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Exploring the Role of CACNA1C, ZNF804A and SLC6A4 in Schizophrenia through Epigenomics and Bioinformatics

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ABSTRACT

Schizophrenia (SCZ) is a complex neuropsychiatric condition in which genetic vulnerability interacts with environmental exposures to influence disease risk and clinical outcomes. Emerging non-genetic causes include early-life stress, substance use and urban living environments, which have been found to interact with inherent genetic predisposition. Recent advances in epigenomics and bioinformatics have illuminated the mechanisms through which these environmental insults may alter gene expression, particularly via DNA methylation, chromatin remodeling and transcription factor binding. Genes such as *CACNA1C*, *ZNF804A* and *SLC6A4* exemplify loci where regulatory changes may mediate gene-environment interactions. Bioinformatics tools like GTEx, ENCODE, 3DSNP, and methylation datasets from epigenome-wide association studies (EWAS) now provide special perspectives into these molecular processes. This review highlights key epigenetic mechanisms linking environmental exposures to SCZ pathogenesis and explores how integrative computational analyses are enhancing our understanding of this complex disorder. A deeper appreciation of gene- environment interactions may ultimately inform personalized interventions and risk stratification in SCZ care.

Keywords: *Schizophrenia, CACNA1C gene, ZNF804A gene, SLC6A4 gene, Genetic association, Polymorphisms, Epigenetics, Risk factors.*

1. INTRODUCTION

SCZ is a chronic, disabling psychiatric disorder characterized by a complex interplay of genetic, environmental and neurodevelopmental factors . While genome-wide association studies (GWAS) have identified numerous risk loci, such as Calcium Voltage-Gated Channel Subunit Alpha1 C (CACNA1C) , Zinc Finger Protein 804A (ZNF804A) and Solute Carrier Family 6 Member 4 (SLC6A4) genes, the presence of risk alleles alone is insufficient to account for disease onset or clinical variability (1,2). This psychiatric illness is marked by high heritability and significant environmental influences. Despite decades of research, the specific etiology remains unknown, owing to the complex interaction between genetic predispositions and environmental exposures (3,4). Recent advances in epigenomics and bioinformatics have revolutionized our understanding of how these gene-environment (G×E) interactions contribute to SCZ risk and phenotypic variability.

1. Genetic Determinants and the Central Role of CACNA1C, ZNF804A and SLC6A4 Evidence implicates dysregulation across multiple systems, including neurotransmitters (dopamine, serotonin (5-HT), glutamate, GABA), neuroinflammation, glial activity, HPA axis disruption, gut microbiota imbalance, oxidative stress, and mitochondrial dysfunction. These interconnected mechanisms contribute to psychotic symptoms and inform emerging treatment strategies involving multimodal pharmacotherapy and biomarker identification, highlighting the need for integrative research approaches considering comorbidities and sex-specific differences (5).

Genetic studies have consistently demonstrated that SCZ has a strong heritable component, with twin heritability estimates ranging from 64% to 81%. GWAS and candidate gene studies have identified hundreds of risk loci, however, only a subset of these variants exhibit consistent replication across diverse populations. Among the most robustly associated are three genes, CACNA1C, ZNF804A and SLC6A4, each of which plays a pivotal role in neurodevelopment, synaptic regulation, and stress response mechanisms, and all of which are crucial pathways implicated in G×E interactions. Moreover, these

genes show strong regulatory potential based on available epigenomic and bioinformatic datasets, making them ideal candidates for examining how environmental exposures may influence SCZ risk through non-genetic mechanisms.

CACNA1C encodes the α1C subunit of the L-type voltage-gated calcium channel (LTCC) and influences neuronal excitability, plasticity and emotion regulation. The risk variant rs1006737 (A allele) has been associated with altered prefrontal cortex activity and impaired cognitive control in SCZ patients(6,7). ZNF804A, a zinc finger transcription factor, was one of the first genes to be implicated through GWAS (1). Its risk variant rs1344706 has been associated with disrupted functional connectivity between the prefrontal cortex and hippocampus, impacting cognition and stress processing (8,9). SLC6A4, encoding the 5-HT transporter, regulates serotonergic signaling critical for emotional regulation and environmental sensitivity. Polymorphisms such as 5-HTTLPR and STin2 VNTR not only influence gene expression but also moderate the impact of stress and trauma on psychiatric outcomes (10–12).

The "Two-Hit Hypothesis"

SCZ exhibits a strong genetic component, with heritability estimates as high as 79% in studies (13), however, when G×E interactions are accounted for, heritability estimates drop significantly, highlighting the substantial role of environmental factors (14). Key environmental associated with heightened risk of psychosis include risk factors like prenatal infections, psychosocial stress, cannabis use, childhood adversity, urban upbringing, social isolation and immigrant status (3,4,15). The "Two-Hit Hypothesis" posits that genetic susceptibility and environmental insults interactively precipitate SCZ, explaining why concordance rates in monozygotic twins are only about 50% (16,17). This hypothesis is illustrated in Figure 1.

SCZ is increasingly understood as a neurodevelopmental disorder resulting from interactions between genetic and environmental risk factors during critical developmental windows such as the prenatal period and adolescence. These factors disrupt macro and microconnectivity, particularly in the prefrontal, temporal, parietal cortices, and hippocampus, leading to impaired synaptic plasticity, oligodendrocyte loss, and abnormal myelination. Environmental risks like obstetric complications, maternal infections and childhood trauma, along with genetic variants identified in GWAS, contribute to these changes. Neuroimaging, post-mortem studies, and patient-derived neuronal models support this view and highlight the need for further research on the timing and mechanisms of these interacting factors (18–20).

Emerging animal model studies support these findings. For instance, rodent models with partial gene deletions exposed to adolescent stress or cannabinoid stimulation exhibit SCZ-like behaviors, supporting the two-hit hypothesis. A study used a two-hit animal model to mimic SCZ risk, combining prenatal immune activation via poly(I:C), a substance that mimics viral infection, and adolescent stress (footshock). Offspring were treated with pioglitazone, an anti-inflammatory PPARγ agonist. The drug reduced microglial inflammation and prevented social and cognitive deficits, as well as dopamine overactivity in the ventral tegmental area. These findings suggest pioglitazone may counteract SCZ-like changes by modulating neuroinflammation (21). Another study also developed a two-hit mouse model of SCZ by combining serine racemase gene deletion (genetic risk) with early maternal separation (environmental stress). The model showed increased locomotion, working memory deficits, and cognitive impairments, resembling SCZ-related behaviors. This approach improves the translational relevance of the model by incorporating both genetic susceptibility and early-life environmental stress, reflecting the multifactorial etiology of SCZ (22).

Figure 1

The Two-Hit Hypothesis in Schizophrenia

2. ENVIRONMENTAL RISK FACTORS IN SCHIZOPHRENIA

SCZ is increasingly recognized as a disorder shaped by cumulative exposure to environmental stressors, particularly during vulnerable periods of neurodevelopment. These risk factors often precede the onset of clinical symptoms by years and can act independently or in interaction with genetic susceptibility to influence disease manifestation.

Prenatal and perinatal complications

Complications during pregnancy and childbirth, such as maternal infections (e.g., ***Toxoplasma gondii***, cytomegalovirus), obstetric complications (e.g., hypoxia, emergency C-section), and nutritional deprivation have consistently been linked to SCZ risk (18). These factors may induce maternal immune activation or impair early brain development, thereby creating a pro-inflammatory environment that affects neuronal growth and synaptic function (23,24).

No significant association was found between perinatal complications and later development of SCZ, while decreased gestation length and early vitamin K administration were linked to increased risk of affective psychosis, suggesting perinatal factors may play a greater role in affective disorders than SCZ (25). But, a birth cohort study linked pregnancy, delivery, and neonatal data to adult SCZ outcomes, finding that low birth weight and preterm birth were more common in individuals who developed SCZ. These results suggest that fetal and perinatal insults may contribute to SCZ risk (26) and women with SCZ have increased risks of pregnancy and neonatal complications, such as placental issues and low birth weight, influenced by genetic and maternal factors (27). A meta-analysis of prospective population-based studies identified three groups of obstetric complications, pregnancy complications (e.g., bleeding, preeclampsia), abnormal fetal growth (e.g., low birthweight, congenital malformations), and delivery complications (e.g., asphyxia, emergency cesarean), as significantly associated with increased SCZ risk, though effect sizes were generally modest (<2) (28).

Significant associations were found between SCZ and certain pregnancy and delivery complications, including premature rupture of membranes, preterm birth and neonatal resuscitation. These findings suggest that perinatal hypoxia may contribute to SCZ risk, indicating the need for precise measurement of hypoxic exposure in future research (29). A population-based cohort study revealed that pregnant women with SCZ have significantly higher risks of pregnancy, delivery, and neonatal complications like genito-urinary infection, gestational diabetes, gestational hypertension, intrauterine growth retardation and threatened preterm labour, compared to matched controls without severe mental disorders. These findings emphasize the need for targeted health policies and intensified care to address the disparities and improve outcomes for both mothers with

SCZ and their newborns (30). A meta-analysis and population-based cohort study examined obstetric and neonatal complications in women with SCZ-spectrum disorders (SSD), accounting for confounders and antipsychotic use. While the meta-analysis found SSD associated with increased risks across multiple adverse outcomes (relative risks 1.12–2.10), the cohort study revealed that most risks were attenuated after adjusting for confounders, except for prolonged hospitalization, preterm birth, and neonatal special-care admission. Antipsychotic treatment was linked only to higher neonatal special-care admission. These findings suggest that maternal comorbidities and substance use largely explain elevated risks, highlighting the need for targeted interventions in prenatal care for SSD women (31). The results suggest that distinct prenatal adversities, maternal gestational factors, and early-life trauma contribute to the etiological heterogeneity of SCZ and bipolar disorder (BD) within families, highlighting the critical role of G×E interactions in modulating individual susceptibility to these psychotic disorders (32).

