



## Review Article



## Multi-Epigenetic Landscapes of Schizophrenia

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## ABSTRACT

Schizophrenia is a debilitating neurodevelopmental disorder affecting approximately 1% of the global population. Traditional genetic models have provided limited insight into its complex etiology. This review synthesizes recent advances in epigenetic research related to schizophrenia, focusing on dynamic and reversible genome modifications. The study analyzed multi-omics and epigenomic profiling studies published between 2020 and 2025 that explore DNA methylation, histone modifications, non-coding RNAs and gene-environment interactions in schizophrenia. Epigenetic mechanisms, including DNA methylation, chromatin remodeling and non-coding RNAs, mediate environmental influences during critical neurodevelopmental periods, contributing to long-term gene expression changes associated with schizophrenia. These findings integrate genetic liability with environmental exposures and highlight potential biomarkers and therapeutic targets. Understanding schizophrenia through the lens of epigenetics may inform novel diagnostic and treatment approaches, advancing precision psychiatry.

## INTRODUCTION

Schizophrenia is a severe psychiatric disorder characterized by persistent cognitive, emotional and perceptual disturbances [1]. Despite extensive research, treatment resistance remains a significant challenge, especially regarding negative and cognitive symptoms [2]. Traditional models have primarily focused on dopaminergic dysfunction; however, these models do not fully explain the complex etiology or heterogeneity of schizophrenia symptoms. Emerging evidence suggests that epigenetics, the study of heritable and reversible modifications to gene expression without alterations in the DNA sequence. It offers a promising framework to bridge the gap between genetic predisposition and environmental influences [3]. Epigenetic mechanisms such as DNA methylation, histone modifications and non-coding RNAs regulate gene activity

and can mediate the effects of environmental stressors on gene expression [4]. This integrative approach may provide novel insights into schizophrenia pathophysiology. That may surpass the explanatory limits of dopaminergic hypotheses.

**Factors Influencing Schizophrenia**

Schizophrenia is a multifactorial disorder resulting from the complex interplay between genetic predispositions and environmental exposures. Advances in genomics and population studies have enhanced our understanding of how these factors interact to influence neurodevelopmental trajectories, ultimately contributing to disease onset and progression [5].

**Genetic and Environmental Contributions**

The heritability of schizophrenia is estimated between



60% and 80%, as supported by large-scale twin and family studies [6]. Monozygotic (MZ) twins show approximately 50% concordance for schizophrenia, whereas dizygotic (DZ) twins exhibit around 15% concordance, underscoring a strong genetic component alongside critical environmental influences [6] (Table 1).

**Table 1:** Prevalence and Genetic Factors Associated with Schizophrenia

Metric	Value
Global Prevalence	~1%
Heritability	60–80%
MZ Twin Concordance	~50%
DZ Twin Concordance	~15%

### Epigenetic Mechanisms in Schizophrenia

Epigenetic modifications regulate gene expression without altering the DNA sequence, playing a crucial role in the pathophysiology of schizophrenia. The principal epigenetic mechanisms implicated include DNA methylation, histone modifications, non-coding RNAs and chromatin remodeling complexes.

#### DNA Methylation

DNA methylation involves the addition of methyl groups to cytosine bases in CpG dinucleotides, mediated by DNA methyl-transferases (DNMTs). It includes DNMT1 (maintenance methylation) and DNMT3A/3B (de novo methylation). Aberrant methylation patterns have been repeatedly observed in schizophrenia-associated genes, including RELN, GAD1, and COMT in postmortem brain tissues [7]. Early-life adversity appears to induce persistent methylation changes that potentially increase long-term disease risk [8] (Table 2).

**Table 2:** Schizophrenia-Associated Genes, Their Functions, and Related Epigenetic Modifications

Gene	Function	Epigenetic Change
RELN	Neuronal migration	Promoter hypermethylation
GAD1	GABA synthesis	Downregulated by methylation
COMT	Dopamine metabolism	Methylation-sensitive allele

#### Histone Modifications

Histone modifications regulate chromatin structure, affecting DNA accessibility and gene transcription. Histone acetylation, catalyzed by histone acetyltransferases (HATs), generally promotes transcriptional activation by loosening chromatin. Conversely, histone deacetylases (HDACs) remove acetyl groups, leading to chromatin compaction and transcriptional repression [8]. In schizophrenia, increased expression of HDAC1 and HDAC2 has been observed in the prefrontal cortex and hippocampus of postmortem brains, potentially silencing genes crucial for synaptic plasticity and neuronal development [9]. Chromatin immunoprecipitation sequencing (ChIP-seq) studies have revealed enrichment

of the repressive histone mark H3K27me3 in schizophrenia, particularly affecting genes involved in synaptic signaling and immune responses [10]. Additionally, reductions in the active mark H3K4me3 have been reported in genes related to GABAergic neurotransmission [11]. Histone deacetylase inhibitors (HDACi) such as valproic acid and vorinostat have demonstrated potential in preclinical models by partially restoring gene expression and synaptic function; however, their clinical efficacy remains under investigation [12–14].

