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# Epigenetic Mechanisms in Schizophrenia: A Review of Evidence from the Past Five Years

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## Abstract

Schizophrenia is a highly heritable yet polygenic and clinically heterogeneous psychiatric disorder for which DNA sequence variation alone does not fully explain individual risk, age of onset, or treatment response. Over the past five years, epigenome-wide association studies, chromatin profiling, and non-coding RNA analyses have provided convergent evidence that DNA methylation, histone modification, and regulatory RNAs mediate the interaction between genetic vulnerability and environmental exposure across the lifespan. This narrative review synthesizes literature published between 2021 and 2026 on three major epigenetic mechanisms implicated in schizophrenia: DNA methylation dysregulation, histone post-translational modification, and dysregulated non-coding RNA networks, together with emerging evidence on prenatal and childhood adversity as upstream triggers and antipsychotic medication, particularly clozapine, as both a downstream confound and a potential epigenetic modulator. Differentially methylated positions identified through recent epigenome-wide association studies converge with risk loci identified by large genome-wide association studies, histone acetylation and methylation are altered in postmortem cortical tissue and oligodendroglial-lineage cells, and long non-coding RNAs such as GOMAFU together with several microRNAs are dysregulated in blood and brain. Epigenetic clocks and methylation risk scores show promise as peripheral biomarkers, yet tissue specificity, medication confounding, and a scarcity of longitudinal data remain major barriers to clinical translation. Continued integration of multi-omic and longitudinal study designs is required before epigenetic markers can be translated into tools for early detection, patient stratification, or treatment monitoring in schizophrenia.

***Keywords:*** *Epigenetics, DNA methylation, Histone modification, Non-coding RNA, Schizophrenia*

## Abstrak

**Mekanisme Epigenetik pada Skizofrenia.** Skizofrenia merupakan gangguan psikiatri dengan heritabilitas tinggi namun bersifat poligenik dan sangat heterogen secara klinis, sehingga variasi sekuens DNA semata tidak dapat menjelaskan seluruh risiko individu, usia onset, maupun respons terhadap pengobatan. Dalam lima tahun terakhir, studi asosiasi epigenom, pemetaan profil kromatin, dan analisis RNA non-coding memberikan bukti yang konvergen bahwa metilasi DNA, modifikasi histon, dan RNA regulator menjadi penghubung antara kerentanan genetik dan pajanan lingkungan sepanjang siklus hidup. Tinjauan naratif ini merangkum literatur yang diterbitkan antara tahun 2021 hingga 2026 mengenai tiga mekanisme epigenetik utama pada skizofrenia, yaitu disregulasi metilasi DNA, modifikasi pascatranslasi histon, dan jejaring RNA non-coding yang terganggu, disertai bukti terkini mengenai kesulitan masa prenatal dan masa kanak-kanak sebagai pemicu awal, serta pengobatan antipsikotik sebagai faktor perancu sekaligus modulator epigenetik potensial. Posisi termetilasi diferensial yang diidentifikasi melalui studi asosiasi epigenom terbaru berkonvergensi dengan lokus risiko yang ditemukan melalui studi asosiasi genom skala besar, asetilasi dan metilasi histon berubah pada jaringan korteks pascamortem dan sel galur oligodendroglial, serta RNA non-coding panjang seperti GOMAFU dan beberapa microRNA mengalami disregulasi pada darah dan otak. Jam epigenetik dan skor risiko metilasi menjanjikan sebagai biomarker perifer, namun spesifisitas jaringan, perancu akibat obat, dan terbatasnya data longitudinal tetap menjadi kendala utama bagi translasi klinis. Integrasi desain penelitian multi-omik dan longitudinal yang berkelanjutan diperlukan sebelum penanda

epigenetik dapat diterjemahkan menjadi alat untuk deteksi dini, stratifikasi pasien, maupun pemantauan pengobatan skizofrenia.

