Histone modifications, including acetylation and methylation, are also accessible for investigation in clinical research. These protein alterations can affect the expression of genes involved in brain development and function and are particularly relevant to studies of neuronal plasticity and cognitive circuitry. Changes in histone modification patterns have been observed in several psychiatric disorders, including schizophrenia. Mapping these modifications may offer a more detailed understanding of the molecular mechanisms underlying the disease and assist in identifying early indicators of brain dysfunction.[20]

*Implications for early diagnosis*

Studies suggest that combining multiple epigenetic biomarkers - such as DNA methylation of specific genes and histone modifications - may improve the characterization of schizophrenia-related molecular profiles, although evidence supporting clinical diagnostic accuracy remains heterogeneous.[7,9,10,16,21] For instance, Lin and Huang (2020)[17] demonstrated that patients with schizophrenia exhibited significantly higher methylation levels in the BDNF

promoter IV region compared to healthy controls, which was associated with decreased gene expression and correlated with cognitive impairment[10]. Similarly, Vitorakis and Piperi (2023)[16] found that aberrant histone H3K27 methylation has been reported in post-mortem studies of the prefrontal cortex of individuals with schizophrenia, suggesting a potential role of this modification in the dysregulation of genes involved in synaptic plasticity and neurodevelopment.[7] Furthermore, Khavari and Cairns (2020)[13] reported that altered methylation of the RELN promoter region in peripheral blood samples substitute by differentiates schizophrenia patients from controls in individual studies; however, robust and replicated diagnostic accuracy metrics remain limited.[13, 24]

These findings underscore the potential of epigenetic markers not only for understanding pathophysiological mechanisms but also for developing accessible and non-invasive diagnostic tools, especially if combined in predictive panels. However, further longitudinal studies are necessary to determine the temporal stability of these markers and their predictive value before symptom onset.

## *Challenges and future of Epigenetics in diagnosis*

Despite its promising potential, the clinical application of epigenetics in schizophrenia diagnosis faces substantial challenges. These include individual variability, the complexity of epigenetic regulation, and the lack of consensus on which epigenetic patterns are most effective for diagnostic purposes.[11] Moreover, there is a critical need to better understand how environmental factors influence epigenetic changes and how these, in turn, relate to schizophrenia-associated genes. The study of gene-environment interactions and their reflection in epigenetic biomarkers is a growing but still emerging field of research.[12]

The future application of epigenetic biomarkers in the diagnosis of schizophrenia will require additional longitudinal studies that correlate these epigenetic alterations with disease onset and progression. With advances in high-resolution sequencing technologies, it may become feasible to implement these biomarkers quickly and affordably in clinical settings, enabling earlier and more personalized interventions for patients.

## *Epigenetic alterations and schizophrenia treatment*

Schizophrenia is a complex psychiatric disorder, and conventional treatment primarily relies on antipsychotic medications to control psychotic symptoms such as hallucinations and delusions. However, treatment remains challenging due to the heterogeneous nature of the disorder and the variability in patient responses. Antipsychotics remain the cornerstone of schizophrenia treatment and are categorized into first-generation (typical) and second-generation (atypical) drugs. While typical antipsychotics, such as haloperidol, primarily act by blocking dopamine receptors, atypical antipsychotics - such as clozapine and olanzapine - have broader mechanisms of action and are associated with a lower risk of motor side effects.[23, 30] These medications are effective in managing positive symptoms of schizophrenia, but they have limited impact on negative symptoms - such as apathy and anhedonia - or cognitive deficits, which are also core features of the disorder. Furthermore, many patients do not respond adequately to these treatments, underscoring the need for more effective therapeutic alternatives[23].

Antipsychotic drugs, in addition to targeting dopaminergic and serotonergic receptors, also induce relevant epigenetic modifications that can modulate the gene expression associated with schizophrenia. Studies have shown that compounds such as clozapine and risperidone directly influence DNA methylation patterns in genes like BDNF, COMT, and RELN, which are crucial regulators of neuroplasticity, neurotransmission, and neural development. These epigenetic changes not only affect the manifestation of symptoms but also contribute to individual variability in treatment response[12,18]. For instance, clozapine has demonstrated the ability to reverse aberrant methylation patterns, restoring the expression of previously silenced genes. Moreover, atypical antipsychotics can modulate the activity of epigenetic enzymes such as DNMTs and HDACs, further influencing the patients' epigenomic profile. These findings highlight the importance of considering both genetic and epigenetic factors in the selection and evaluation of antipsychotic therapy, paving the way for more personalized approaches in the treatment of schizophrenia.[9,18]