Cannabis or Substance Use

The role of cannabis use as a risk factor for the emergence of psychosis has been consistently evidenced through prospective studies. However, as is typical in multifactorial complex disorders, cannabis use is neither sufficient nor necessary for the development of SCZ or related conditions. Sensitivity to the effects of cannabis has been proposed to be mediated by genetic variability in the Catechol-O-methyltransferase (COMT) gene, which encodes an enzyme involved in the degradation of catecholamines such as dopamine. Cannabis use, especially during adolescence, is one of the most well-documented environmental risk factors. Cannabis interacts with neurodevelopmental processes and modulates dopaminergic signaling pathways implicated in psychosis. Notably, the effect is more pronounced in individuals with certain genetic polymorphisms, such as ***COMT*** Val158Met, suggesting a gene × cannabis interaction. An association was found between cannabis use and earlier onset of psychosis, with a significant interaction between cannabis use and the COMT Val158Met genotype influencing both age of onset and duration of untreated psychosis (DUP). The delay in onset typically observed in Met/Met carriers was not present among cannabis users, suggesting that cannabis may negate the protective effect of the Met allele (33). Early cannabis use is linked to an earlier onset of psychiatric disorders, especially in individuals with the COMT Val/Val genotype. This suggests a G×E interaction where COMT modulates vulnerability to cannabis-related early psychosis (34). A large longitudinal study found no consistent interaction between COMT genotype and cannabis use on psychotic outcomes. The results suggested that cannabis increases the risk of psychosis regardless of COMT variation, challenging previous G×E interaction claims and reinforcing a universal public health warning (35). Early cannabis use may interact with the COMT Val158Met (rs4680) variant to influence the age of onset of psychosis, with Val/Val carriers showing the earliest onset (36). In patients with chronic SCZ, cannabis use interacts with COMT genotype, with Val/Val individuals showing worse cognitive performance than Met carriers. This supports a G×E interaction where the COMT Val/Val genotype may increase vulnerability to cannabis-related cognitive deficits, especially in verbal fluency and processing speed (37), and has been implicated in triggering SCZ (38).

Substance abuse was highly prevalent among Australian outpatients with SCZ, particularly involving alcohol, cannabis, and amphetamines. These patients were more symptomatic and began treatment earlier, with patterns differing from North American samples due to local drug availability, and were more likely to be young, single males with criminal histories, though no significant differences were observed in suicide attempts, hospitalizations, or antipsychotic dosage. The findings suggest a potential GxE interaction, where individuals SCZ, likely carrying genetic vulnerabilities, may be more prone to substance use when exposed to environmental risk factors such as drug availability, social instability or early-life stress, which in turn worsens clinical outcomes like symptom severity and earlier treatment onset (39). Substance use disorders affect 40–50% of individuals with SCZ and are linked to poor outcomes (40). Substance use is common in SCZ and may stem from shared genetic and neurobiological vulnerabilities affecting circuits linked to both psychosis and addiction. Early substance use in adolescence could increase risk for both substance use disorders and psychosis (41). Circadian rhythm alterations observed in SCZ and comorbid substance use disorders with SCZ, indicate a GxE interaction, wherein endogenous vulnerabilities interact with exogenous factors such as substance use and sleep-wake disruption, contributing to neurobiological dysregulation (42).

Psychosocial stress

Stress arising from social and psychological factors, childhood adversity (e.g., abuse, neglect), and urbanicity also show strong associations with increased SCZ risk. These factors may influence hypothalamic-pituitary-adrenal (HPA) axis regulation, heighten allostatic load, and disrupt the stress response system. G×E studies have shown that individuals with a high polygenic risk score (PRS) for SCZ are more vulnerable to these exposures. Despite HPA axis dysregulation being implicated in SCZ, salivary cortisol levels, both at baseline and post-stress, do not consistently differ from controls, limiting its current utility as a diagnostic biomarker. Methodological heterogeneity and confounding factors (e.g., medication, stress exposure) likely account for the observed variability (43).

Neuroendocrine and Inflammatory Dysregulation as Environmental Biological Risk Interactions

SCZ's etiology involves complex interactions among genetic, epigenetic, environmental, and immune-inflammatory factors. Metabolic profiles characterized by elevated glucose, triglycerides, insulin resistance and inflammation were found to be

worse in patients with SCZ spectrum disorders compared to healthy controls. A significant association between a history of adverse childhood experiences, increased insulin levels and insulin resistance was observed specifically in these patients, whereas no significant links were identified between lifetime or perceived stress and metabolic parameters. These findings indicate that early-life stress may contribute to cardiometabolic risk in SCZ spectrum disorders, suggesting that therapeutic strategies addressing adverse childhood stress should be considered to manage cardiovascular comorbidities in this population (44). Elevated levels of pro-inflammatory cytokines, early-life immune challenges, and epidemiological links to infections and autoimmune disorders support the involvement of immune dysregulation. The vulnerability-stress-inflammation model suggests that genetic predisposition, environmental stressors, and immune activation interact to trigger and sustain psychotic symptoms. Neurotransmitter imbalances and structural brain changes associated with low-grade neuroinflammation further implicate inflammatory pathways, that lead to SCZ (45).

SCZ is often associated with low-grade systemic inflammation, whose source may involve both gut–brain axis dysfunction and endocrine imbalance. A study investigated plasma inflammatory markers like c-reactive protein (CRP), lipopolysaccharide-binding protein (LBP), soluble CD14 (sCD14) and IgG antibodies to food antigens in 409 individuals with SCZ, stratified by presence of gastrointestinal (GI) and/or endocrine comorbidities. Results showed that GI and endocrine conditions had additive effects on gut-related inflammation (notably LBP), while general inflammation (CRP) was more strongly linked to endocrine issues, especially obesity. GI issues like gastroesophageal reflux disease (GERD) were associated with higher immune reactivity (e.g., S. cerevisiae IgG) and more severe psychiatric symptoms, suggesting that GI and endocrine dysfunctions may independently or interactively drive inflammation in SCZ (46). The gut dysbiosis significantly disrupts the microbiota-gut-brain axis, contributing to neuropsychiatric disorders through mechanisms such as neuroinflammation, oxidative stress and impairment of intestinal and blood-brain barrier integrity. Consequently, non-therapeutic interventions, including probiotics, prebiotics, synbiotics, postbiotics, specific diets and fecal microbiota transplantation, have been identified as promising approaches to restore microbial balance and improve gut–brain communication, thereby offering potential management strategies for neuropsychiatric conditions (47).

Immune system alterations, particularly cytokine imbalances, are evident early in the disorder and support the neurodevelopmental hypothesis, suggesting that abnormal brain development underlies SCZ onset in adolescence or early adulthood. A combined neurodevelopmental and neurodegenerative model is increasingly recognized to explain the progressive brain abnormalities seen in SCZ (48). SCZ results from diverse risk factors that disrupt synaptic signaling, neuroplasticity, and brain homeostasis, reflected by biomarkers such as elevated allostatic load, mitochondrial dysfunction and neuroinflammation. These biomarkers highlight the individual variability in SCZ etiology and symptom expression (49). Environmental risk factors for psychosis converge on shared neurochemical mechanisms, potentially influencing dopaminergic dysregulation implicated in symptom development (50). Altered glucocorticoid receptor signalling and elevated FKBP5 expression in the midbrain suggest impaired stress responsivity in SCZ, particularly under conditions of neuroinflammation. These molecular changes may contribute to dopaminergic dysregulation, supporting a model of SCZ as a disorder of chronic stress-induced neurochemical imbalance (51). Disruptions in cognitive map formation, driven by neurophysiological abnormalities (e.g., attractor instability from excitation-inhibition imbalance) and psychosocial stressors, may underlie core symptoms of SCZ, implicating the hippocampal–prefrontal network in impaired structure learning and representational processes (52).

Sex and Season of Birth as Environmental Modifiers

Epidemiological studies have long suggested that sex and season of birth act as modulators of SCZ risk, likely through their interaction with environmental exposures during critical neurodevelopmental periods. Men and women differ in both the onset and expression of SCZ. Males tend to exhibit earlier onset, more negative symptoms, and poorer long-term outcomes. Females often show a later onset, better premorbid functioning, and stronger response to antipsychotic treatment. This disparity may arise from sex-specific hormonal influences, with estrogens in females exerting a neuroprotective effect by modulating dopamine pathways and reducing oxidative stress (53).

Moreover, gene × sex interactions have been reported for multiple SCZ-related loci, including, *CACNA1C*, where differential prefrontal cortex activation is observed between male and female carriers. *A sex × genotype interaction involving the CACNA1C variant rs10774035 was observed in SCZ-spectrum disorders, where male carriers of the minor allele showed better psychosocial functioning and recovery, while female carriers showed impaired recovery (54), and gender stratification analysis revealed a significant association between the rs2283291 genotype of CACNA1C and SCZ in male patients (55). A significant interaction between 5-HTTLPR genotype, gender, and anxiety was observed, with females homozygous for the Short allele showing the highest anxiety scores and larger right amygdala volume under subclinical anxiety conditions. These findings suggest that gender modulates the genetic influence of 5-HTTLPR on brain structure and anxiety-related traits (56). These findings highlight the importance of gene × sex interactions in modulating disease outcomes.*

Meta-analyses have shown a significant increase in SCZ incidence among individuals born in winter and early spring. This pattern is consistent across geographic regions, suggesting that seasonal environmental exposures during gestation may contribute to altered fetal brain development. A small but consistent seasonal pattern in SCZ risk was identified, with winter

births showing a statistically significant increase in risk (OR 1.05) and summer births a decreased risk (OR 0.96), regardless of hemisphere (57). Maternal infections (e.g., influenza, respiratory viruses) that elevate pro-inflammatory cytokines and interfere with neuronal proliferation (58,59). Reduced maternal sunlight exposure during winter months leading to low vitamin D levels, which affects fetal neurogenesis, synaptic plasticity, and dopaminergic development (60,61). Nutritional deficiencies, such as folate or omega-3 fatty acids, common in colder seasons, may also play a role (62,63).

3. EPIGENETIC MECHANISMS MEDIATING ENVIRONMENTAL INFLUENCE

Epigenetics provides a powerful framework for understanding how environmental exposures can become biologically embedded to influence gene expression without altering the underlying DNA sequence. In SCZ, this regulatory layer is essential for bridging the gap between polygenic risk and environmental triggers, particularly during neurodevelopmental windows of vulnerability.

