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REVIEW

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Epigenetics factors in schizophrenia: future directions for etiologic and therapeutic study approaches

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Abstract

Schizophrenia is a complex, heterogeneous, and highly disabling severe mental disorder whose pathogenesis has not yet been fully elucidated. Epigenetics, as a bridge between genetic and environmental factors, plays an important role in the pathophysiology of schizophrenia. Over the past decade, epigenetic-wide association studies have rapidly become an important branch of psychiatric research, especially in deciphering the molecular mechanisms of schizophrenia. This review systematically analyzes recent advances in epigenome-wide association studies (EWAS) of schizophrenia, focusing on technological developments. We synthesize findings from large-scale EWAS alongside emerging evidence on DNA methylation patterns, histone modifications, and regulatory networks, emphasizing their roles in disease mechanisms and treatment responses. In addition, this review provides a prospective outlook, evaluating the impact that technological developments may have on future studies of schizophrenia. With the continuous advancement of high-throughput sequencing technology and the increasing maturity of big data analysis methods, epigenetics is expected to have a significant impact on the early diagnosis, prognosis assessment and even personalized treatment of schizophrenia.

Keywords Schizophrenia, Epigenetics, DNA methylation, Histone modifications, Non-coding RNA

Introduction

Schizophrenia is a serious mental disorder with an insidious, heterogeneous and complicated onset and poor prognosis, characterized by a series of symptoms such as hallucinations, delusions, disorganized thinking, emotional flatness, cognitive deficits, or behavioral abnormalities, which affects about 1% of the global population, resulting in a huge burden of disease [1–3]. Even though research in the past decades has yielded remarkable genetic findings that schizophrenia is a polygenic disorder, the etiology of schizophrenia remains poorly understood.

Genome-wide association studies (GWAS) have provided genetic evidence for the pathogenesis of schizophrenia, with 287 genetic loci associated with schizophrenia reported in 2022 [4]. On the other hand, the "second hit" hypothesis of schizophrenia has enormous implications in etiology, indicating that a variety of environmental factors, such as adverse events before and after pregnancy, as well as childhood and adolescent traumas including abuse or neglect, stressful events and social ostracism, may interact with genetic risk factors to trigger the onset of schizophrenia [5, 6]. Epigenetics, for its part, explores the interrelationships

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between environmental risk factors and genetics, providing a novel perspective on the pathophysiological mechanisms and genetic variation of schizophrenia, and potentially revealing new therapeutic targets [7]. Recent technological advances in epigenome-wide association studies (EWAS) have revolutionized our understanding of the epigenetic landscape of schizophrenia.

In recent years, the emergence of high-throughput sequencing and comprehensive methylation arrays has facilitated the identification of novel epigenetic signatures associated with disease onset, progression, and treatment response, with recent EWAS employing these technologies to assess epigenetic marks across the genome [8, 9]. These EWASs have been instrumental in identifying differentially methylated regions and histone modification patterns that are associated with schizophrenia [10, 11]. Indeed, by comparing the epigenetic profiles of schizophrenia patients with those of healthy controls, researchers have begun to unravel the complex epigenetic architecture that may underlie the disorder's phenotypic variability [6]. Recent EWAS have revealed several key findings: the identification of differential methylation patterns in specific genomic regions, the discovery of novel epigenetic markers associated with treatment response, and the integration of methylation data with genetic risk factors [11–13]. Furthermore, EWAS have identified numerous epigenetic modifications in schizophrenia that are involved in critical biological pathways, including neurodevelopment, synaptic plasticity and immune function [5, 14, 15]. For instance, aberrant methylation patterns have been found in genes related to dopaminergic and glutamatergic neurotransmission, suggesting a link between epigenetic regulation and the neurotransmitter imbalances observed in schizophrenia [16, 17].

The etiology of schizophrenia is intricate and this brief review highlights the potential pathophysiologic role of epigenetics in schizophrenia and the relationship with clinical symptoms and therapies. Integrating epigenetic data with schizophrenia information will provide a more holistic view of the disease mechanisms.

Literature selection approach

While this is not a systematic review, we applied specific criteria to ensure the quality and relevance of included studies. We focused on peer-reviewed publications from 2000 to 2024, with emphasis on recent developments since 2020. For inclusion, studies needed to: (1) directly investigate epigenetic mechanisms in schizophrenia; (2) employ validated measurement methods; (3) include appropriate controls; and (4) provide clear statistical analysis. We prioritized studies with larger sample sizes ($\geq$50 participants for human studies) and those that provided replication or validation of findings. Both clinical and basic research studies using various sample types (post-mortem brain tissue, peripheral blood, and animal models) were considered.