***Kata Kunci:*** *Epigenetik, Metilasi DNA, Modifikasi histon, RNA non-coding, Skizofrenia*

## Introduction

Schizophrenia affects approximately 1% of the population worldwide and remains among the leading causes of disability in young adults, with chronic disruption of thought, perception, affect, and social function.[1,2] Twin and family studies have long established that liability to schizophrenia is highly heritable, and the largest genome-wide association study to date implicated over 280 genomic loci enriched in synaptic biology, while complementary exome sequencing identified rare coding variants conferring substantial individual risk.[3,4] Yet common and rare genetic variation together explain only a fraction of the variance in liability, and monozygotic twins who share an essentially identical genome are frequently discordant for the disorder. This gap between genetic risk and clinical manifestation has directed sustained attention toward epigenetic mechanisms, which are heritable, reversible, and environmentally responsive modifications that regulate gene expression without altering the underlying DNA sequence.

Epigenetics has increasingly been framed as the molecular bridge linking genetic vulnerability with environmental exposure across development.[2] Three broad classes of epigenetic mechanism have received the most attention in schizophrenia research: DNA methylation, in which methyl groups are added predominantly to cytosine residues within CpG dinucleotides to modulate transcriptional accessibility; histone post-translational modification, including acetylation, methylation, and related marks that alter chromatin compaction around gene promoters and enhancers; and a growing repertoire of non-coding RNAs, including microRNAs and long non-coding RNAs, that fine-tune gene expression post-transcriptionally. Because each of these mechanisms is dynamic and tissue- and time-dependent, they offer a plausible explanation for why phenotypically discordant outcomes can arise from a shared genetic background, and why environmental exposures occurring decades before illness onset, such as prenatal infection or childhood adversity, can leave a lasting molecular signature.

The past five years have seen a marked expansion of well-powered epigenome-wide association studies, chromatin profiling experiments in human postmortem neurons, and systematic reviews of non-coding RNA expression in schizophrenia, driven in part by methodological advances in methylation arrays, single-cell and single-nucleus chromatin assays, and bioinformatic integration with genetic association data.[2,5,6] At the same time, this expanding evidence base has clarified important confounds, most notably the substantial and previously underappreciated epigenetic footprint of antipsychotic medication itself, which complicates the interpretation of case-control comparisons performed in peripheral blood.[7,8]

Parallel to this observational literature, a smaller but rapidly growing body of functional and technological work has begun to test causal hypotheses directly, using genome and epigenome editing tools to manipulate specific loci in cellular and animal models of schizophrenia, and to explore whether reversing a given epigenetic mark can restore normal gene expression or behaviour. This mechanistic layer of evidence is important because the great majority of the observational epigenetic literature, by its correlational nature, cannot distinguish cause from consequence, and functional validation is therefore essential before any candidate epigenetic mechanism can be considered a plausible therapeutic target rather than a downstream marker of illness or its treatment.

This review aims to synthesize literature published between 2021 and 2026 on epigenetic mechanisms implicated in schizophrenia, organized around three core mechanistic themes: DNA methylation, histone modification, and non-coding RNA dysregulation. It further considers the developmental and environmental triggers thought to initiate these epigenetic changes, the confounding and potentially therapeutic role of antipsychotic treatment, emerging genome- and epigenome-editing approaches for functional validation, and the translational prospects and limitations of epigenetic biomarkers for clinical psychiatry. A summary table

consolidating representative studies across mechanisms is provided in the Results and Discussion section to orient readers to the overall evidence landscape before each mechanism is discussed in narrative detail.

## Literature Search Strategy

This review adopts a narrative, structured-search approach rather than a formal systematic review protocol, reflecting the breadth of mechanistic subtopics covered. The PubMed/MEDLINE, Scopus, and Web of Science databases were searched for peer-reviewed articles published from January 2021 through mid-2026, using combinations of the terms "schizophrenia", "epigenetics", "DNA methylation", "histone modification", "non-coding RNA", "microRNA", "long non-coding RNA", "epigenome-wide association study", "clozapine", "antipsychotic", "prenatal stress", and "childhood adversity". English-language original research articles, systematic reviews, and meta-analyses involving human subjects, postmortem human brain tissue, or directly relevant animal or cell models were eligible. Case reports, conference abstracts without peer-reviewed full text, and non-English sources were excluded except where an abstract provided otherwise unavailable mechanistic detail. Reference lists of identified reviews were hand-searched to capture additional primary studies. Because the field intersects substantially with genetics and clinical pharmacology, a small number of foundational genome-wide association and clinical pharmacology studies published within the same five-year window are cited to provide context for the epigenetic findings discussed.