Epigenomics as a Bridge Between Genes and Environment

The environmental exposures may leave lasting epigenetic imprints, through processes such as DNA methylation and chromatin remodeling, that affect gene regulation during critical periods of brain development. Understanding how non-genetic variables interact with inherited vulnerabilities is critical for developing a more complex understanding of SCZ etiology. Epigenetic mechanisms, such as DNA methylation and histone modification, mediate the effects of environmental exposures on gene expression without altering DNA sequence. Environmental factors can induce epimutations, leading to dysregulated gene expression patterns implicated in SCZ pathogenesis (17,64,65). For example, prenatal immune activation or early-life stress can alter the epigenetic landscape, modifying the expression of genes involved in neurodevelopment and synaptic function. These epigenetic changes are dynamic and potentially reversible, offering promising targets for therapeutic intervention (3,66,67).

DNA Methylation

DNA methylation at CpG sites is the most extensively studied epigenetic mechanism in SCZ. Environmental insults such as prenatal stress, malnutrition and cannabis exposure can induce stable changes in DNA methylation patterns (68). This in turn affects the transcriptional activity of neurodevelopmental genes. Notably, SCZ-associated methylation changes have been observed in promoters of RELN, GAD1 and SLC6A4 genes, impacting GABAergic and serotonergic pathways. For instance, hypermethylation of the SLC6A4 promoter has been reported in blood samples from drug-naïve SCZ patients, linking serotonergic dysfunction with environmental stress exposure (66). Additionally, methylation quantitative trait loci (meQTLs) have been shown to co-localize with SCZ risk loci, suggesting that genetic susceptibility may shape an individual's methylation response to environmental stimuli (4,66).

In a large-scale meta-analysis of blood DNA methylation variance, significant variability in methylation patterns was identified in individuals with SCZ compared to non-psychiatric controls. Although only a small proportion of variably methylated positions (variance or heterogeneity of methylation levels in SCZ patients) overlapped with differentially methylated positions (average level of DNA methylation in between SCZ and controls), these ariably methylated positions were enriched in genes linked to SCZ and brain function. Concordant methylation changes were also observed in multiple brain regions, and associations were noted with clinical features such as age of onset, cognitive deficits, and symptom severity. These findings highlight that altered DNA methylation variance may underlie the phenotypic heterogeneity seen in SCZ (69). In a recent study, sex-stratified epigenome-wide association studies (EWAS) were performed to improve the identification of SCZ-associated DNA methylation changes. A greater number of differentially methylated regions (DMRs) were identified using sex-stratified models compared to sex-adjusted analyses. Polymethylation scores derived from the sex-stratified approach were shown to more accurately predict SCZ, particularly in males. These findings suggest that sex-specific epigenetic alterations may be implicated in SCZ and should be considered in the development of precision psychiatry and sex-stratified treatment approaches (70).

Significant differential methylation at 1,094 CpG sites was observed in association with SCZ clinical phenotypes such as cognitive impairment, earlier age of onset, treatment resistance, and functional status. These epigenetic alterations were enriched in genes previously implicated in psychiatric disorders and correlated with SCZ polygenic risk scores. Furthermore, epigenetic markers linked to treatment-resistant SCZ were significantly associated with clozapine exposure, indicating a potential role in therapeutic response. These findings support the contribution of DNA methylation changes to the molecular heterogeneity and clinical variability in SCZ (71). In the same time, antipsychotic medications were found to induce distinct epigenomic modifications, including DNA methylation and histone changes, which may underlie interindividual variability in therapeutic response and tolerability. Haloperidol was consistently associated with global DNA hypermethylation, whereas clozapine induced widespread hypomethylation and altered histone modifications in genes related to neurotransmission. Gene-specific and brain region-dependent epigenetic effects were also reported for risperidone and quetiapine. These findings support the hypothesis that antipsychotic drugs exert pharmacodynamic effects through selective epigenetic mechanisms, highlighting the potential of epigenomic profiling in advancing personalized psychiatric treatment (72).

Histone Modifications

Histone modifications have been implicated in the pathophysiology of SCZ, primarily through their role in regulating gene expression critical to neurodevelopment and synaptic function (73). Cell-type-specific chromatin profiling in SCZ implicated cortical histone modifications, particularly H3K4me3 and H3K27ac, as enriched at SCZ risk loci. Thousands of histone QTLs were identified, with neuronal-specific enhancer and promoter regions showing significant overlap with genetic variants associated with SCZ and related traits (74). Elevated levels of repressive marks such as H3K9me2 and dysregulated expression of histone-modifying enzymes including HDAC1, HDAC3, and HDAC4 have been reported in both peripheral and central tissues of SCZ patients. Functional consequences, such as reduced GAD1 expression linked to disrupted promoter histone methylation and chromatin looping, have been observed in the prefrontal cortex. These epigenetic abnormalities, along with associations from GWAS studies, suggest that chromatin remodeling and histone post-translational modifications (PTMs) contribute significantly to the transcriptional dysregulation underlying SCZ (75).

PTMs of histones such as methylation, acetylation, phosphorylation and ubiquitination play a key role in regulating chromatin accessibility and gene expression. SCZ brains have shown increased repressive marks like H3K9me2 (histone 3 lysine 9 dimethylation) and reduced histone acetylation in the prefrontal cortex and hippocampus. Enzymes such as HDAC1 and HDAC2 (histone deacetylases 1 and 2) have been found to be overexpressed in SCZ, correlating with cognitive deficits and treatment resistance. Animal models exposed to social isolation or prenatal stress exhibit alterations in histone marks, which are reversible with antidepressant treatment or HDAC inhibitors. These findings suggest that histone modifications serve as a reversible epigenetic switch in stress-related pathways (66). Histone acetylation and methylation have been predominantly investigated, with acetylation associated with enhanced transcription and methylation (particularly at H3K9) linked to transcriptional repression. Other modifications, including phosphorylation, ubiquitination, serotonylation, lactylation, palmitoylation, and dopaminylation, have also been reported to contribute to chromatin dynamics in SCZ. These findings suggest that aberrant histone modification patterns may underlie dysregulated gene expression observed in the disorder (76). Global alterations in histone PTMs were observed in the dorsolateral prefrontal cortex of individuals with SCZ, characterized by increased levels of permissive marks (H3K9ac, H3K27ac, H3K4me3) and reduced HDAC activity and HDAC4 expression. These changes were particularly evident in antipsychotic-treated patients, suggesting that antipsychotic drugs may contribute to an aberrantly permissive epigenomic state (77).

Chromatin Remodeling and 3D Genome Structure

Neuroplasticity is supported not just by synaptic remodeling but also by activity-dependent reconfiguration of nuclear and chromatin structure, making chromatin architecture a critical target for understanding and potentially treating brain disorders like SCZ (78). SCZ is increasingly understood as a disorder of chromatin architecture, where abnormal chromatin remodeling and 3D genome misfolding interfere with proper gene regulation in the brain (79). Beyond methylation and histone PTMs, chromatin remodelers and long-range DNA interactions have also been implicated in SCZ. Bioinformatics platforms such as 3DSNP and Hi-C data have enabled the mapping of chromatin loops and enhancer-promoter interactions, especially in fetal brain tissue. These interactions often encompass risk loci like ***ZNF804A*** and ***CACNA1C***, providing a mechanistic explanation for their regulatory disruption under environmental conditions (3,66). Chromosomal organization across multiple scales, from nucleosomes to megabase domains, has been characterized in the adult prefrontal cortex through histone modification mapping (H3K27ac and H3K4me3). Thousands of cis-regulatory domains (CRDs) were identified and found to align with Hi-C defined topologically associating domains (TADs), reflecting chromatin architecture integrated with nuclear topography. Large clusters of hyper-acetylated CRDs, enriched for SCZ heritability loci, were observed, particularly involving regulatory elements linked to fetal brain development and glutamatergic signaling. These findings demonstrate that SCZ and BD are associated with coordinated dysregulation of risk-associated regulatory chromosomal domains spanning kilobase to megabase scales (80).

Experimental Epigenomics

Recent advances in mass spectrometry, ChIP-seq, and MeDIP-seq have allowed high-resolution mapping of epigenetic changes in human postmortem brain and peripheral samples. However, SCZ-specific studies remain technically limited due to sample availability and tissue heterogeneity. Still, emerging integrative studies combining transcriptomics, chromatin marks, and splicing analyses (e.g., TWAS + chromatin profiling) have identified over 150 SCZ-associated genes with epigenetic dysregulation, strengthening the hypothesis that epigenomics is central to disease pathogenesis (66).

4. GENE-SPECIFIC EVIDENCE OF G×E INTERACTIONS

The concept of G×E is crucial in understanding why certain individuals with a genetic predisposition to SCZ develop the disorder following environmental exposure, while others do not. Focus has been placed on three consistently replicated SCZ-associated genes, CACNA1C, ZNF804A and SLC6A4, to illustrate how their expression and regulation are influenced by environmental factors through epigenetic mechanisms. Evidence supporting these interactions has been provided by bioinformatics analyses and experimental studies, indicating that environmental exposures can modulate gene function via changes in DNA methylation, histone modifications and chromatin accessibility.

CACNA1C - Environmental Sensitivity of a Neuroplasticity Gene

CACNA1C encodes the α1C subunit of the LTCC, which plays a critical role in calcium signaling, neuronal excitability, synaptic plasticity, and stress response. The SNP rs1006737 within ***CACNA1C*** is strongly associated with SCZ, BD and depression. Carriers of the A allele of rs1006737 show altered activation in the prefrontal cortex and hippocampus during emotional and cognitive tasks. Animal studies show that stress exposure during adolescence alters ***CACNA1C*** expression and histone acetylation in the hippocampus, supporting its environmental responsiveness. Epigenetic studies have shown increased H3K27ac and reduced methylation at ***CACNA1C*** promoter regions following stress paradigms.

Data from ENCODE and Roadmap Epigenomics indicate that ***CACNA1C*** is surrounded by DNase hypersensitive sites and enhancer elements active in fetal brain tissue. GTEx eQTL data suggest rs1006737 modulates ***CACNA1C*** expression in the brain cortex. 3DSNP reveals that rs1006737 lies within a chromatin loop that interacts with multiple transcription start sites in neurons, suggesting it may serve as a regulatory hub. JASPAR predicts that this SNP may disrupt transcription factor binding sites for MEF2C and EGR1, both implicated in synaptic development and stress response.