Regulatory processes in epigenetics

Epigenetic studies have revealed that many exogenous and endogenous factors, such as environmental exposures, developmental processes and gene-environment interactions influence gene expression without altering gene sequences via a variety of primary processes that include DNA methylation, histone modification and non-coding RNA (ncRNA) expression [18, 19]. DNA methylation is a complex and dynamic epigenetic modification process, wherein a methyl group (-CH3) is added to the fifth carbon atom of cytosine in DNA molecules by specific enzymes—DNA methyltransferases—predominantly occurring at the cytosine and guanine (CG) dinucleotide sequences, known as CpG sites [20, 21]. This chemical modification not only regulates gene expression and affects gene activity but also plays a crucial role in cell differentiation, development, and various physiological and pathological processes. Histone modification refers to the post-translational chemical modifications of histone proteins within chromatin, including but not limited to acetylation, methylation, and phosphorylation [22]. These modifications predominantly occur on the tails or globular domains of histones in nucleosomes, the fundamental units of chromatin [23]. By altering the interaction between histones and DNA, these modifications can influence chromatin structure and dynamics, thereby regulating gene expression and other DNA-dependent processes [24]. The ncRNA molecules do not encode proteins but can be involved in regulating gene expression, such as preventing the production of proteins by interfering with the translation or stability of mRNAs [25]. The etiology of schizophrenia is still uncertain, and existing research has indicated that it may be the result of a combination of genetic and environmental risk factors that are directly related to relevant regulatory mechanisms of epigenetics.

Relationship between environmental risk factors and schizophrenia

The pathogenesis of schizophrenia is multifaceted, with genetic, biochemical and neuroanatomical factors having a significant impact on the onset of schizophrenia; however, environmental risk factors as "second-hit" predisposing factors such as maternal pregnancy, stress, trauma and other undesirable factors play an important role in the occurrence of this disorder. As shown in Fig. 1.

Pregnancy is a crucial period for fetal brain development. Although previous study suggested that