## Epigenetic Mechanisms In Schizophrenia

Epigenetic regulation operates at multiple, partly interacting layers of the genome. DNA methylation at CpG-rich promoter and enhancer regions is generally, though not universally, associated with transcriptional repression, whereas hydroxymethylation, an oxidized methylation intermediate generated by ten-eleven translocation enzymes, appears to mark sites of active, dynamic regulation, particularly in neurons.[9] Histones can be acetylated, methylated, phosphorylated, or otherwise modified at specific lysine and arginine residues, with combinations of these marks forming a chromatin "code" that determines whether a gene locus is transcriptionally permissive or repressive. Non-coding RNAs add a further post-transcriptional layer: microRNAs typically bind to the 3' untranslated regions of target messenger RNAs to suppress translation or trigger degradation, while long non-coding RNAs can scaffold chromatin-modifying complexes, sequester transcription factors, or act as competing endogenous RNAs that sponge microRNAs away from their targets.[10,11]

A recent comprehensive review framed these three mechanisms as components of a single regulatory network that interacts bidirectionally with both common and rare genetic risk variants identified through genome-wide association and exome sequencing studies, and with environmental exposures spanning the prenatal period through adulthood.[2] This integrative framing helps explain a long-standing puzzle in schizophrenia genetics: that most genome-wide association signals fall in non-coding regulatory regions rather than coding sequence, implying that many risk variants act, at least in part, by altering the epigenetic landscape and downstream gene expression rather than protein structure directly.[3]

### *DNA Methylation Alterations*

DNA methylation remains the most extensively studied epigenetic mechanism in schizophrenia, owing largely to the relative ease of genome-wide profiling in accessible tissues such as peripheral blood. A landmark meta-analysis of blood DNA methylation across seven independent cohorts comprising 4,483 participants identified 1,048 differentially methylated positions associated with schizophrenia and 95 associated with psychosis more broadly, with evidence that the differentially methylated sites colocalized with regions previously implicated by genetic association studies.[12] Notably, many of the schizophrenia-associated methylation differences were detected almost exclusively among patients with treatment-resistant illness,

raising the possibility that they partly reflect long-term exposure to clozapine rather than the disorder itself, a confound discussed further below.[12]

**Table 1.** Representative studies of epigenetic mechanisms in schizophrenia published 2021-2026.

| Mechanism | Representative Study | Key Finding | Tissue / Design |
|---|---|---|---|
| DNA methylation (EWAS) | Hannon et al., 2021[12] | 1,048 DMPs associated with schizophrenia across 7 cohorts; overlap with treatment-resistant status | Blood; case-control meta-analysis |
| DNA methylation variance | Tesfaye et al., 2024[13] | 213 variably methylated positions; largely distinct from mean-level DMPs; sex-dependent power | Blood; multi-cohort meta-analysis |
| Methylation & clinical features | Kiltschewskij et al., 2024[14] | 1,094 probes linked to cognition, onset age, treatment resistance, functioning | Blood; deeply phenotyped cohort |
| Histone acetylation/methylation | Chen et al., 2024[16] | Increased H3K9ac, H3K27ac, H3K4me3; reduced HDAC4 in DLPFC | Postmortem cortex |
| Chromatin/BET proteins | Farrelly et al., 2022[18] | Aberrant histone acetylation and BET-protein dysregulation in neurons | Human cortical neurons |
| Oligodendroglial chromatin | Li, Xiao & Chen, 2022[19] | Histone acetylation/methylation impair OPC-to-oligodendrocyte differentiation | Review; cellular models |
| Long non-coding RNA | Zakutansky & Feng, 2022[22] | GOMAFU/MIAT dysregulation linked to genetic risk and neuronal development | Review; patient tissue |
| Non-coding RNA network | Ghafouri-Fard et al., 2021[10] | Multiple lncRNAs/miRNAs dysregulated in peripheral blood | Blood; review |
| Prenatal stress methylation | PACE consortium, 2023[25] | Maternal stressful life events linked to cord-blood methylation at ALKBH3, APTX, MyD88 | Cord blood; 12-cohort meta-analysis |
| Childhood adversity mediation | EU-GEI, 2023[26] | DNA methylation partially mediates adversity-to-psychosis pathway | Blood; multinational case-control |
| Clozapine exposure | Gillespie et al., 2024[8] | 37 DMPs and B-cell shifts associated with time on clozapine | Blood; 6-month longitudinal cohort |
| Epigenetic clock | Li et al., 2023[31] | Altered epigenetic age in drug-naive, first-episode patients | Blood; drug-naive first-episode cohort |