ZNF804A - A Hub of Chromatin Interaction and Neurodevelopmental Regulation

ZNF804A encodes a zinc finger transcription factor involved in neurodevelopment, synaptic transmission and long-range chromatin interactions. The SNP rs1344706 in the intronic region of ***ZNF804A*** has been implicated in modulating brain connectivity and cognition in SCZ. rs1344706 carriers show disrupted default mode network connectivity, which correlates with poor stress coping and social functioning. The risk allele has been linked to blunted stress-induced cortisol responses, indicating potential HPA axis modulation by this gene. rs1344706 overlaps with epigenetically active enhancers marked by H3K4me1 and H3K27ac in fetal brain. 3D genome mapping (Hi-C and 3DSNP) identifies long-range chromatin interactions with other SCZ risk loci, suggesting ZNF804A may act as a regulatory node. Postmortem SCZ brains show hypomethylation in regulatory regions near rs1344706.

HaploReg annotations confirm its overlap with enhancer elements and transcriptional repressors. PROMO/JASPAR predict that environmental exposure could influence binding of key factors such as REST and CTCF at this site, altering gene regulation during early neurodevelopment.

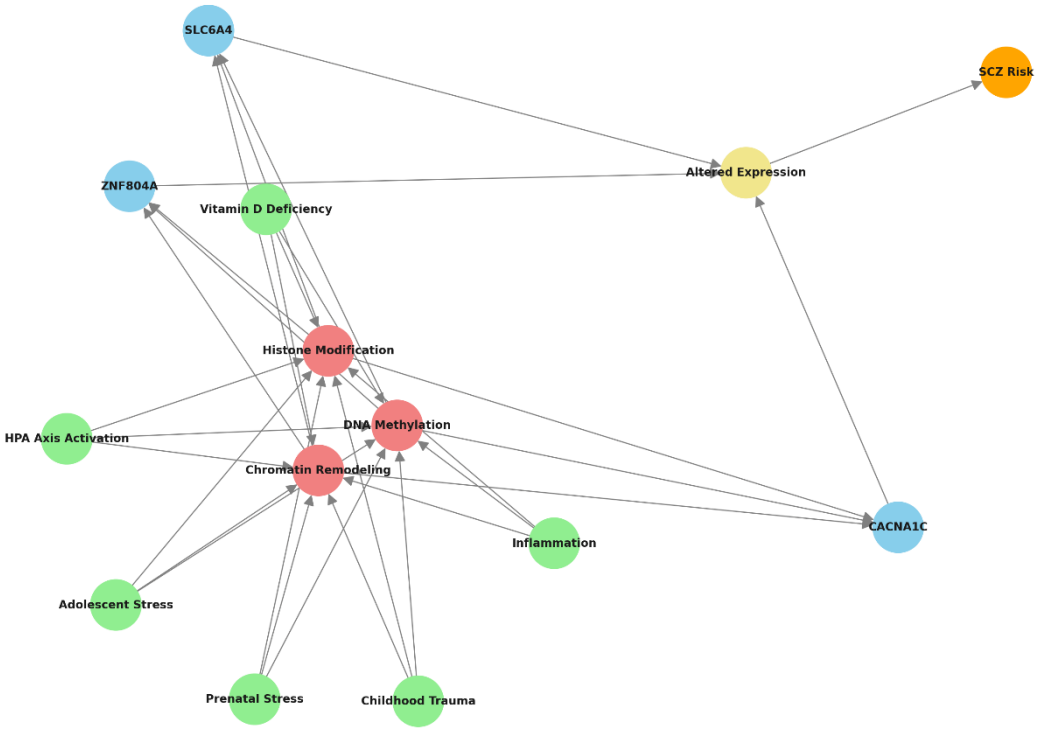
SLC6A4 - The Environmental Gatekeeper of 5-HT Transport

SLC6A4 encodes the 5-HT transporter, critical for 5-HT reuptake and emotional regulation. Two polymorphisms, 5-HTTLPR and STin2 VNTR, are widely studied for their sensitivity to environmental influence, especially early-life stress. The short (S) allele of 5-HTTLPR has been repeatedly associated with increased sensitivity to stress and higher risk for depression and SCZ when exposed to adversity. Individuals with the S/S genotype show hyperreactivity of the amygdala and increased cortisol release under stress. Studies show hypermethylation of the 5-HTTLPR promoter in SCZ, particularly among patients with a history of childhood trauma. The STin2 12-rpt/12-rpt genotype, linked with lower SLC6A4 expression, is more frequent in SCZ populations, as supported by both molecular and bioinformatics studies.

JASPAR predicts that the S allele may alter binding affinity for stress-responsive transcription factors like AP-1 and NR3C1. GTEx and QTLbase show variable expression of ***SLC6A4*** in the brainstem and frontal cortex depending on VNTR and methylation status. Functional annotation from RegulomeDB suggests regulatory potential for both polymorphisms under inflammatory or stress conditions.

Figure 2

Gene–Environment Interactions in SCZ - Epigenetic Mediation of CACNA1C, ZNF804A, and SLC6A4



Note. The interaction between environment, epigenetic regulation and gene expression forms the core of G×E models of SCZ.

Figure 2, illustrates the multidimensional framework through which environmental exposures influence SCZ risk via epigenetic regulation of key genes. Environmental factors such as adolescent stress, childhood trauma, inflammation, and prenatal vitamin D deficiency initiate epigenetic modifications, including DNA methylation, histone modification and chromatin remodeling. These changes dynamically regulate the expression of SCZ susceptibility genes, ***CACNA1C***, ***ZNF804A*** and ***SLC6A4***. The downstream consequence of this altered gene expression is a shift in neuronal function and increased susceptibility to SCZ. The model demonstrates how genetic risk loci can act as environmentally sensitive molecular hubs.

Comprehensively, *CACNA1C*, *ZNF804A*, and *SLC6A4* illustrate the multifaceted ways in which genetic architecture, environmental exposures and epigenetic mechanisms interact to shape SCZ risk. The integration of G×E models with bioinformatics tools has provided compelling evidence that these genes are not only genetic risk loci but also dynamic regulators influenced by the environment, making them central to the future of precision psychiatry.

5. BIOINFORMATICS APPROACHES TO STUDY G×E INTERACTIONS IN SCZ

Bioinformatics has revolutionized the ability to investigate complex psychiatric disorders like SCZ by integrating genetic, epigenetic, transcriptomic and chromatin based data. In the context of G×E interactions, bioinformatics enables the identification of regulatory regions responsive to environmental stimuli, prioritization of risk variants, and functional annotation of non-coding regions that traditional GWAS often overlook. Key tools and databases have been outlined as instrumental in the dissection of G×E interactions for SCZ-associated genes such as *CACNA1C*, *ZNF804A* and *SLC6A4*.

The GWAS and gene expression datasets like Gene Expression Omnibus (GEO) used to identify key SCZ associated genes and pathways (81). Recent studies employing gene-based statistical epistatic analysis have uncovered millions of genetic interactions, many of which are enriched in brain and nervous system-related processes. Hub genes such as CACNA1C, DRD3, MTHFR, *KCNIP4*, *WWOX* and *NRXN3, etc.* have been identified as central players in SCZ risk, each interacting with multiple partners to modulate disease susceptibility (81). Tools such as GTEx, 3DSNP, JASPAR, and ENCODE have enhanced our understanding of how risk alleles may exert their effects through long-range chromatin interactions, altered transcription factor binding, or context-specific gene expression regulation.

GTEx Portal and eQTL Databases

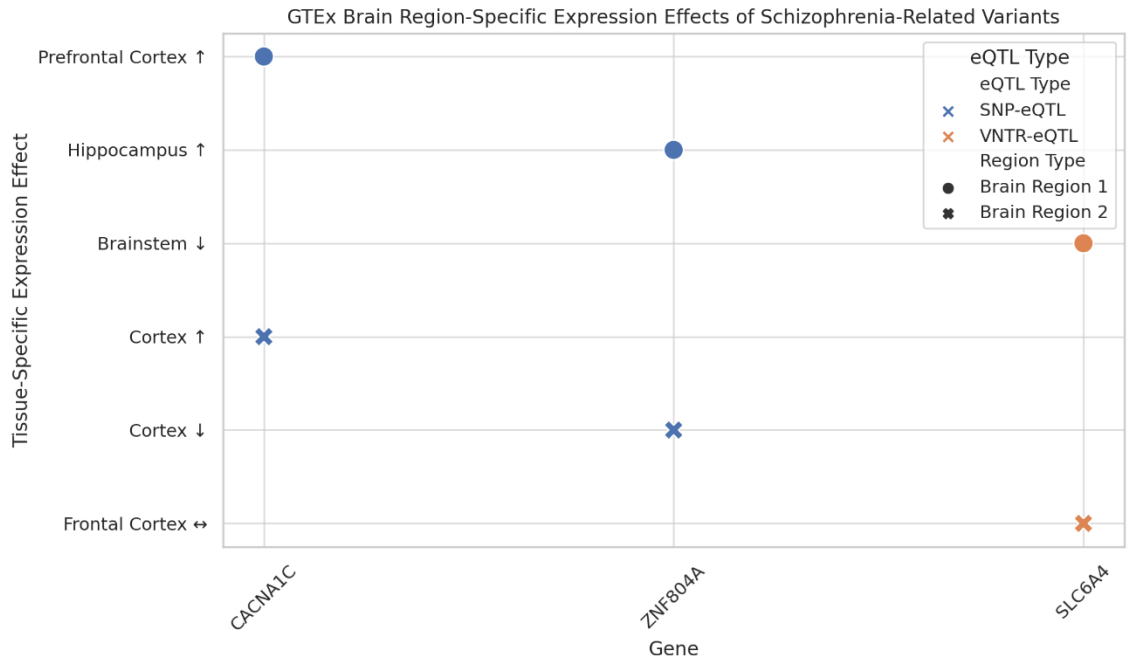
The Genotype-Tissue Expression (GTEx) project provides tissue-specific gene expression and expression quantitative trait loci (eQTL) mapping across multiple human tissues. In SCZ, GTEx has revealed the brain-region-specific ***CACNA1C***

expression modulation by rs1006737, the ***ZNF804A*** eQTL effects in the hippocampus and cortex, and the variable ***SLC6A4*** expression in the brainstem depending on polymorphisms and methylation patterns. GTEx enables detection of how non-coding SNPs regulate gene expression in relevant tissues under potentially environmentally modifiable conditions.