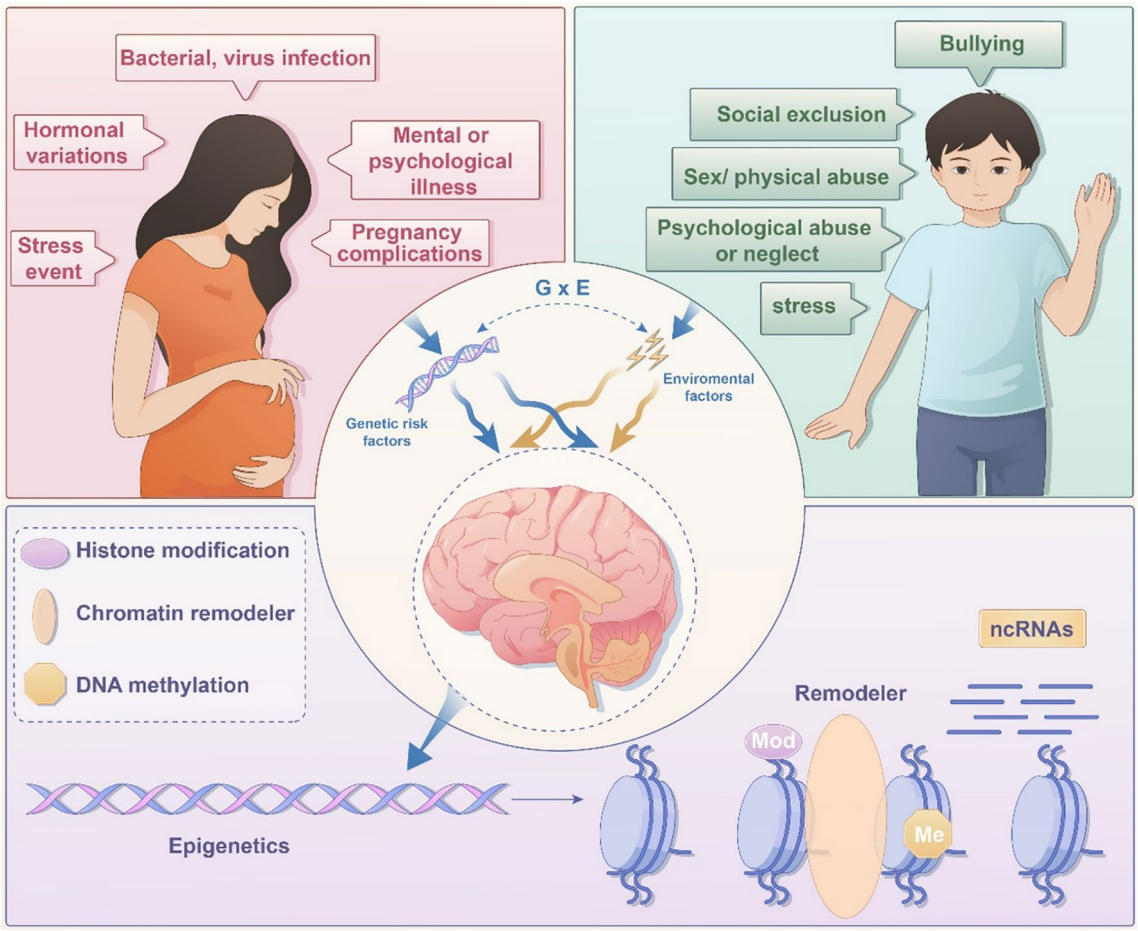

Fig. 1 Overview of the epigenetics of schizophrenia. Genetic and environmental risk factors interact and play an important role in the pathogenesis of schizophrenia. Negative factors during maternal pregnancy and adverse life events during childhood and adolescence may possibly trigger altered epigenetics

adverse events during this period may activate microglia in the fetal brain, potentially leading to significant impacts on future psychological health, the evidence in this area was still variable and influenced by factors such as sex and the timing of gestation [26]. Existing research provides the first empirical evidence that early-life environmental conditions during pregnancy can lead to epigenetic alterations in humans, which persist throughout an individual's lifetime [27]. It has been shown that experiencing extreme stress and adverse life events such as famine, emotional stress and substance abuse may stimulate alterations in the epinephrine system, increasing the risk of development of schizophrenia in offspring [28, 29]. Trauma suffered by individuals during childhood or adolescence, such as abuse or neglect, affects the stress system and may contribute to long-term neurodevelopmental and emotional regulation difficulties, and has been recognized as an important predictor of the onset of schizophrenia [30–32]. Chronic stress or sudden major stressful life events, including unemployment and loss of a loved one, among other factors, has also been implicated in the onset of schizophrenia [33–35]. Stressful events may trigger or exacerbate schizophrenia, especially in adolescents and those who are genetically predisposed to the disease [36, 37]. Alterations in hormone and cytokine levels and neuronal plasticity resulting from the stress response may also be an important factor in the pathogenesis of schizophrenia [38–40]. Furthermore, prolonged social exclusion has been shown to increase the likelihood of schizophrenic episodes by increasing an individual's psychological stress and disrupting social support systems [41, 42]. Likewise, social exclusion has been found to be associated with cognitive deficits, decreased self-efficacy and increased negative emotions [43, 44].

Environmental factors may play a crucial role in the development of schizophrenia, especially when

they interact with genes. Early interventions targeting environmental factors and ongoing psychosocial support may help to reduce the onset of schizophrenia and improve patient prognosis. Future research needs to focus on how to fine-tune interactions between environmental factors interact genes to develop more effective prevention and treatment strategies.

Epigenetics and schizophrenia

DNA methylation and schizophrenia

DNA methylation levels are altered in patients with schizophrenia and correlated with clinical symptoms

Development and functional maintenance of the nervous system depend on precise, spatiotemporal-specific regulation of gene expression, which is affected by DNA methylation-mediated gene modifications that in turn regulate neuronal differentiation and maturation as well as regulate neural network formation [45]. For example, the regulation of brain-derived neurotrophic factor (BDNF), which plays a key role in brain developmental processes and neuroplasticity [46, 47], is strongly associated with DNA methylation. Furthermore, the *BDNF* gene and its methylation are known to be significantly associated with the etiology of schizophrenia [48, 49]. Several studies have demonstrated that abnormal DNA methylation of genes such as *GAD67*, *MARLIN-1*, *KCNJ6*, *HELT*, *DRDs* and *NR3B*, which encode for γ-aminobutyric acid (GABA), glutamate, 5-hydroxytryptophan, N-methyl-D-aspartate receptors (NMDAR) and dopamine, among others—neurotransmitters associated with the pathological mechanisms of schizophrenia—occurs in schizophrenic patients [10, 16, 50]. Mill et al. conducted a comprehensive DNA methylation analysis of the major psychosis, revealing distinct epigenetic profiles in schizophrenia [51]. Their seminal work demonstrated significant disease-associated methylation differences at numerous loci, particularly in genes involved in neurotransmitter metabolism and neurodevelopment. The affected genes are also involved in a variety of key processes in neurodevelopment and neurotransmission, such as the methylation the *MB-COMT* promoter and *DRD2* and *NR3C1* genes, all of which are closely related to the dopamine D2 receptor. Interestingly, expression of these genes is significantly altered in schizophrenia patients compared with healthy controls, and has been shown to affect neurotransmitter signaling [52] and the DNA methylation status of the *TCF4* promoter region [53]. Changes in the methylation of *CCL17*, *MMP10* and *PRG2* have also been shown to be significantly associated with the core symptom of cognitive dysfunction in schizophrenia [13]. In addition, hypermethylation of the *SHANK3* promoter has been found to be negatively correlated with the left inferotemporal cortex surface volume and positively correlated with negative symptoms in patients with schizophrenia [54]. A study of postmortem brain examinations in patients with schizophrenia found altered methylation of *RELN*, *GAD67*, *COMT*, *NR3B*, *GRIA2* and *FOXP2* genes [10]. DNA methylation is associated with the pathophysiology of schizophrenia, providing new perspectives on explaining the etiology of this complex disorder.