Subsequent work has extended these findings by examining methylation variance rather than mean methylation differences alone. A large meta-analysis encompassing more than 1,000 cases and nearly 1,000 controls found that variably methylated positions associated with schizophrenia were largely distinct from differentially methylated positions identified through conventional case-control comparisons, and that statistical power to detect these signals was substantially affected by sex-stratified analysis, indicating that aggregate, sex-naive designs may obscure biologically meaningful methylation heterogeneity.[13] Other investigators have moved beyond simple diagnostic status to examine methylation correlates of clinically important features within schizophrenia itself; in a deeply phenotyped Australian cohort of 381 patients, differential methylation was associated with cognitive status, age of onset, treatment resistance, and overall functioning, with several implicated genes also linked to other psychiatric conditions and to medical comorbidities such as elevated inflammatory markers, suggesting shared epigenetic substrates across phenotypic domains.[14]

Technological refinement has also enabled examination of the methylation code beyond simple 5-methylcytosine. A 2024 review highlighted distinctive patterns of 5-methylcytosine and its oxidized derivative, 5-hydroxymethylcytosine, in schizophrenia, with evidence that the two marks may carry partly independent and even opposing regulatory information, complicating interpretation of methylation array data that typically cannot distinguish between them.[9] Complementary genome-wide methylation risk score approaches, which aggregate methylation signal across many sites into a single weighted score, have shown that scores derived from independent blood- and brain-based epigenome-wide association studies are associated with schizophrenia case status and interact with polygenic genetic risk stratification, supporting methylation risk scores as a potential composite biomarker that adds information beyond genetic risk scores alone.[15] Collectively, this body of work indicates that DNA methylation changes in schizophrenia are extensive, heterogeneous across clinical subgroups, only partially overlapping between mean-level and variance-level analyses, and substantially shaped by sex and medication exposure, underscoring the need for carefully stratified and longitudinally designed studies going forward,[2,13]

## *Histone Modifications*

Histone modification has emerged as a complementary, mechanistically distinct layer of epigenetic dysregulation in schizophrenia. Chromatin profiling of postmortem dorsolateral prefrontal cortex from individuals with schizophrenia has found global increases in activating histone marks, including H3K9 acetylation, H3K27 acetylation, and H3K4 trimethylation, accompanied by reduced histone deacetylase activity and HDAC4 protein expression, with these activating marks further enhanced specifically among patients treated with antipsychotics that possess histone deacetylase-inhibiting properties, again illustrating the difficulty of separating illness-related from medication-related signal in postmortem and clinical samples.[16,17] A high-resolution chromatin profiling study of human cortical neurons reported aberrant histone acetylation and dysregulation of bromodomain and extra-terminal (BET) family reader proteins in schizophrenia, implicating disrupted chromatin reader function, rather than histone marks alone, as a contributor to aberrant transcriptional output.[18]

Cell-type-specific vulnerability has also become a focus of recent histone research. Oligodendroglial lineage cells, which myelinate axons and have long been implicated in schizophrenia white-matter pathology, show altered patterns of histone acetylation and methylation that appear to impair the differentiation of oligodendrocyte precursor cells into mature, myelin-producing oligodendrocytes, offering a candidate mechanistic link between epigenetic dysregulation and the white-matter abnormalities repeatedly observed on neuroimaging in schizophrenia.[19] Gene-specific studies have implicated BRD1, a schizophrenia-associated chromatin reader gene, in maintaining normal histone H3 acetylation; brain-specific inactivation of BRD1 in animal models produces abnormal histone H3 acetylation and N-terminal tail clipping alongside failure-to-thrive and increased seizure susceptibility, providing causal, rather than purely correlational, evidence that disruption of a single schizophrenia risk gene can propagate broader chromatin dysregulation.[20] Consistent with the cortical findings above, a 2024 postmortem study reported that several permissive histone modifications were broadly enhanced in the dorsolateral prefrontal cortex of individuals with schizophrenia relative to controls, reinforcing a picture of generalized, rather than locus-restricted, chromatin de-repression in this brain region.[17]