The SNP ***rs1006737*** in the ***CACNA1C*** gene is associated with increased expression in the prefrontal cortex and cortex. The intronic SNP ***rs1344706*** in ***ZNF804A*** shows elevated expression in the hippocampus but variable patterns in the cortex. The variable number tandem repeat (VNTR) polymorphism 5-HTTLPR in ***SLC6A4*** shows reduced expression in the brainstem and neutral effects in the frontal cortex. These gene–tissue–expression profiles highlight the region-specific regulatory roles of non-coding SCZ-associated variants, as illustrated in Figure 3.

Figure 3

GTEx Brain Region-Specific Expression Effects of Schizophrenia-Related Variants



Note. This diagram illustrates tissue-specific expression changes associated with key SCZ risk variants, *CACNA1C*, *ZNF804A*, and *SLC6A4*, based on GTEx eQTL data, which are differentially regulated across brain regions relevant to SCZ. The up (↑), down (↓), and neutral (↔) arrows indicate directionality of gene expression relative to the risk allele or polymorphism.

QTLbase and eQTL Catalogue

These platforms aggregate data from numerous studies, including those focusing on environmental exposures, inflammation and tissue-specific expression. For SCZ, the QTLbase maps meQTLs and eQTLs under different conditions, helping clarify how stress or inflammation alters gene regulation at risk loci. It helps integrate G×E evidence by showing context-dependent regulatory effects of variants like ***rs1344706*** or ***5-HTTLPR***.

3DSNP and Chromatin Interaction Tools

3DSNP and Hi-C–based tools (e.g., 3D Genome Browser) use chromatin conformation capture data to link distal regulatory elements to target promoters. They reveal that rs1344706 in ***ZNF804A*** interacts with enhancers in fetal brain, suggesting developmental epigenetic regulation, and rs1006737 in ***CACNA1C,*** is within a chromatin loop that modulates neural gene networks involved in stress response and plasticity. Such tools are essential for uncovering long-range G×E interactions not visible from linear genome annotation alone.

JASPAR and PROMO

These transcription factor binding site prediction tools help assess whether specific alleles at SNPs or VNTRs alter binding motifs for stress and inflammation responsive transcription factors. In ***SLC6A4***, the S allele of 5-HTTLPR may disrupt binding for NR3C1 (glucocorticoid receptor). In ***CACNA1C***, rs1006737 may affect MEF2 and CREB binding, both critical

in activity-dependent gene regulation. Such motif-based predictions give mechanistic hypotheses for how stress exposure alters gene regulation via epigenetic sensitivity.

ENCODE and Roadmap Epigenomics

These collaborative research projects provide genome-wide maps of histone modifications, DNase hypersensitivity and chromatin state segmentation across multiple tissues, including fetal and adult brain. ***ZNF804A*** shows enhancer marks (H3K4me1, H3K27ac) in developing cortex. ***CACNA1C*** and ***SLC6A4*** show chromatin accessibility shifts under neuroinflammatory states, linking environmental response to epigenetic architecture.

Functional Annotation Tools (HaploReg, RegulomeDB, VEP)

These tools integrate epigenetic marks, TFBS, and eQTLs to prioritize functional non-coding variants. HaploReg annotates rs1344706 as overlapping with enhancer elements in brain tissues. RegulomeDB gives rs1006737 a high regulatory potential score based on DNase evidence and TF binding sites. Ensembl VEP links risk SNPs to transcript consequences and conservation scores. These platforms bridge GWAS signals with functional hypotheses, particularly under environmental perturbation.

Bioinformatics tools have become essential for understanding how genes and the environment work together in SCZ. They help show how certain genetic variants can make the brain more sensitive to environmental influences, and how these interactions affect brain development and function. By combining insights from both genetics and environmental factors, these tools give us a more complete picture of what drives SCZ risk.

6. IMPLICATIONS FOR PRECISION PSYCHIATRY

The convergence of genetic, environmental and epigenetic factors in SCZ has significant implications for the development of precision psychiatry, for prevention, diagnosis, and treatment strategies based on individual biological and environmental profiles.

Understanding G×E interactions enables a more nuanced stratification of SCZ risk. For instance, individuals carrying the short allele of 5-HTTLPR or the A allele of rs1006737 (CACNA1C) may not exhibit disease symptoms unless exposed to specific stressors such as childhood trauma or cannabis use. This conditional penetrance underscores the need for personalized risk assessment models that combine genetic variants, environmental history, and epigenetic biomarkers. Advanced predictive algorithms incorporating polygenic risk scores and environmental risk profiles (e.g., urbanicity, adversity, infections) are beginning to emerge. Integrating these with methylation-based age acceleration markers, for example, may allow clinicians to identify high-risk individuals before clinical onset.

Epigenetic marks such as DNA methylation signatures in blood or saliva offer promising avenues for biomarker discovery. Because epigenetic states are dynamic and reversible, they serve as real-time indicators of both genetic predisposition and environmental impact. Several studies have identified disease-specific methylation changes at SCZ-related genes like ***SLC6A4***, ***BDNF*** and ***RELN*** in peripheral samples. Such biomarkers could be used to track treatment response, monitor relapse risk and assess impact of psychosocial interventions. Moreover, longitudinal methylome studies could potentially reveal early warning signals of SCZ progression or environmental vulnerability. Altered DNA methylation patterns in response to adverse childhood experiences were identified after correcting for cell-type composition in saliva samples. These patterns were found to correlate with trauma exposure and mental health phenotypes, suggesting potential as biomarkers (82). Peripheral tissues have been shown to reflect epigenomic alterations, offering potential for biomarker development and personalized treatment strategies (83). A three-step AutoML-driven pipeline identified a novel blood-based epigenetic biosignature for SCZ, comprising methylation markers in IGF2BP1, CENPI and PSME4, with diagnostic discrimination validated in first-episode drug-naïve patients. This approach demonstrated potential for objective SCZ diagnostics using peripheral blood methylation profiles (84). Cross-tissue meQTLs were found to be prevalent and enriched in SCZ risk loci and expression QTLs, with one co-methylation network shared between brain and blood significantly associated with SCZ. These findings support the relevance of peripheral tissues for studying genetic-epigenetic interactions in psychiatric disorders (85).

Epigenetic mechanisms are inherently plastic, making them attractive therapeutic targets. Several histone deacetylase inhibitors (HDACi) and DNA methyltransferase inhibitors (DNMTi) are under investigation for cognitive and mood disorders. In SCZ, preclinical evidence suggests that HDAC inhibitors may reverse stress-induced chromatin alterations, improve synaptic plasticity, and reduce behavioral deficits. Personalized pharmacological interventions that modulate specific epigenetic states, such as ***SLC6A4*** promoter methylation or ***CACNA1C*** enhancer accessibility could complement antipsychotics and offer more targeted symptom relief (86).

The integration of multi-omics like genomics, transcriptomics, proteomics, metabolomics, epigenomics, connectomics and gut microbiomics technologies has been highlighted as a promising strategy to unravel the complex molecular mechanisms underlying SCZ (87,88). Such an integrative model would allow prediction of treatment response based on transcriptomic signatures, tailored psychosocial interventions based on environmental sensitivity genotypes, early preventive strategies for

at-risk individuals based on eQTL or chromatin accessibility maps. Machine learning approaches applied to these datasets have already begun to uncover subtypes of SCZ based on shared molecular signatures, aiding in differential diagnosis and individualized therapy planning.

Implications and Future Directions

Understanding G×E interactions via epigenomic and bioinformatic approaches provides a more nuanced view of SCZ's etiology, moving beyond single-gene or single-environment models (3,4,89). The utility of circadian biomarkers in evaluating treatment adherence and functional recovery in SCZ, as well as in identifying potential endophenotypes, is supported. These insights can inform risk prediction, personalized prevention strategies and the development of novel therapeutics targeting epigenetic modifications. Future research should focus on integrating multi-omics data, validating findings across diverse populations, and translating bioinformatic discoveries into clinical practice (81,90).

Future research should prioritize mechanistic clarity, temporal sequencing, and subgroup-specific risk profiling to inform precision-targeted preventive strategies.

Conclusion

G×E interactions, explored through the lenses of epigenomics and bioinformatics, are crucial for understanding the complexities of SCZ. Advances in these fields are not only deepening our understanding of disease mechanisms but are also paving the way for precision medicine approaches in psychiatry. While GWAS have identified a range of risk loci, such as *CACNA1C, ZNF804A* and *SLC6A4*, these genetic markers alone do not account for the full spectrum of disease risk or clinical variability. Emerging research highlights that G×E interactions, mediated through epigenetic mechanisms, provide a crucial framework for understanding individual susceptibility.

Recent advances in bioinformatics and epigenomic profiling have made it possible to map these dynamic regulatory landscapes and predict functional outcomes of genetic variants in specific cellular and environmental contexts. Integrating genetic, environmental, and computational data enhances understanding of SCZ pathogenesis, and supports the development of personalized, preventative and patient- centered interventions in mental health, thereby advancing both precision psychiatry and personalized treatment approaches.

Abbreviations

5-HT	Serotonin
BD	Bipolar disorder
COMT	Catechol-O-methyltransferase
CRDs	Cis-regulatory domains
CRP	c-reactive protein
eQTL	Expression quantitative trait loci
GWAS	Genome wide association studies
G×E	Gene-environment
GEO	Gene Expression Omnibus
GI	Gastrointestinal
GTEx	Genotype-Tissue Expression
HPA	Hypothalamic-pituitary-adrenal
LBP	Lipopolysaccharide-binding protein
PRS	Polygenic risk score

PTMs	Post-translational modifications
sCD14	soluble CD14
SCZ	Schizophrenia
SSD	Schizophrenia-spectrum disorders

REFERENCES

[1] O'Donovan MC, Craddock N, Norton N, Williams H, Peirce T, Moskvina V, et al. Identification of loci associated with schizophrenia by genome-wide association and follow-up. Nat Genet [Internet]. 2008 Sep [cited 2023 Dec 1];40(9):1053–5. Available from: https://www.nature.com/articles/ng.201

[2] Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014 Jul 24;511(7510):421–7.