All this, together with the above mentioned findings of changed DNA methylation and histone modifications patterns in schizophrenia suggests that these mechanisms may influence treatment response. For instance, specific methylation patterns have been associated with enhanced responsiveness to antipsychotic medications, while others may indicate treatment resistance. Methylation of genes such as DISC1 and BDNF, which are implicated in schizophrenia, may modulate therapeutic response to antipsychotic drugs. This implies that analyzing these epigenetic changes could aid in tailoring treatment strategies based on each patient's individual epigenetic profile. In fact, recent studies in animal models and in human clinical trials have shown that compounds such as HDAC inhibitors and agents affecting DNA methylation, including valproate and sulforaphane, have potential in modulating gene expression and improving negative and cognitive symptoms of the disorder. These therapeutic strategies have been tested in preclinical models to explore molecular mechanisms,[10,18] and some have advanced to human studies, where changes in gene methylation - such as in BDNF, RELN, and DISC1 - were observed following pharmacological treatment.[9,10,12]

HDAC inhibitors, in particular, have been investigated as adjunctive therapies in clinical trials, targeting histone acetylation and DNA methylation patterns. By restoring the expression of genes affected by epigenetic dysregulation, these compounds show promise in enhancing cognitive function and alleviating negative symptoms that are often resistant to conventional antipsychotic treatments. Recent studies also explore the role of environment exposures such as cannabis and how they modulate epigenetic pathways relevant to psychosis.[22]

Other emerging treatments include DNA methylation modulators, which may directly influence the expression of genes such as BDNF that are involved in the pathophysiology of schizophrenia. The ability to manipulate methylation to correct abnormal epigenetic patterns could open new avenues for treatment, particularly for patients who do not respond adequately to standard antipsychotics.[9,24]

### *Challenges and Future of Epigenetic treatment*

Despite encouraging advances, the development of safe and effective epigenetic therapies for schizophrenia faces several challenges. One of the primary difficulties is the precise control of epigenetic modifications, given that alterations in different genes can produce variable and sometimes unpredictable effects. This necessitates highly individualized therapeutic approaches.[9,25,32]

Another critical challenge lies in identifying the most reliable epigenetic biomarkers to guide the selection of appropriate treatments. As more data emerges on the role of epigenetic changes in schizophrenia and treatment response, more effective and personalized therapeutic strategies are expected to become available. [9]

## Discussion

Epigenetic alterations play a critical role in enhancing our understanding of schizophrenia, offering novel insights into how genetic and environmental factors interact to influence the manifestation of this complex disorder. DNA methylation and histone modifications have been shown to contribute to the development and progression of schizophrenia, providing valuable insights into disease mechanisms with potential relevance for future diagnostic approaches.[8,14,24]

Advances in epigenetic research have underscored the importance of DNA methylation and histone modifications in schizophrenia, suggesting that these alterations may be both causal and reactive to the pathology. Aberrant methylation of genes such as DISC1, COMT, RELN and BDNF have been consistently associated with altered gene expression, affecting neuronal function and brain circuitry involved in the disorder.[7-9,11,16] In addition, histone modifications have also been shown to play a crucial role in regulating gene expression, indicating that epigenetic dysregulation may contribute to the cognitive and negative symptoms of schizophrenia.[14,22]

Beyond offering insights into the underlying biological mechanisms, epigenetic findings open up new possibilities for more efficient treatments. The identification of specific methylation and histone modification patterns may enable the development of more targeted and effective therapies, improving treatment outcomes, especially for patients who are unresponsive to traditional antipsychotic medications.[10,18,24]

### *Challenges and limitations*

Despite promising progress, significant challenges remain in research and treatment of schizophrenia based on epigenetic modifications. The complex interplay between genetic and environmental factors makes it difficult to establish clear epigenetic patterns that can be universally applied to all patients.[9,13,14]