DNA methylation correlates with treatment response in schizophrenia

DNA methylation positions (DMPs) or regions (DMRs) influence patient response to treatment, as found in patients treated with the antipsychotic drug risperidone. Interestingly, *CYP46A1*, *SPATS2* and *ATP6V1E1* have a significant number of DMPs, whereas the two most significant DMRs were located on Chr7 and Chr9, corresponding to the *PTPRN2* and *EHMT1 gene, respectively*, suggesting that alterations in the methylation of specific genes associated with the response to antipsychotics are related to synaptic function and neurotransmission [55]. Recently, the latest epigenome-wide study identified 82 major methylation loci related to antipsychotic drug treatment [56]. In particular, *MTHFR*, which is significantly associated with schizophrenia, was shown to affect histamine metabolism, catecholamine metabolism, serotonin metabolism, oxidative stress, DNA methylation and nicotinamide synthesis, and has become a hot research area in the targeted treatment of severe mental disorders [57]. Furthermore, the interaction of the risk genes *LINC01795*, *DDHD2*, *SBNO1*, *KCNG2*, *SEMA7A* and *RUFY1* and epigenetics, by methylation quantitative trait loci analysis, relevant to schizophrenia has been linked to treatment response [58]. In patients with tardive dyskinesia (TD), a severe adverse reaction to medications in schizophrenia, the methylation level of the *CYP2E1* gene promoter at the CpG sites was lower than that of healthy controls and non-TD patients, suggesting that aberrant DNA methylation may be a potential etiology of TD [59]. The DNA methyltransferase 1 inhibitor RG108 was found to reduce the hypermethylation status of *Gad67*, *Reln* and *Bdnf* in a mouse model, providing a new research approach for the treatment of schizophrenia [60]. Recent review has highlighted the potential role of epigenetic regulation in TRS, particularly focusing on the relationship between DNA methylation patterns of genes such as *Gad1*, *Reln*, and *Bdnf*, and the therapeutic effects

Table 1 Key DNA methylation findings in schizophrenia studies

Gene/Region	Sample type	Key findings	References
BDNF	Blood	BDNF Val66Met polymorphism is associated with positive symptoms, cognitive function, and antipsychotic treatment response in schizophrenia	Farcas et al. [48]
MB-COMT, DRD2, NR3C1	Blood	Methylation status of MB-COMT, DRD2, and NR3C1 differentiates schizophrenia from controls	Aytac et al. [52]
TCF4	Peripheral Blood	Altered methylation and expression profiles in drug-free patients	Yazarlou et al. [53]
SHANK3	PBMCs	Methylation levels correlated with negative symptoms and left inferotemporal cortex volume	Ni et al. [54]
CYP2E1	Blood	Lower methylation levels in promoter region of CYP2E1 gene associated with schizophrenia and tardive dyskinesia	Zhang et al. [59]
Gad67, Reln, Bdnf	Brain tissue	Hypermethylation reduced by DNA methyltransferase 1 inhibitor RG108	Wawrzczak-Bargiela et al. [60]

of antipsychotics including clozapine and mGlu2/3 receptor agonists [61]. As shown in Table 1. However, the results of studies on the association of DNA methylation with treatment-resistant schizophrenia (TRS) have been inconsistent. The inconsistent results regarding DNA methylation in TRS may be attributed to several factors: (1) the intrinsic pathophysiological characteristics of TRS, (2) interspecies differences between human and murine models, and crucially, (3) tissue-specific variations in epigenetic modifications. For instance, while Chen et al. demonstrated that specific blood DNA methylation patterns correlate with functional alterations in the dorsolateral prefrontal cortex and hippocampus [62], the direct extrapolation of peripheral findings to brain tissue necessitates careful consideration.