[3] Karl T, Arnold JC. Schizophrenia: a consequence of gene-environment interactions? Front Behav Neurosci [Internet]. 2014 Dec 23 [cited 2025 May 27];8. Available from: https://www.frontiersin.org/journals/behavioral-neuroscience/articles/10.3389/fnbeh.2014.00435/full

[4] Wahbeh MH, Avramopoulos D. Gene-Environment Interactions in Schizophrenia: A Literature Review. Genes (Basel) [Internet]. 2021 Nov 23 [cited 2025 May 27];12(12):1850. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8702084/

[5] Rawani NS, Chan AW, Dursun SM, Baker GB. The Underlying Neurobiological Mechanisms of Psychosis: Focus on Neurotransmission Dysregulation, Neuroinflammation, Oxidative Stress, and Mitochondrial Dysfunction. Antioxidants [Internet]. 2024 Jun [cited 2025 May 30];13(6):709. Available from: https://www.mdpi.com/2076-3921/13/6/709

[6] Bhat S, Dao DT, Terrillion CE, Arad M, Smith RJ, Soldatov NM, et al. *CACNA1C* (Cav1.2) in the pathophysiology of psychiatric disease. Progress in Neurobiology [Internet]. 2012 Oct 1 [cited 2024 Mar 12];99(1):1–14. Available from: https://www.sciencedirect.com/science/article/pii/S0301008212000998

[7] Cai W, Zhou X, Chen Y, Gui S, Xu Y, Zhang J, et al. Association between CACNA1C gene polymorphism rs1006737 and risk of Bipolar disorder: a meta-analysis [Internet]. In Review; 2024 [cited 2025 May 21]. Available from: https://www.researchsquare.com/article/rs-3987637/v1

[8] Alsheikh AM. ZNF804A variants relation to schizophrenia: a systematic review. International Journal Of Community Medicine And Public Health [Internet]. 2022 Jul 27 [cited 2024 Jan 12];9(8):3297–303. Available from: https://www.ijcmph.com/index.php/ijcmph/article/view/9930

[9] Chang H, Xiao X, Li M. The schizophrenia risk gene ZNF804A: clinical associations, biological mechanisms and neuronal functions. Mol Psychiatry [Internet]. 2017 Jul [cited 2024 Dec 1];22(7):944–53. Available from: https://www.nature.com/articles/mp201719

[10] Bednarova A, Habalova V, Krivosova M, Marcatili M, Tkac I. Association Study of BDNF, SLC6A4, and FTO Genetic Variants with Schizophrenia Spectrum Disorders. Journal of Personalized Medicine [Internet]. 2023 Apr [cited 2023 Jun 21];13(4):658. Available from: https://www.mdpi.com/2075-4426/13/4/658

[11] Ikegame T, Bundo M, Okada N, Murata Y, Koike S, Sugawara H, et al. Promoter activity-based case-control association study on SLC6A4 highlighting hypermethylation and altered amygdala volume in male patients with schizophrenia [Internet]. bioRxiv; 2020 [cited 2025 May 16]. p. 2020.05.06.058792. Available from: https://www.biorxiv.org/content/10.1101/2020.05.06.058792v1

[12] Vijayan N, Iwayama Y, Koshy L, Natarajan C, Nair C, Allencherry PM, et al. Evidence of association of serotonin transporter gene polymorphisms with schizophrenia in a South Indian population. Journal of Human Genetics [Internet]. 2009 [cited 2023 Jun 30]; Available from: https://consensus.app/details/these-results-suggest-role-slc6a4-schizophrenia-possibly-vijayan/56bb337493595658b891fa131e9f8899/

[13] Baron M. Genetics of schizophrenia: I. Familial patterns and mode of inheritance. Biological Psychiatry [Internet]. 1986 Sep 1 [cited 2023 Jun 30];21(11):1051–66. Available from: https://www.biologicalpsychiatryjournal.com/article/0006-3223(86)90286-6/abstract

[14] Zhang H, Khan A, Kushner SA, Rzhetsky A. Dissecting schizophrenia phenotypic variation: the contribution of genetic variation, environmental exposures, and gene–environment interactions. Schizophr [Internet]. 2022

May 10 [cited 2025 May 27];8(1):1–5. Available from: https://www.nature.com/articles/s41537-022-00257-5

[15] van Os J, Rutten BP, Poulton R. Gene-Environment Interactions in Schizophrenia: Review of Epidemiological Findings and Future Directions. Schizophrenia Bulletin [Internet]. 2008 Nov 1 [cited 2025 May 27];34(6):1066–82. Available from: https://doi.org/10.1093/schbul/sbn117

[16] Narayan CL, Shikha D, Shekhar S. Schizophrenia in identical twins. Indian J Psychiatry [Internet]. 2015 [cited 2025 May 27];57(3):323–4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4623659/

[17] Tsuang MT, Stone WS, Faraone SV. Genes, environment and schizophrenia. Br J Psychiatry Suppl. 2001 Apr;40:s18-24.

[18] Pugliese V, Bruni A, Carbone EA, Calabrò G, Cerminara G, Sampogna G, et al. Maternal stress, prenatal medical illnesses and obstetric complications: Risk factors for schizophrenia spectrum disorder, bipolar disorder and major depressive disorder. Psychiatry Research [Internet]. 2019 Jan 1 [cited 2025 May 27];271:23–30. Available from: https://www.sciencedirect.com/science/article/pii/S0165178118306012

[19] Schmitt A, Falkai P, Papiol S. Neurodevelopmental disturbances in schizophrenia: evidence from genetic and environmental factors. J Neural Transm [Internet]. 2023 Mar 1 [cited 2024 Jan 31];130(3):195–205. Available from: https://doi.org/10.1007/s00702-022-02567-5

[20] Zhang H, Khan A, Kushner SA, Rzhetsky A. Dissecting schizophrenia phenotypic variation: the contribution of genetic variation, environmental exposures, and gene–environment interactions. Schizophr [Internet]. 2022 May 10 [cited 2024 Feb 27];8(1):1–5. Available from: https://www.nature.com/articles/s41537-022-00257-5

[21] Sonego AB, Prado DS, Uliana DL, Cunha TM, Grace AA, Resstel LBM. Pioglitazone attenuates behavioral and electrophysiological dysfunctions induced by two-hit model of schizophrenia in adult rodent offspring. European Neuropsychopharmacology [Internet]. 2024 Dec 1 [cited 2025 May 29];89:28–40. Available from: https://www.sciencedirect.com/science/article/pii/S0924977X24007272

[22] Billard JM, Lahogue C, Boulouard M, Menager F, Freret T, Billard JM, et al. A new 2-hit model combining serine racemase deletion and3 maternal separation displays behavioral and cognitive4 deficits associated with schizophrenia [Internet]. 2024 [cited 2025 May 29]. Available from: https://hal.science/hal-04627091

[23] Allswede DM, Cannon TD. Prenatal inflammation and risk for schizophrenia: A role for immune proteins in neurodevelopment. Development and Psychopathology [Internet]. 2018 Aug [cited 2025 May 27];30(3):1157–78. Available from: https://www.cambridge.org/core/journals/development-and-psychopathology/article/abs/prenatal-inflammation-and-risk-for-schizophrenia-a-role-for-immune-proteins-in-neurodevelopment/6B8DCC5ED1C343D79D4140B5A207599B

[24] Han VX, Patel S, Jones HF, Dale RC. Maternal immune activation and neuroinflammation in human neurodevelopmental disorders. Nat Rev Neurol [Internet]. 2021 Sep [cited 2025 May 27];17(9):564–79. Available from: https://www.nature.com/articles/s41582-021-00530-8

[25] Done DJ, Johnstone EC, Frith CD, Golding J, Shepherd PM, Crow TJ. Complications of pregnancy and delivery in relation to psychosis in adult life: data from the British perinatal mortality survey sample. BMJ [Internet]. 1991 Jun 29 [cited 2025 May 28];302(6792):1576–80. Available from: https://www.bmj.com/content/302/6792/1576

[26] Jones PB, Rantakallio P, Hartikainen AL, Isohanni M, Sipila P. Schizophrenia as a Long-Term Outcome of Pregnancy, Delivery, and Perinatal Complications: A 28-Year Follow-Up of the 1966 North Finland General Population Birth Cohort. AJP [Internet]. 1998 Mar [cited 2025 May 28];155(3):355–64. Available from: https://psychiatryonline.org/doi/full/10.1176/ajp.155.3.355

[27] Jablensky AV, Morgan V, Zubrick SR, Bower C, Yellachich LA. Pregnancy, Delivery, and Neonatal Complications in a Population Cohort of Women With Schizophrenia and Major Affective Disorders. AJP [Internet]. 2005 Jan [cited 2025 May 28];162(1):79–91. Available from: https://psychiatryonline.org/doi/full/10.1176/appi.ajp.162.1.79

[28] Cannon M, Jones PB, Murray RM. Obstetric Complications and Schizophrenia: Historical and Meta-Analytic Review. AJP [Internet]. 2002 Jul [cited 2025 May 28];159(7):1080–92. Available from: https://psychiatryonline.org/doi/full/10.1176/appi.ajp.159.7.1080

[29] Geddes JR, Verdoux H, Takei N, Lawrie SM, Bovet P, Eagles JM, et al. Schizophrenia and Complications of Pregnancy and Labor: An Individual Patient Data Meta-analysis. Schizophrenia Bulletin [Internet]. 1999 Jan 1 [cited 2025 May 28];25(3):413–23. Available from: https://doi.org/10.1093/oxfordjournals.schbul.a033389

[30] Fabre C, Pauly V, Baumstarck K, Etchecopar-Etchart D, Orleans V, Llorca PM, et al. Pregnancy, delivery and neonatal complications in women with schizophrenia: a national population-based cohort study. The Lancet Regional Health – Europe [Internet]. 2021 Nov 1 [cited 2025 May 28];10. Available from:

https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00186-1/fulltext

[31] Chan JKN, Lee KCK, Correll CU, So YK, Chan CY, Wong CSM, et al. Adverse obstetric and neonatal outcomes associated with maternal schizophrenia-spectrum disorders and prenatal antipsychotic use: a meta-analysis of 37,214,330 pregnancy deliveries and propensity-score weighted population-based cohort study assessing confounder dependency of risk estimates. Mol Psychiatry [Internet]. 2025 Mar [cited 2025 May 28];30(3):954–67. Available from: https://www.nature.com/articles/s41380-024-02723-1

[32] Nunes RG, Carrilho CG, Alves GS, Malaspina D, Kahn JP, Nardi AE, et al. Comparison of early risk factors between healthy siblings and subjects with schizophrenia and bipolar disorder. Front Psychiatry [Internet]. 2024 Apr 30 [cited 2025 May 28];15. Available from: https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2024.1374216/full