A 2023 narrative review synthesized this evidence to argue that histone deacetylases and histone methyltransferases constitute plausible, druggable therapeutic targets in schizophrenia, noting that several histone deacetylase inhibitors already used in oncology or under investigation for other psychiatric disorders produce measurable changes in schizophrenia-relevant gene expression in preclinical models, although clinical efficacy and safety data in schizophrenia specifically remain limited.[21] Taken together, the histone modification literature of the past five years converges on a model in which both global chromatin de-repression in cortical tissue and gene-specific disruption at risk loci such as BRD1 contribute to aberrant transcription, with cell-type specificity, particularly within the oligodendroglial lineage, helping to explain region- and circuit-specific aspects of the schizophrenia phenotype.

### *Non-Coding RNA Dysregulation*

Non-coding RNAs constitute a third major axis of epigenetic dysregulation in schizophrenia. A comprehensive 2021 review of peripheral blood expression studies catalogued numerous long non-coding RNAs and microRNAs with altered expression in schizophrenia, noting that transcripts such as Gomafu, PINT, GAS5, IFNG-AS1, FAS-AS1, PVT1, and TUG1 were generally down-regulated, whereas MEG3, THRIL, HOXA-AS2, Linc-ROR, SPRY4-IT1, UCA1, and MALAT1 were up-regulated, alongside dysregulation of several microRNAs including miR-30e, miR-130b, miR-193a-3p, miR-181b, miR-34a, miR-346, and miR-7.[10] The authors noted that dysregulation of these transcripts in accessible blood samples could in principle serve a diagnostic or stratification function, although replication across independent cohorts and standardization of measurement platforms remain limited.[10]

Among individual long non-coding RNAs, GOMAFU, also known as MIAT or RNCR2, has received particular mechanistic attention. A focused 2022 review described how GOMAFU is implicated in genetic risk for schizophrenia, regulates neuronal development through interaction with RNA-binding splicing factors, and shows altered expression in patient-derived tissue, positioning it as both a candidate disease mechanism and a potential biomarker.[22] A separate 2022 review broadened this analysis to long non-coding RNAs as a class, summarizing evidence on disease-associated genetic variation within long non-coding RNA loci, expression changes associated with treatment response to second-generation antipsychotics, and candidate downstream signaling pathways, while emphasizing that most findings to date derive from relatively small, cross-sectional case-control cohorts.[11,23]

Bioinformatic and network-based approaches have further mapped how long non-coding RNAs may interact with microRNAs and messenger RNAs within competing endogenous RNA networks relevant to schizophrenia, integrating publicly available expression datasets to nominate candidate regulatory axes for downstream functional validation.[24] While these non-coding RNA findings are generally less mature than the DNA methylation and histone modification literature, in part because standardized, well-powered genome-wide non-coding RNA association studies analogous to methylation EWAS remain less common, the convergence of genetic, expression, and functional evidence around specific transcripts such as GOMAFU suggests that non-coding RNAs are unlikely to be epiphenomenal and instead represent a biologically meaningful, if still incompletely characterized, layer of epigenetic dysregulation in schizophrenia.[22]

## Gene-Environment Interactions And Developmental Origins

A central premise of epigenetic research in schizophrenia is that epigenetic marks, unlike the DNA sequence itself, can be shaped by environmental exposure, providing a plausible biological substrate for the well-replicated clinical observation that obstetric complications, prenatal infection, urbanicity, migration, cannabis use, and childhood adversity each independently elevate schizophrenia risk. The past five years have produced increasingly large, prospective studies examining how such exposures become biologically embedded through DNA methylation.

### *Prenatal Exposures*

At the prenatal stage, large consortium-based studies have examined cord blood methylation in relation to maternal stress exposure during pregnancy. Cumulative maternal stressful life events during pregnancy have been associated with differential methylation of specific genes involved in neurodegeneration, immune signalling, and cellular function in newborn cord blood, with somewhat distinct methylation signatures associated with different stressor subtypes such as interpersonal conflict, abuse, and bereavement.[25] While these cord blood studies were not restricted to schizophrenia outcomes specifically, they provide direct mechanistic support for the broader Developmental Origins of Health and Disease framework that has long informed the neurodevelopmental hypothesis of schizophrenia, in which adverse prenatal exposures are

thought to programme later vulnerability to psychiatric illness via epigenetic, rather than purely structural, mechanisms.