Moreover, the long-term safety of epigenetic therapies, such as HDAC inhibitors[11] and DNA methylation modulators, still requires validation through larger clinical trials. An additional challenge lies in identifying reliable biomarkers that can be used to accurately diagnose schizophrenia and monitor treatment response. Although epigenetics presents a promising avenue for the development of such biomarkers, further research is needed to confirm their clinical utility.[9,13,14]

Despite the growing interest in epigenetic biomarkers for schizophrenia, several limitations currently hinder their clinical implementation. Although several studies suggest the potential diagnostic relevance of epigenetic alterations in schizophrenia, quantitative diagnostic performance metrics such as sensitivity, specificity, and area under the curve (AUC) were not consistently reported across the included literature. As a result, formal aggregation of diagnostic accuracy measures was not feasible within the scope of this review.

Moreover, substantial heterogeneity was observed across studies in terms of tissue type, epigenetic targets, analytical platforms, and clinical characterization of participants. Longitudinal data assessing temporal stability of epigenetic markers were limited, and few studies evaluated the incremental diagnostic value of epigenetic markers beyond established clinical variables. These factors currently constrain the translation of epigenetic findings into validated diagnostic tools.

### *Future perspectives*

The future of schizophrenia and epigenetics research lies in the development of more effective and personalized therapies. As understanding of epigenetic mechanisms deepens, it is anticipated that epigenetic therapies could be

integrated with conventional treatments to improve efficacy and reduce adverse effects.[9, 18, 25]

A particularly promising strategy is the use of combination therapies, involving both traditional antipsychotics and epigenetic modulators. This approach may enhance treatment outcomes for patients with severe forms of schizophrenia or those who are unresponsive to conventional medications. Furthermore, research using animal models and clinical trials will be essential to determine the most effective and safe implementation of epigenetic therapies.[10,12,18]

Advances in gene-editing technologies, such as CRISPR, may also enable more precise manipulation of epigenetic alterations, offering a potentially revolutionary approach to treating schizophrenia at the molecular level.[26,27] However, long-term safety remains a major concern, especially due to the pleiotropic effects of epigenetic drugs and the risk of off-target alterations.[25, 32]

Further research using human tissue, peripheral biomarkers and advanced sequencing tools will be essential to validate the predictive power of epigenetic profiles and to identify reliable therapeutic targets.[28-31]

### *Tissue specificity and confounding factors*

The included studies investigated epigenetic alterations in both post-mortem brain tissue and peripheral blood samples. Brain-based studies provide greater biological relevance for understanding schizophrenia pathophysiology, particularly regarding DNA methylation and histone modifications affecting genes such as RELN and BDNF [1,5,7,13,25]. However, their applicability is limited by sample availability and post-mortem effects.

Peripheral blood studies were more prevalent and offer greater translational potential for biomarker research,[8,18,21,22] although they are influenced by cell-type heterogeneity and may not fully reflect brain-specific epigenetic regulation.[8,18,21] Several studies accounted for demographic and clinical confounders such as age and sex, while adjustment for smoking status, antipsychotic medication, and cellular composition was inconsistently reported across the literature.[18,19,21,31] These methodological differences contribute to heterogeneity among findings and limit direct comparability across studies.

### *Methodological considerations:*

Recent methodological advances in epigenomic research may help strengthen causal inference and robustness in future studies of schizophrenia. Approaches such as Mendelian randomization–based methylome-wide association studies (MR-based MWAS) offer the potential to disentangle causal relationships between epigenetic variation and disease risk, while spatial methylation modeling enables finer resolution of region- and cell-type–specific epigenetic patterns in brain tissue. In addition, improved statistical frameworks accounting for correlation structure and multiple testing may enhance reproducibility across epigenome-wide studies.

Although these methodologies were not systematically applied in the studies included in this scoping review, their integration into future research may substantially improve the interpretability and translational relevance of epigenetic findings in schizophrenia.

## Conclusion

Schizophrenia remains a highly complex disorder with multiple factors contributing to its etiology and manifestation. Discoveries regarding epigenetic alterations provide new insights into the biological mechanisms underlying the disease and pave the way for more personalized treatments. However, further studies are essential to validate these findings and address the challenges associated with epigenetic therapies.[9,21,26,28,32]

Ultimately, the integration of epigenetics research with advancements in neuroscience and psychiatry may lead to more effective, targeted treatments, improving patients' quality of life and offering new options for the management of schizophrenia[9, 26,32]

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