Perspectives on DNA methylation in schizophrenia studies

DNA methylation has become a promising biomarker for the diagnosis and treatment of schizophrenia due to its dynamic and reversible nature, which is the focus of ongoing research as to whether it can be used for early identification of schizophrenia patients, monitoring of disease progression and prediction of treatment effects. Meanwhile, specific blood DNA methylation characteristics of schizophrenia are associated with functional alterations in the dorsolateral prefrontal cortex and hippocampus, as well as with methylation differences in postmortem brain samples [62], and epigenetic clocks may bridge the gap between risk factors and aging in schizophrenia and potentially predict aging outcomes [63]. Further studies integrating large-scale cohort analyses and molecular mechanism investigations are essential to elucidate the complex role of epigenetics in schizophrenia and translate this knowledge into clinical applications to enhance patient quality of life.

Histone modifications and schizophrenia

Histone modifications constitute an important epigenetic mechanism that affects chromatin structure and gene expression, and mainly comprise four forms: histone methylation, deacetylation, histone acetylation and phosphorylation. Histone acetylation is commonly associated with the activation of gene expression, whereas histone methylation can induce the activation or inhibition of gene expression depending on the amino acid residue and the extent to which it occurs [64–66]. It is important to note that histone modification patterns exhibit substantial tissue specificity. While postmortem brain studies provide direct evidence of epigenetic alterations in relevant neural tissues (e.g., HDAC2 changes in the dorsolateral prefrontal cortex) [67, 68], findings from peripheral tissues should be interpreted with caution.

Histone modifications are altered in schizophrenia and correlate with clinical symptoms

Histone modifications alter the compactness of chromatin, which in turn affects the accessibility of regulatory proteins, such as transcription factors, to DNA [69, 70]. It has been shown that variants in the histone deacetylase of NAD+, commonly known as acetylase (SIRT)− 1, increase the risk of developing schizophrenia [71]. Furthermore, schizophrenia risk gene variants are enriched in the histone H3K4me methylation region of the prefrontal cortex, and multiple loci related to the upper- and lower-regulation of schizophrenia risk gene expression were identified in the H3K4me chromatin region [72]. Variations in histone modifications have been considered as one of the possible molecular bases of clinical symptoms in schizophrenia. Interestingly, histone acetylation and methylation have been found to determine oligodendrocyte and myelin susceptibility in schizophrenia, and histone acetylase and methylase activities are severely

dysregulated in schizophrenia [14]. Meanwhile, the histone modification-related genes *H3F3B* and *NSD2* have been found to be associated with clinical symptoms schizophrenia [73], and the relationship between histone acetylation and cognitive deficits in schizophrenia has also been reported [74]. Furthermore, significantly reduced levels of the histone deacetylase HDAC2 in the dorsolateral prefrontal cortex were found in a study of the postmortem brain of patients with schizophrenia [67]. Taken together these findings suggest that histone modifications may be important epigenetic regulators affecting schizophrenia.

Histone modifications associated with schizophrenia treatment

Abnormalities in histone modifications may be related with schizophrenia pathogenesis, treatment response and genetic predisposition [75]. Histone modifications have become the centerpiece of the therapeutic outcomes of several antipsychotics such as quetiapine, clozapine, risperidone, olanzapine and aripiprazole, and may be possible predictors of therapeutic effects [76, 77]. In addition, histone modifying enzymes may have potential therapeutic roles in schizophrenia. For example, as reported by Kurita et al. [78] the mGlu2 receptor gene was found to be downregulated by histone deacetylation in the frontal cortex of schizophrenia patients and mice administered long-term doses clozapine and risperidone. The authors also found increased expression of *HDAC2* and decreased expression of mGlu2 in the prefrontal cortex of mouse models induced to have schizophrenia-like behavior. Furthermore, the expression of three H3K9me-specific scavenging histone demethylases, KDM4B, KDM1A and PHF2, were found to be increased in olanzapine-treated rats [79]. These findings provide new ideas for therapeutic research to understand histone modification abnormalities in schizophrenia. Targeting specific histone modification by using pharmacological interventions that modify enzymes may help to correct modification abnormalities. For example, HDAC inhibitors of histone deacetylase have been demonstrated to modulate gene expression and improve cognitive dysfunction and other related schizophrenia symptoms [61]. Although the application of such agents is still in the exploratory phase, the findings suggest the possibility of histone-modifying enzymes as potential therapeutic targets for schizophrenia. Histone modifications in schizophrenia and treatment response as shown in Table 2.