[33] Pelayo-Terán JM, Pérez-Iglesias R, Mata I, Carrasco-Marín E, Vázquez-Barquero JL, Crespo-Facorro B. Catechol-O-Methyltransferase (COMT) Val158Met variations and cannabis use in first-episode non-affective psychosis: Clinical-onset implications. Psychiatry Research [Internet]. 2010 Oct 30 [cited 2025 May 27];179(3):291–6. Available from: https://www.sciencedirect.com/science/article/pii/S016517810900328X

[34] Estrada G, Fatjó-Vilas M, Muñoz MJ, Pulido G, Miñano MJ, Toledo E, et al. Cannabis use and age at onset of psychosis: further evidence of interaction with COMT Val158Met polymorphism. Acta Psychiatrica Scandinavica [Internet]. 2011 [cited 2025 May 27];123(6):485–92. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1600-0447.2010.01665.x

[35] Zammit S, Owen MJ, Evans J, Heron J, Lewis G. Cannabis, COMT and psychotic experiences. The British Journal of Psychiatry [Internet]. 2011 Nov [cited 2025 May 27];199(5):380–5. Available from: https://www.cambridge.org/core/journals/the-british-journal-of-psychiatry/article/cannabis-comt-and-psychotic-experiences/933997569274F0AF17FD3BE0451399D6

[36] Lodhi RJ, Wang Y, Rossolatos D, MacIntyre G, Bowker A, Crocker C, et al. Investigation of the COMT Val158Met variant association with age of onset of psychosis, adjusting for cannabis use. Brain and Behavior [Internet]. 2017 [cited 2025 May 27];7(11):e00850. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/brb3.850

[37] Bosia M, Buonocore M, Bechi M, Stere LM, Silvestri MP, Inguscio E, et al. Schizophrenia, cannabis use and Catechol-O-Methyltransferase (COMT): Modeling the interplay on cognition. Progress in Neuro-Psychopharmacology and Biological Psychiatry [Internet]. 2019 Jun 8 [cited 2025 May 27];92:363–8. Available from: https://www.sciencedirect.com/science/article/pii/S0278584618307206

[38] Grechuk K, Azizi H, Sharma V, Khan T, Jolayemi A, Grechuk K, et al. Cannabis, Schizophrenia Risk and Genetics: A Case Report of a Patient With Homozygous Valine Catechol-O-Methyltransferase Polymorphism. Cureus [Internet]. 2021 Jun 18 [cited 2025 May 28];13(6). Available from: https://www.cureus.com/articles/54315-cannabis-schizophrenia-risk-and-genetics-a-case-report-of-a-patient-with-homozygous-valine-catechol-o-methyltransferase-polymorphism

[39] Fowler IL, Carr VJ, Carter NT, Lewin TJ. Patterns of Current and Lifetime Substance Use in Schizophrenia. Schizophrenia Bulletin [Internet]. 1998 Jan 1 [cited 2025 May 28];24(3):443–55. Available from: https://doi.org/10.1093/oxfordjournals.schbul.a033339

[40] Blanchard JJ, Brown SA, Horan WP, Sherwood AR. Substance use disorders in schizophrenia: Review, integration, and a proposed model. Clinical Psychology Review [Internet]. 2000 Mar 1 [cited 2025 May 28];20(2):207–34. Available from: https://www.sciencedirect.com/science/article/pii/S0272735899000331

[41] Khokhar JY, Dwiel LL, Henricks AM, Doucette WT, Green AI. The link between schizophrenia and substance use disorder: A unifying hypothesis. Schizophrenia Research [Internet]. 2018 Apr 1 [cited 2025 May 28];194:78–85. Available from: https://www.sciencedirect.com/science/article/pii/S0920996417302037

[42] Adan A, Marquez-Arrico JE, Río-Martínez L, Navarro JF, Martinez-Nicolas A. Circadian rhythmicity in schizophrenia male patients with and without substance use disorder comorbidity. Eur Arch Psychiatry Clin Neurosci [Internet]. 2024 Mar 1 [cited 2025 May 28];274(2):279–90. Available from: https://doi.org/10.1007/s00406-023-01560-7

[43] Paganin W, Signorini S. Salivary cortisol in Schizophrenia: a selective review and meta-analysis of controlled studies of the past decade. Biomarkers in Neuropsychiatry [Internet]. 2024 Dec 1 [cited 2025 May 28];11:100098. Available from: https://www.sciencedirect.com/science/article/pii/S2666144624000169

[44] Misiak B, Piotrowski P, Beszłej JA, Kalinowska S, Chęć M, Samochowiec J. Metabolic Dysregulation and Psychosocial Stress in Patients with Schizophrenia Spectrum Disorders: A Case-Control Study. Journal of Clinical Medicine [Internet]. 2020 Dec [cited 2025 May 29];9(12):3822. Available from: https://www.mdpi.com/2077-0383/9/12/3822

[45] Müller N. Inflammation in Schizophrenia: Pathogenetic Aspects and Therapeutic Considerations. Schizophrenia Bulletin [Internet]. 2018 Aug 20 [cited 2025 May 30];44(5):973–82. Available from: https://doi.org/10.1093/schbul/sby024

[46] Severance EG, Dickerson F, Yolken RH. Complex Gastrointestinal and Endocrine Sources of Inflammation in Schizophrenia. Front Psychiatry [Internet]. 2020 Jun 16 [cited 2025 May 30];11. Available from: https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2020.00549/full

[47] Anand N, Gorantla VR, Chidambaram SB. The Role of Gut Dysbiosis in the Pathophysiology of Neuropsychiatric Disorders. Cells [Internet]. 2023 Jan [cited 2025 May 29];12(1):54. Available from: https://www.mdpi.com/2073-4409/12/1/54

[48] Altamura AC, Pozzoli S, Fiorentini A, Dell'Osso B. Neurodevelopment and inflammatory patterns in schizophrenia in relation to pathophysiology. Progress in Neuro-Psychopharmacology and Biological Psychiatry [Internet]. 2013 Apr 5 [cited 2025 May 29];42:63–70. Available from: https://www.sciencedirect.com/science/article/pii/S0278584612002084

[49] Fišar Z. Biological hypotheses, risk factors, and biomarkers of schizophrenia. Progress in Neuro-Psychopharmacology and Biological Psychiatry [Internet]. 2023 Jan 10 [cited 2025 May 29];120:110626. Available from: https://www.sciencedirect.com/science/article/pii/S027858462200118X

[50] Oliver D, Chesney E, Cullen AE, Davies C, Englund A, Gifford G, et al. Exploring causal mechanisms of psychosis risk. Neuroscience & Biobehavioral Reviews [Internet]. 2024 Jul 1 [cited 2025 May 28];162:105699. Available from: https://www.sciencedirect.com/science/article/pii/S0149763424001684

[51] Debs SR, Rothmond DA, Zhu Y, Weickert CS, Purves-Tyson TD. Molecular evidence of altered stress responsivity related to neuroinflammation in the schizophrenia midbrain. Journal of Psychiatric Research [Internet]. 2024 Sep 1 [cited 2025 May 28];177:118–28. Available from: https://www.sciencedirect.com/science/article/pii/S0022395624003844

[52] Nour MM, Liu Y, El-Gaby M, McCutcheon RA, Dolan RJ. Cognitive maps and schizophrenia. Trends in Cognitive Sciences [Internet]. 2025 Feb 1 [cited 2025 May 28];29(2):184–200. Available from: https://www.cell.com/trends/cognitive-sciences/abstract/S1364-6613(24)00254-7

[53] Neill E, Tan EJ, Toh WL, Selvendra A, Morgan VA, Rossell SL, et al. Examining which factors influence age of onset in males and females with schizophrenia. Schizophrenia Research [Internet]. 2020 Sep 1 [cited 2024 Feb 5];223:265–70. Available from: https://www.sciencedirect.com/science/article/pii/S0920996420304394

[54] Heilbronner U, Malzahn D, Strohmaier J, Maier S, Frank J, Treutlein J, et al. A common risk variant in *CACNA1C* supports a sex-dependent effect on longitudinal functioning and functional recovery from episodes of schizophrenia-spectrum but not bipolar disorder. European Neuropsychopharmacology [Internet]. 2015 Dec 1 [cited 2025 May 31];25(12):2262–70. Available from: https://www.sciencedirect.com/science/article/pii/S0924977X15003077

[55] Zhu X, Li R, Kang G, Kang Q, Rao W, Yang M, et al. CACNA1C Polymorphism (rs2283291) Is Associated with Schizophrenia in Chinese Males: A Case-Control Study. Disease Markers [Internet]. 2019 [cited 2025 May 31];2019(1):8062397. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1155/2019/8062397

[56] Cerasa A, Quattrone A, Piras F, Mangone G, Magariello A, Fagioli S, et al. 5-HTTLPR, anxiety and gender interaction moderates right amygdala volume in healthy subjects. Social Cognitive and Affective Neuroscience [Internet]. 2014 Oct 1 [cited 2025 May 31];9(10):1537–45. Available from: https://doi.org/10.1093/scan/nst144

[57] Coury SM, Lombroso A, Avila-Quintero VJ, Taylor JH, Flores JM, Szejko N, et al. Systematic review and meta-analysis: Season of birth and schizophrenia risk. Schizophrenia Research [Internet]. 2023 Feb 1 [cited 2025 May 31];252:244–52. Available from: https://www.sciencedirect.com/science/article/pii/S0920996422004637

[58] Brown AS, Patterson PH. Maternal Infection and Schizophrenia: Implications for Prevention. Schizophrenia Bulletin [Internet]. 2011 Mar 1 [cited 2025 May 31];37(2):284–90. Available from: https://doi.org/10.1093/schbul/sbq146

[59] Khandaker GM, Zimbron J, Lewis G, Jones PB. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. Psychological Medicine [Internet]. 2013 Feb [cited 2025 May 31];43(2):239–57. Available from: https://www.cambridge.org/core/journals/psychological-medicine/article/abs/prenatal-maternal-infection-neurodevelopment-and-adult-schizophrenia-a-systematic-review-of-populationbased-studies/16A33FBE1245E2EA234933B4FB4BB9F2

[60] Albiñana C, Boelt SG, Cohen AS, Zhu Z, Musliner KL, Vilhjálmsson BJ, et al. Developmental exposure to vitamin D deficiency and subsequent risk of schizophrenia. Schizophrenia Research [Internet]. 2022 Sep 1

[cited 2025 May 31];247:26–32. Available from: https://www.sciencedirect.com/science/article/pii/S0920996421002164