#### Non-Coding RNAs and Chromatin Remodelers

Non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), contribute to epigenetic regulation by modulating gene expression at transcriptional and post-transcriptional levels [15]. MicroRNAs (miRNAs): MiR-137, identified through genome-wide association studies (GWAS), plays a central role in neurogenesis and synaptic plasticity. Dysregulation of miR-137 and other schizophrenia-related miRNAs, such as miR-132 and miR-219, affects neurotransmitter signaling and neuronal integrity [16, 17]. Long Non-Coding RNAs (lncRNAs): lncRNAs like NEAT1 and MALAT1 are implicated in chromatin remodeling and transcription regulation, with altered expression observed in schizophrenia. Chromatin remodeling complexes, including CHD8 and SWI/SNF (e.g., SMARCA2, SMARCB1), dynamically reposition nucleosomes to regulate DNA accessibility. Mutations or dysregulation of these remodelers have been linked to neurodevelopmental deficits relevant to schizophrenia [18, 19].

#### Interactions Between Gene and Environment

The pathogenesis of schizophrenia increasingly supports a gene-environment interaction (G×E) model, whereby environmental exposures modulate gene expression through epigenetic mechanisms, especially during sensitive developmental periods [20]. This framework integrates genetic susceptibility with environmental insults to explain the heterogeneous clinical presentation of schizophrenia. A seminal study by Kular and Kular, [21] demonstrated that individuals carrying the COMT Val158 allele who used cannabis during adolescence had an elevated risk of psychotic symptoms compared to Met/Met carriers, providing early empirical support for G×E in psychiatry. Subsequent research has expanded this model to include other genes and environmental factors: BDNF (Brain-Derived Neurotrophic Factor): Early-life trauma and stress induce hypermethylation of the BDNF promoter, leading to reduced neurogenesis and impaired synaptic plasticity. NRG1 (Neuregulin 1): Prenatal immune activation affects NRG1 expression through methylation and histone modification, disrupting neural circuit formation [22]. Inflammatory Genes (e.g., IL-6, TNF-α): Maternal infection and perinatal immune challenges cause persistent

epigenetic alterations in immune-related genes, contributing to neuro-inflammation and neuronal dysfunction [23] (Table 3).

**Table 3:** Genes, Environmental Triggers, Epigenetic Modifications and Impacts in Schizophrenia

Gene	Environmental Trigger	Epigenetic Effect	Impact
COMT	Cannabis (adolescence)	Altered enzymatic activity	Increased psychosis risk
BDNF	Early-life trauma	Promoter hypermethylation	Reduced neuroplasticity
NRG1	Prenatal immune activation	Histone modification	Disrupted neural development
IL-6	Maternal infection	Epigenetic priming	Chronic inflammation

### Developmental Timing and Epigenetic Windows

Unlike static genetic mutations, epigenetic mechanisms are highly dynamic and responsive to environmental inputs during critical developmental windows. These sensitive periods, spanning prenatal, perinatal, and early childhood phases, coincide with intense neurogenesis, synaptogenesis and structural brain remodeling. Environmental factors such as maternal stress, malnutrition, infections and inadequate caregiving during these windows can induce long-lasting epigenetic alterations that disrupt neurodevelopmental trajectories. Animal studies have shown that prenatal stress increases DNA methylation at genes regulating the hypothalamic-pituitary-adrenal (HPA) axis, such as NR3C1 (encoding the glucocorticoid receptor), resulting in dysregulated stress responses, cognitive deficits and structural brain changes in offspring [24]. Importantly, epigenetic plasticity persists beyond early development. DNA methyltransferase (DNMT) activity and histone deacetylase (HDAC) expression remain active in adult neurons, particularly in brain regions involved in learning, memory and executive function, such as the prefrontal cortex and hippocampus [25]. This suggests that environmental insults during adolescence or adulthood, such as trauma or substance use, can continue to modify gene expression and contribute to disease onset or relapse. Recent temporal epigenomic mapping studies indicate that schizophrenia-associated epigenetic alterations often emerge between mid-gestation and early adolescence, coinciding with established periods of heightened disease risk. These findings support a model in which schizophrenia results from the cumulative effect of epigenetic insults across developmental stages rather than from a singular event [26].