The ncRNA and schizophrenia

The microRNA and schizophrenia

The microRNAs (miRNAs) are a class of small molecule RNAs of about 22 nucleotides, which regulate gene expression by complementary pairing with the 3' non-coding region of target messenger RNA (mRNA). In the nervous system, miRNAs regulate a variety of life activities such as neuronal differentiation, synapse formation, and plasticity, which are essential for the normal development and function of the nervous system [80]. For example, miRNAs are able to respond to environmental stimuli and participate in cognitive processes such as learning and memory by precisely regulating the stability of target mRNAs or their protein synthesis [81, 82]. In individuals with schizophrenia, several studies have identified altered expression levels of a range of miRNAs, several of which may be involved in in pathophysiological processes such as altered dopamine, glutamate, GABA serotonin synthesis; BDNF expression, oxidative stress, inflammation and immunity [83]. A series of miRNAs target genes are generally implicated in neurotransmitter release, related signaling pathways, and neurodevelopmental processes [84]. Clinical studies suggest that abnormal miRNA expression may be associated with clinical symptoms, course of illness and medication response in schizophrenia [85, 86]. A longitudinal study by Antimonic et al. in a population of at extreme high risk for psychosis patients showed that plasma miR-150-5p and miR-3191-5p variants were significantly correlated with psychotic episodes, and that the correlations were independent of age, sex, cannabis and substance use [87].

In patients with TRS, the proteins p53, SIRT1, MDM2 and TRIM28 may play a mediating role between TRS and

Table 2 Histone modifications in schizophrenia and treatment response

Modification/Target	Brain region/sample	Key findings	References
SIRT-1	Not specified	Variants increase schizophrenia risk	Leite et al. [71]
H3K4me	Prefrontal Cortex	Schizophrenia risk gene variants enriched in methylation region	Bilecki and Mackowiak, [72]
HDAC2	Dorsolateral Prefrontal Cortex	Reduced levels in postmortem brain	Schroeder et al. [67]
mGlu2 receptor	Frontal Cortex	Downregulated by histone deacetylation in patients and mouse models treated with clozapine and risperidone	Kurita et al. [78]
KDM4B, KDM1A, PHF2	Rat model	Increased expression in olanzapine-treated rats	Su et al. [79]

the stress response, and that miRNA-regulated molecular pathways may be correlated with symptoms of TRS [88]. A Mendelian randomization study suggested a causal relationship between six miRNAs: hsa-miR-570-3p, hsa-miR-550a-3p, hsa-miR-130a-3p, hsa-miR-210, hsa-miR-337-3p, and hsa-miR-130b-3p and schizophrenia [89]. In a mouse model, miRNA-124-3p expression was found to be upregulated in the medial prefrontal cortex, which in turn increased GRIA2-deficient calcium channel-type AMPA receptor permeability and disrupted AMPA receptor-mediated excitatory synaptic transmission. Taken together the results suggest that the miRNA-124-3pAMPAR pathway is involved in the generation of schizophrenia-like behavior [90].

Long non-coding RNAs and schizophrenia

Long non-coding RNAs (lncRNAs) are large RNA molecules more than 200 nucleotides in length, capable of forming complex three-dimensional structures through various mechanisms such as pairing and folding, thus participating in the regulation of gene expression [91]. Recent studies have revealed that specific lncRNAs are dysregulated in schizophrenia; for instance, Eghtedarian et al. found that *Lnc-FOXF1* expression was significantly elevated in the blood of schizophrenic patients compared with healthy controls [92]. In addition, lower expression levels of LINC0046-lncRNA predicted a lower transcriptional level of LINC00461 in the hippocampus [93]. Furthermore, increased PNKY-lncRNA expression in TRS patients has strong diagnostic validity compared to *BDNF* and other lncRNAs such as *BDNF-AS*, *MIR137HG*, *MIAT* [94]. Mukhopadhyay et al. found that rs2072806 in the lncRNA hsaLB_IO39983 had a regulatory role in BTN3A2, which was associated with schizophrenia, and that rs2710323 in hsaLB_IO_2331 played a role in the dysregulation of ITIH1, which was associated with tardive dyskinesia. The authors also found that four lncRNA single nucleotide polymorphisms were associated with cognitive impairment [95]. The above mentioned lncRNAs may be involved in the progression of schizophrenia by regulating gene expression through influencing chromatin structure, miRNA stability and interactions with proteins [96, 97]. Establishing the exact role and clinical potential of these ncRNAs in schizophrenia will be an important aspect of schizophrenia research as future studies are conducted. Table 3 showed non-coding RNA studies in schizophrenia.