[61] Chiang M, Natarajan R, Fan X. Vitamin D in schizophrenia: a clinical review. Evid Based Mental Health [Internet]. 2016 Jan 21 [cited 2025 May 31];19(1). Available from: https://mentalhealth.bmj.com/content/19/1/6

[62] Brown AS, Susser ES. Prenatal Nutritional Deficiency and Risk of Adult Schizophrenia. Schizophrenia Bulletin [Internet]. 2008 Nov 1 [cited 2025 May 31];34(6):1054–63. Available from: https://doi.org/10.1093/schbul/sbn096

[63] Firth J, Carney R, Stubbs B, Teasdale SB, Vancampfort D, Ward PB, et al. Nutritional Deficiencies and Clinical Correlates in First-Episode Psychosis: A Systematic Review and Meta-analysis. Schizophrenia Bulletin [Internet]. 2018 Oct 17 [cited 2025 May 31];44(6):1275–92. Available from: https://doi.org/10.1093/schbul/sbx162

[64] Akbarian S. Epigenetic mechanisms in schizophrenia. Dialogues in Clinical Neuroscience [Internet]. 2014 Sep 30 [cited 2024 Feb 16];16(3):405–17. Available from: https://doi.org/10.31887/DCNS.2014.16.3/sakbarian

[65] Delphin N, Aust C, Griffiths L, Fernandez F. Epigenetic Regulation in Schizophrenia: Focus on Methylation and Histone Modifications in Human Studies. Genes [Internet]. 2024 Mar [cited 2024 Oct 20];15(3):272. Available from: https://www.mdpi.com/2073-4425/15/3/272

[66] Föcking M, Doyle B, Munawar N, Dillon ET, Cotter D, Cagney G. Epigenetic Factors in Schizophrenia: Mechanisms and Experimental Approaches. Molecular Neuropsychiatry [Internet]. 2019 Feb 15 [cited 2025 May 27];5(1):6–12. Available from: https://doi.org/10.1159/000495063

[67] Moran P, Stokes J, Marr J, Bock G, Desbonnet L, Waddington J, et al. Gene × Environment Interactions in Schizophrenia: Evidence from Genetic Mouse Models. Neural Plasticity [Internet]. 2016 [cited 2025 May 27];2016(1):2173748. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1155/2016/2173748

[68] Pries LK, Gülöksüz S, Kenis G. DNA Methylation in Schizophrenia. In: Delgado-Morales R, editor. Neuroepigenomics in Aging and Disease [Internet]. Cham: Springer International Publishing; 2017 [cited 2025 May 30]. p. 211–36. Available from: https://doi.org/10.1007/978-3-319-53889-1_12

[69] Kiltschewskij DJ, Reay WR, Cairns MJ. Schizophrenia is associated with altered DNA methylation variance. Mol Psychiatry [Internet]. 2025 Apr [cited 2025 May 30];30(4):1383–95. Available from: https://www.nature.com/articles/s41380-024-02749-5

[70] Tesfaye M, Spindola LM, Stavrum AK, Shadrin A, Melle I, Andreassen OA, et al. Sex effects on DNA methylation affect discovery in epigenome-wide association study of schizophrenia. Mol Psychiatry [Internet]. 2024 Aug [cited 2025 May 30];29(8):2467–77. Available from: https://www.nature.com/articles/s41380-024-02513-9

[71] Kiltschewskij DJ, Reay WR, Geaghan MP, Atkins JR, Xavier A, Zhang X, et al. Alteration of DNA Methylation and Epigenetic Scores Associated With Features of Schizophrenia and Common Variant Genetic Risk. Biological Psychiatry [Internet]. 2024 Apr 1 [cited 2025 May 31];95(7):647–61. Available from: https://www.sciencedirect.com/science/article/pii/S0006322323014336

[72] Marques D, Vaziri N, Greenway SC, Bousman C. DNA methylation and histone modifications associated with antipsychotic treatment: a systematic review. Mol Psychiatry [Internet]. 2025 Jan [cited 2025 May 31];30(1):296–309. Available from: https://www.nature.com/articles/s41380-024-02735-x

[73] Delphin N, Aust C, Griffiths L, Fernandez F. Epigenetic Regulation in Schizophrenia: Focus on Methylation and Histone Modifications in Human Studies. Genes [Internet]. 2024 Mar [cited 2025 May 31];15(3):272. Available from: https://www.mdpi.com/2073-4425/15/3/272

[74] Girdhar K, Hoffman GE, Jiang Y, Brown L, Kundakovic M, Hauberg ME, et al. Cell-specific histone modification maps in the human frontal lobe link schizophrenia risk to the neuronal epigenome. Nat Neurosci [Internet]. 2018 Aug [cited 2025 May 31];21(8):1126–36. Available from: https://www.nature.com/articles/s41593-018-0187-0

[75] Abdolmaleky HM, Thiagalingam S. Chapter 14 - Pathogenic histone modifications in schizophrenia are targets for therapy. In: Peedicayil J, Grayson DR, Avramopoulos D, editors. Epigenetics in Psychiatry (Second Edition) [Internet]. Academic Press; 2021 [cited 2025 May 31]. p. 309–19. Available from: https://www.sciencedirect.com/science/article/pii/B9780128235775000064

[76] Chen Y zhou, Zhu X mei, Lv P, Hou X kai, Pan Y, Li A, et al. Association of histone modification with the development of schizophrenia. Biomedicine & Pharmacotherapy [Internet]. 2024 Jun 1 [cited 2025 May 31];175:116747. Available from: https://www.sciencedirect.com/science/article/pii/S0753332224006310

[77] Martínez-Peula O, Morentin B, Callado LF, Meana JJ, Rivero G, Ramos-Miguel A. Permissive epigenetic regulatory mechanisms at the histone level are enhanced in postmortem dorsolateral prefrontal cortex of individuals with schizophrenia. Journal of Psychiatry and Neuroscience [Internet]. 2024 Feb 1 [cited 2025 May 31];49(1):E35–44. Available from: https://www.jpn.ca/content/49/1/E35

[78] Medrano-Fernández A, Barco A. Nuclear organization and 3D chromatin architecture in cognition and neuropsychiatric disorders. Mol Brain [Internet]. 2016 Sep 5 [cited 2025 May 31];9(1):83. Available from: https://doi.org/10.1186/s13041-016-0263-x

[79] Duan J. Chapter 14 - Chromatin modification and remodeling in schizophrenia. In: Binda O, editor. Chromatin Signaling and Neurological Disorders [Internet]. Academic Press; 2019 [cited 2025 May 31]. p. 303–30. (Translational Epigenetics; vol. 12). Available from: https://www.sciencedirect.com/science/article/pii/B9780128137963000146

[80] Girdhar K, Hoffman GE, Bendl J, Rahman S, Dong P, Liao W, et al. Chromatin domain alterations linked to 3D genome organization in a large cohort of schizophrenia and bipolar disorder brains. Nat Neurosci [Internet]. 2022 Apr [cited 2025 May 31];25(4):474–83. Available from: https://www.nature.com/articles/s41593-022-01032-6

[81] Periyasamy S, Youssef P, John S, Thara R, Mowry BJ. Genetic interactions of schizophrenia using gene-based statistical epistasis exclusively identify nervous system-related pathways and key hub genes. Front Genet [Internet]. 2024 Jan 8 [cited 2025 May 27];14. Available from: https://www.frontiersin.org/journals/genetics/articles/10.3389/fgene.2023.1301150/full

[82] Bearer EL, Mulligan BS. Epigenetic Changes Associated with Early Life Experiences: Saliva, A Biospecimen for DNA Methylation Signatures. Current Genomics. 2018 Dec 1;19(8):676–98.

[83] Khavari B, Cairns MJ. Epigenomic Dysregulation in Schizophrenia: In Search of Disease Etiology and Biomarkers. Cells [Internet]. 2020 Aug [cited 2025 May 31];9(8):1837. Available from: https://www.mdpi.com/2073-4409/9/8/1837

[84] Karaglani M, Agorastos A, Panagopoulou M, Parlapani E, Athanasis P, Bitsios P, et al. A novel blood-based epigenetic biosignature in first-episode schizophrenia patients through automated machine learning. Transl Psychiatry [Internet]. 2024 Jun 17 [cited 2025 May 31];14(1):1–12. Available from: https://www.nature.com/articles/s41398-024-02946-4

[85] Lin D, Chen J, Perrone-Bizzozero N, Bustillo JR, Du Y, Calhoun VD, et al. Characterization of cross-tissue genetic-epigenetic effects and their patterns in schizophrenia. Genome Med [Internet]. 2018 Feb 26 [cited 2025 May 31];10(1):13. Available from: https://doi.org/10.1186/s13073-018-0519-4

[86] Bahari-Javan S, Varbanov H, Halder R, Benito E, Kaurani L, Burkhardt S, et al. HDAC1 links early life stress to schizophrenia-like phenotypes. Proceedings of the National Academy of Sciences [Internet]. 2017 Jun 6 [cited 2025 May 31];114(23):E4686–94. Available from: https://www.pnas.org/doi/abs/10.1073/pnas.1613842114

[87] Guan F, Ni T, Zhu W, Williams LK, Cui LB, Li M, et al. Integrative omics of schizophrenia: from genetic determinants to clinical classification and risk prediction. Mol Psychiatry [Internet]. 2022 Jan [cited 2025 May 31];27(1):113–26. Available from: https://www.nature.com/articles/s41380-021-01201-2

[88] Modai S, Shomron N. Molecular Risk Factors for Schizophrenia. Trends in Molecular Medicine [Internet]. 2016 Mar 1 [cited 2025 May 31];22(3):242–53. Available from: https://www.cell.com/trends/molecular-medicine/abstract/S1471-4914(16)00017-4

[89] Moran P, Stokes J, Marr J, Bock G, Desbonnet L, Waddington J, et al. Gene × Environment Interactions in Schizophrenia: Evidence from Genetic Mouse Models. Neural Plasticity [Internet]. 2016 [cited 2025 May 27];2016(1):2173748. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1155/2016/2173748

[90] Shokrgozar A, Rahimi M, Shoraka S. Identification of key genes and pathways in schizophrenia: a bioinformatics analysis based on GWAS and GEO. Front Psychiatry [Internet]. 2025 Apr 7 [cited 2025 May 27];16. Available from: https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2025.1464676/full