### Transgenerational Epigenetics

Transgenerational epigenetics explores how environmentally induced epigenetic modifications can be inherited through the germline, potentially explaining the persistence of psychiatric risk across generations even in the absence of direct genetic mutations. This emerging

field provides a novel perspective on familial vulnerability in schizophrenia. Animal models have demonstrated that maternal stress, malnutrition and substance exposure induce methylation changes in genes such as BDNF and NR3C1, which are transmitted to offspring via sperm or oocytes. These inherited epigenetic marks correlate with behavioural abnormalities, altered stress reactivity and disrupted neural circuitry [27]. In humans, preliminary studies on populations exposed to large-scale trauma, such as Holocaust survivors or victims of famine and war, suggest that descendants exhibit distinct methylation patterns in genes related to stress response and neuroplasticity, including FKBP5, SLC6A4 and OXTR, despite no direct trauma exposure [28]. Although the precise mechanisms and extent of transgenerational epigenetic inheritance in humans remain under investigation, these findings indicate that psychiatric vulnerability may be epigenetically primed by ancestral environmental experiences, contributing to the complex heritability of schizophrenia.

### Clinical and Therapeutic Implications

Recognition of persistent and modifiable epigenetic changes in schizophrenia offers promising avenues for diagnosis and treatment, advancing the field toward precision psychiatry.

### Epigenetic Therapies

Histone deacetylase inhibitors (HDACis) such as valproic acid and vorinostat have demonstrated efficacy in animal models by restoring the expression of key genes like RELN and GAD1, improving synaptic plasticity and cognitive functions [29, 30]. Early-phase clinical trials suggest potential benefits as adjunctive therapies; however, challenges regarding optimal dosing, safety and target specificity remain [31].

### Targeted Epigenome Editing

Recent developments in CRISPR-dCas9-based epigenome editing allow precise targeting of gene promoters with modifiers such as DNA demethylases or HDAC inhibitors without altering DNA sequences [32]. Although still in preclinical stages, these tools hold considerable promise for gene-specific reprogramming in psychiatric disorders, including schizophrenia.

### Biomarkers for Diagnosis and Monitoring

Peripheral blood DNA methylation profiles are under investigation as diagnostic and prognostic biomarkers for schizophrenia. Candidate genes include SLC6A4 (serotonin transporter), which is linked to stress reactivity; NR3C1 (glucocorticoid receptor), reflecting hypothalamic-pituitary-adrenal axis sensitivity; and microRNAs such as miR-137 and miR-132, regulators of synaptic and neurodevelopmental pathways. Ongoing research aims to develop methylation panels to facilitate early detection, treatment stratification and relapse prediction [33].

## CONCLUSIONS

Epigenetic research has significantly advanced our understanding of schizophrenia, bridging the gap between genetic predisposition and environmental exposure. Unlike static genomic markers, epigenetic modifications are dynamic, reversible and influenced by developmental timing, offering a more nuanced model for disease pathogenesis. The integration of genome-wide methylation studies, transcriptomic analyses and multi-omic profiling has revealed that alterations in DNA methylation, histone modifications and non-coding RNAs are involved in synaptic regulation, neuro-inflammation, and stress responsiveness, all processes disrupted in schizophrenia. Emerging evidence of transgenerational epigenetic inheritance and gene-environment interactions suggest that psychiatric vulnerability is not solely determined by DNA sequence but also by inherited and acquired epigenetic states. These insights may provide new avenues for preventive interventions, diagnostic biomarkers, and therapeutic strategies. Nonetheless, significant challenges remain. Future studies must address the causal relevance of specific epigenetic marks, improve tissue specificity in peripheral biomarker studies, and evaluate long-term effects and safety of epigenetic therapies. With ongoing advancements, epigenetics may contribute meaningfully to a more personalized and mechanistically grounded approach to the treatment and management of schizophrenia.

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All authors have read and agreed to the published version of the manuscript

## Conflicts of Interest

All the authors declare no conflict of interest.

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