Epigenetic regulatory networks

A complex interplay between epigenetic factors exists, and factors such as DNA methylation, specific histone modifications and ncRNAs may act synergistically to regulate gene expression and affect neurotransmitters in the brain through different pathways [10, 56, 98, 99]. In schizophrenia, such interactions may contribute to persistent alterations in gene expression that could affect brain function and behavior. Recent studies have shown that the *piggyBac* transposable element-derived gene 1 (PGBD1) has DNA-binding activity, and DNA-binding assays have demonstrated specific binding of PGBD1 in the lncRNA NEAT1 promoter and the region within the gene itself [100]. Aberrant expression of specific miRNAs may alter DNA methylation patterns, which in turn affects the expression of related genes. In turn, changes in histone modifications may also affect miRNA expression, generating complex epigenetic feedback regulatory mechanisms [101, 102]. Epigenetic regulatory networks maintain normal nervous system function by regulating the expression of a large number of genes [103]. In the pathogenesis of schizophrenia, these networks may be disturbed due to genetic factors, environmental exposures and their interactions, and these disturbances may affect neuronal differentiation, migration, synaptic

Table 3 Non-coding RNA studies in schizophrenia

RNA Type	RNA/Target	Study type/sample	Key findings	References
microRNA	miR-137	Clinical samples	Protective effect potentially related to estrogen and prolactin in female patients	Peng et al. [85]
microRNA	miR-124	Not specified	Connected polygenic risks with behavioral changes shared between schizophrenia and bipolar disorder	Namkung et al. [90]
microRNA	Multiple miRNAs	Longitudinal samples	Signature associated with conversion to psychosis	Iftimovici et al. [87]
microRNA	Multiple miRNAs	Clinical samples	Differences related to treatment-resistant schizophrenia	Perez-Rodriguez et al. [88]
lncRNA	Oxytocin-related lncRNAs	Expression analysis	Assessment of expression in schizophrenia	Eghtedarian et al. [92]
lncRNA	LINC00461	Clinical study	Involvement in schizophrenia pathogenesis	Rao et al. [93]
lncRNA	BDNF-associated lncRNAs	Expression analysis	Expression changes in treatment-resistant patients	Badrlou et al. [94]
lncRNA	Multiple lncRNAs	Case–control study	Altered lncRNA landscape in schizophrenia and cognition	Mukhopadhyay et al. [95]
lncRNA	Apoptosis-related lncRNAs	Network analysis	Construction of diagnostic model and ceRNA network	Ma et al. [98]

Table 4 Genetic and epigenetic measurement tools

Name	Type	Purpose	Example
Oxford Nanopore Technologies [111]	Sequencing Platform	Long-read genome and epigenetic sequencing	Used for direct detection of methylation patterns from DNA molecules without bisulfite conversion
EM-seq [112]	Next-Generation Sequencing	Enzyme-based DNA methylation sequencing	Indirect detection of DNA methylation patterns through enzymatic treatment
DM-Seq [113]	Next-Generation Sequencing	Direct detection of methylation sequencing on DNA molecules	Offers an all-enzymatic, non-destructive, faithful, and direct method for the reading of 5-methylcytosine
PacBio Sequel II [114]	Sequencing Platform	Single Molecule Real-Time (SMRT) sequencing	Provides long reads and high accuracy for genome sequencing, useful for structural variant and complex region analysis
10 × Genomics Chromium [115]	Single-Cell Analysis Platform	Single-cell transcriptome and genome sequencing	Enables transcriptomic analysis of thousands of single cells to reveal cellular heterogeneity
Illumina NovaSeq [9]	Sequencing Platform	High-throughput genome and transcriptome sequencing	Used for large-scale whole-genome sequencing, exome sequencing, and RNA-seq, suitable for GWAS and transcriptomic studies
Bisulfite Sequencing [116]	DNA Methylation Sequencing Technique	DNA methylation analysis	Involves treating DNA samples with sodium bisulfite followed by sequencing to identify methylated cytosines
ATAC-seq [117]	Chromatin Accessibility Sequencing Technique	Open chromatin region analysis	Utilizes Tn5 transposase to tag open chromatin regions followed by sequencing to study chromatin accessibility
ChIP-seq [118]	Chromatin Immunoprecipitation Sequencing Technique	Protein-DNA interaction analysis	Identifies the binding sites of specific proteins (e.g., transcription factors or histone modifications) on DNA
Hi-C [119]	Chromosome Conformation Capture Technique	3D genome structure analysis	Studies the spatial organization of chromatin within the nucleus, revealing interactions between distant regulatory elements
Single-cell bisulfite sequencing [120] [e.g. smart RRBS [121], sci-Met [122]]	Single-Cell Sequencing Technique	Single-cell analysis	Analyzes patterns at the single-cell level, providing information on epigenetic heterogeneity between cells
Drop-seq [123]	Single-Cell Analysis Platform	Single-cell transcriptome analysis	Uses microfluidics to capture and sequence RNA from individual cells, enabling gene expression analysis at the single-cell level

plasticity and neurotransmission, ultimately resulting in cognitive impairments, affective symptoms and social dysfunction in patients with schizophrenia [72, 104, 105].