### *Childhood Adversity and Trauma*

At the level of postnatal and childhood adversity, the EU-GEI multinational case-control study examined whether DNA methylation across the epigenome mediated the well-established association between childhood adversity and first-episode psychosis, finding evidence that methylation changes at specific genomic regions partly accounted for this relationship, although a substantial proportion of the adversity-psychosis association remained unexplained by the measured methylation sites, suggesting that childhood adversity acts through multiple convergent biological pathways of which DNA methylation is only one.[26] A complementary, more targeted study examined methylation within CYP17A1, a gene situated within a schizophrenia genetic risk locus and involved in glucocorticoid steroid synthesis, as a candidate mediator between childhood adversity and stress-related symptom phenotypes in patients with schizophrenia, illustrating how candidate-gene and genome-wide approaches are increasingly being combined to test specific, hypothesis-driven mediation pathways rather than relying on hypothesis-free discovery alone.[27]

## Epigenetics And Antipsychotic Treatment

Antipsychotic medication is now recognized as a major, and for some time underappreciated, confound in epigenetic studies of schizophrenia, because nearly all clinically ascertained patients are medicated at the time of sample collection, making it difficult to disentangle illness-related from drug-related epigenetic signal. At the same time, this same property raises the possibility that antipsychotics, and second-generation agents in particular, exert at least part of their therapeutic effect through epigenetic remodeling, an idea that has motivated a distinct line of pharmaco-epigenetic research over the past five years.

A systematic review of DNA methylation and histone modification changes associated with antipsychotic treatment synthesized evidence across cell culture, animal, and human studies, concluding that different antipsychotic classes produce distinguishable methylation signatures, with clozapine in particular associated with widespread hypomethylation across the epigenome relative to other agents.[7] A head-to-head comparison of genome-wide methylation changes associated with several different antipsychotic agents in patients with schizophrenia similarly found agent-specific methylation profiles, reinforcing that "antipsychotic exposure" cannot be treated as a single, undifferentiated confound in case-control methylation studies.[28] Risperidone-induced methylation changes in first-episode, drug-naive patients have additionally been shown to parallel concurrent changes in neuroimaging measures and cognitive performance, suggesting that peripheral methylation changes occurring early in treatment may have functional correlates detectable at the level of brain structure and cognition rather than being purely epiphenomenal blood-based markers.[29]

Clozapine, reserved for treatment-resistant schizophrenia, has received particular attention given its distinctive efficacy and side-effect profile. A longitudinal study following patients with treatment-resistant schizophrenia across two international cohorts for up to six months after clozapine initiation identified significant, non-linear changes in estimated blood cell-type proportions, particularly B-cell fractions, together with 37 differentially methylated positions associated with time on clozapine, and demonstrated that many of the methylation differences previously attributed to schizophrenia or treatment-resistant schizophrenia status in earlier cross-sectional studies likely reflect clozapine exposure itself rather than diagnosis.[8,30] This longitudinal design represents an important methodological advance over earlier cross-sectional clozapine studies, because it allows medication effects to be assessed within the same individuals over time rather than inferred from cross-sectional comparisons confounded by unmeasured baseline differences between treatment groups.[30]

Epigenetic clock analyses, which estimate biological age from methylation patterns and have been used as general markers of accelerated aging and cellular stress across medicine, have also been applied in schizophrenia. A 2023 study of drug-naive, first-episode patients found altered epigenetic age estimates prior

to any antipsychotic exposure, indicating that at least some epigenetic aging signal in schizophrenia precedes treatment and cannot be attributed solely to medication, even though medication clearly contributes additional methylation change once treatment begins.[31] Collectively, this body of work indicates that antipsychotic medication, and clozapine especially, is not merely a nuisance confound to be statistically adjusted away but an active epigenetic modulator in its own right, with both diagnostic and therapeutic implications that future study designs must explicitly account for through drug-naive baseline sampling and longitudinal follow-up.