Given the role of epigenetic regulatory networks in the pathogenesis of schizophrenia, therapeutic strategies that target specific epigenetic factors and their interactions hold great potential. Studies have focused on the development of drugs to modulate DNA methylation, histone modifications, and ncRNA expression with the aim of recovering or optimizing gene expression in patients with schizophrenia [106, 107]. Such therapeutic predictions may not only improve existing symptoms, but may also be valuable in preventing disease progression. Epigenetic regulatory networks are key bridges between genetic background, environmental factors and schizophrenia symptoms. With a deeper understanding of the function of these networks in association with schizophrenia, future strategies for the treatment of schizophrenia may focus more on the fine regulation of gene expression rather than just the traditional pharmacological modulation of the neurotransmission system.

Tissue specificity, methodological and medication considerations

A key consideration in interpreting epigenetic findings in schizophrenia research is the tissue-specificity of epigenetic modifications. Given the limited accessibility of brain tissue, researchers typically utilize blood or saliva as surrogate specimens [108]. While blood-based studies present practical advantages for biomarker development, the relationship between peripheral and central nervous system epigenetic patterns requires careful evaluation. Several studies have demonstrated correlations between blood-based epigenetic markers and brain-specific changes [62], whereas others highlight significant tissue-specific differences [109]. This tissue specificity must be taken into account when interpreting results and designing future studies. Furthermore, the use of different tissue types across studies (blood, postmortem brain tissue, or animal model tissues) may contribute to seemingly contradictory findings in the literature.

In addition to tissue-specific variations, the interpretation of epigenetic findings in schizophrenia research must account for the effects of medication as critical modifying factors [108]. Recent systematic reviews have revealed distinct epigenetic signatures associated with different antipsychotic medications—haloperidol tends to increase global DNA methylation, whereas clozapine promotes genome-wide hypomethylation. Moreover, antipsychotics exhibit selective effects on histone modifications in specific neural circuits, such as clozapine's impact on H3K4me3 at the *Gad1* gene in the prefrontal cortex [110]. This drug-specific epigenetic modulation introduces additional layer of complexity to understanding disease-related epigenetic alterations and emphasizes the importance of medication status in evaluating research findings.

Measurement tools in genetics and epigenetics research

With the rapid development of bioinformatics and statistics, new measurement tools have enabled researchers to analyze large datasets with greater precision, revealing the association between genetic variations and complex diseases, as well as how environmental factors influence gene expression through epigenetic mechanisms. This plays a crucial role in understanding genetic mechanisms and the onset of diseases. Measurement techniques and statistical methods in genetics are summarized in Table 4.

In the field of genetics, the analysis methods for GWAS are continually being optimized, enhancing the detection capability for genetic markers. For example, multivariate analysis methods can consider multiple phenotypes simultaneously, as opposed to traditional univariate GWAS analyses. The latest single-cell research technologies offer potential solutions to the heterogeneity that traditional population-level analysis cannot address [124]. By conducting detailed analyses of gene expression and epigenetic markers in individual cells, single-cell studies have revealed disease-related changes in different cell types within schizophrenia, as well as variations among patients [125, 126]. The advancement of EWAS technologies and analytical methods presents new opportunities for understanding schizophrenia. The integration of multi-omics data with clinical information may lead to more precise diagnostics.

Limitations

Our review has several limitations. First, the heterogeneity of methodologies and populations across studies makes direct comparisons difficult. Second, publication bias may be present, as negative findings are less likely to be published. Third, some of the included studies had relatively small sample sizes, particularly in biomarker identification studies, although we endeavored to focus on those with adequate statistical power and proper validation cohorts. Fourth, when citing review articles, we have made a concerted efforts to clearly differentiate between original research findings and conclusions derived from reviews, in order to prevent potential misinterpretation. Finally, while peripheral

tissues offer more accessible samples for study, the degree to which these findings reflect brain-specific epigenetic changes remains uncertain. Future studies combining multiple tissue types and using advanced single-cell technologies may help overcome these limitations.

Conclusion

In summary, EWAS have revolutionized our understanding of the epigenetic landscape of schizophrenia. The integration of genome-wide methylation data with clinical information has provided novel insights into disease mechanisms and treatment responses. Future research should focus on leveraging these findings to develop personalized therapeutic approaches.

Author contributions

All authors have made substantial and contributions to researching data for this article, to discussions of content, and to writing the manuscript. Haidong Yang and Xiaobin Zhang were involved in the conception, drafting, reviewing, and revising of the manuscript. Haidong Yang, Wenxi Sun, and Jin Li performed the literature search. All authors contributed to and have approved the final paper.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing of interests

The authors declare no competing interests.

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