## Genome And Epigenome Editing: Toward Functional Validation

Because observational epigenome-wide association and histone-profiling studies cannot by themselves establish causality, an important complementary strand of research over the past five years has applied genome and epigenome editing technologies, most notably CRISPR/Cas9 and its catalytically inactive derivative, dCas9, to test whether manipulating specific epigenetic marks at schizophrenia risk loci produces predicted changes in gene expression, cellular phenotype, or behavior.

Fusing dCas9 to functional effector domains creates programmable epigenetic editors capable of activating or repressing a target locus without altering the underlying DNA sequence; commonly used effectors include the KRAB repressor domain, the VP64, p65, and Rta transactivation domains, and catalytic domains derived from the DNA dioxygenase TET1 or histone-modifying enzymes such as p300 and LSD1.[32] A 2023 review of CRISPR/Cas9-based approaches in psychiatric research catalogued applications ranging from correcting risk-associated point mutations in patient-derived induced pluripotent stem cells to generating isogenic cellular models that isolate the functional effect of a single risk variant, concluding that genome and epigenome editing could meaningfully advance mechanistic understanding of schizophrenia even though direct therapeutic application in patients remains distant.[33]

A more detailed 2023 review focused specifically on CRISPR/Cas-based epigenetic editors in schizophrenia and other neurodevelopmental disorders, describing how dCas9-KRAB-mediated repression of specific promoters induces localized histone deacetylation and methylation, producing stable, locus-specific transcriptional silencing that can be used to test the functional consequence of candidate risk genes in neuronal and stem-cell-derived models.[34] The same review distinguished two complementary research strategies: using epigenetic editors to manipulate natural regulatory machinery at known risk loci to establish causal gene-phenotype relationships, and using them as an investigative tool to determine whether a given genome-wide association signal acts through a regulatory, epigenetic mechanism rather than through direct effects on protein-coding sequence.[34]

Non-coding RNA loci have been a particular focus of CRISPR-based functional work, given the difficulty of establishing causality for non-coding regulatory elements using conventional genetic association methods alone. A dedicated review proposed a systematic strategy for using CRISPR/Cas9 to edit schizophrenia-associated microRNA and long non-coding RNA genes in human cell lines and animal models, arguing that this approach could help establish which of the many non-coding RNA associations described in Section 3.3 reflect genuine causal contributors to disease biology rather than secondary correlates.[35] More recent translational work has extended these tools toward therapeutic exploration: preclinical studies using CRISPR/dCas9-p300 epigenome editing to activate BDNF and glutamatergic signaling genes have been reported to ameliorate synaptic impairments in animal models of severe mood disorders, and induced pluripotent stem cell-derived neuronal models from patients with schizophrenia and depression have confirmed disease-associated methylation abnormalities at synaptic plasticity loci, establishing patient-specific cellular platforms on which such editing approaches could eventually be tested.[36]

Despite this promise, substantial obstacles separate current epigenome-editing research from clinical application in schizophrenia. Delivery of large editing constructs to postmitotic neurons in the human brain remains technically demanding, the durability and specificity of induced epigenetic changes in vivo are incompletely characterized, and, as with any powerful gene-regulatory technology, off-target and long-term safety considerations require extensive preclinical characterization before any human application could be

contemplated.[33,34] For the present, the principal value of epigenome editing in schizophrenia research lies in hypothesis testing and mechanistic validation of the correlational findings summarized in the preceding sections, rather than in imminent clinical translation.

## Epigenetic Biomarkers And Clinical Translation

The translational appeal of epigenetic findings in schizophrenia rests on the prospect that peripheral, minimally invasive samples such as blood could one day support early detection, diagnostic stratification, or treatment monitoring, complementing or eventually supplementing purely clinical and genetic risk assessment. Methylation risk scores, which aggregate weighted methylation signal across many genomic sites, have shown association with case status and have demonstrated some ability to explain genetic risk variance beyond polygenic risk scores derived from DNA sequence alone, when scores are derived from either blood or postmortem brain tissue EWAS data, suggesting at least partial cross-tissue informativeness despite the brain being the primary tissue of pathological relevance.[15] Epigenetic clocks similarly offer a single, interpretable composite metric that may capture cumulative biological stress relevant to illness course, although as noted above their interpretation in schizophrenia is complicated by both illness-related and medication-related contributions that current designs cannot always fully separate.[31]

A recent comprehensive review emphasized that continuing technological development, including single-cell and single-nucleus methylation and chromatin profiling, long-read sequencing capable of resolving methylation and hydroxymethylation separately, and integration of methylation data with genetic, transcriptomic, and proteomic datasets within unified multi-omic frameworks, is likely to substantially improve the resolution and interpretability of epigenetic findings in schizophrenia over the coming years.[2] Nonetheless, several structural barriers to clinical translation remain. Tissue specificity is a persistent concern, because the great majority of epigenome-wide association studies use peripheral blood for practical and ethical reasons, yet schizophrenia is fundamentally a disorder of brain tissue, and methylation patterns at many loci differ substantially between blood and brain.[2,14] Medication confounding, discussed at length above, means that case-control comparisons performed in clinically ascertained, medicated cohorts cannot cleanly separate illness biology from treatment effects without drug-naive baseline sampling or longitudinal designs that are logistically demanding and consequently rare.[8,30] Finally, most published studies remain cross-sectional and modestly powered relative to the scale now standard in genetic association research, limiting the precision and replicability of effect size estimates and the feasibility of fine-grained subgroup analyses by sex, ethnicity, or clinical subtype.[13]

## Challenges And Future Directions

Several priorities emerge from this review for the next phase of epigenetic research in schizophrenia. First, longitudinal designs that sample patients before antipsychotic initiation and at multiple subsequent time points are needed to disentangle illness-related from medication-related epigenetic change, building on the methodological model established by recent clozapine cohort studies.[30] Second, sex-stratified and adequately powered analyses should become standard practice given recent evidence that aggregate, sex-naive designs can obscure biologically meaningful methylation variance.[13] Third, greater integration across mechanistic layers, combining DNA methylation, histone modification, and non-coding RNA data within the same cohorts, would help clarify whether these mechanisms act largely independently or converge on shared downstream gene networks, a question that remains largely unresolved because most existing studies examine only a single epigenetic layer in isolation.[2]

Fourth, expanded application of epigenome-editing tools to schizophrenia risk loci nominated by genome-wide association and epigenome-wide association studies would help move the field from correlation toward causal validation, following the strategy already outlined for non-coding RNA genes and further extended by recent CRISPR/dCas9 epigenome-editing work in related psychiatric phenotypes.[34-36] Fifth, single-cell and single-nucleus profiling technologies capable of resolving methylation, hydroxymethylation, and

chromatin accessibility within specific neuronal and glial subpopulations should be prioritized over bulk-tissue approaches, given the cell-type-specific vulnerability already demonstrated within the oligodendroglial lineage.[19] Finally, validation of candidate biomarkers such as methylation risk scores and epigenetic clocks in independent, ethnically diverse, and clinically well-characterized cohorts, ideally including those from under-represented regions such as Southeast Asia, will be necessary before such measures can be responsibly considered for clinical use. For a regional academic and clinical context such as Indonesia, where genetic counseling and psychiatric genomics infrastructure are still developing, prospective collection of well-annotated, drug-naive baseline biospecimens alongside standard clinical assessment would represent a valuable and currently underutilized contribution to this global evidence base.

## Conclusions

Evidence accumulated over the past five years indicates that DNA methylation, histone modification, and non-coding RNA dysregulation each contribute meaningfully to the molecular pathology of schizophrenia, acting as mechanistic intermediaries between polygenic genetic risk and environmental exposures spanning the prenatal period through adulthood. Differentially methylated positions converge with genetic risk loci, histone acetylation and methylation are altered in a regionally and cell-type-specific manner in postmortem cortical tissue, and a growing set of long non-coding RNAs and microRNAs show reproducible dysregulation in blood and brain. At the same time, antipsychotic medication, and clozapine in particular, has emerged as a substantial and previously underappreciated confound that future study designs must explicitly accommodate through drug-naive baseline sampling and longitudinal follow-up. While methylation risk scores and epigenetic clocks offer promising candidate biomarkers, tissue specificity, medication confounding, and a continuing shortage of adequately powered longitudinal and multi-omic studies currently limit clinical translation. Closing these gaps through better-designed, more diverse, and mechanistically integrated studies represents the most promising path toward epigenetically informed early detection, stratification, and treatment of schizophrenia.

### Conflict of Interest

The author declares that there is no conflict of interest associated with this review.

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