Exploring the roots of schizophrenia: Current research and future directions (Review)

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Abstract. Mental health holds critical global significance. However, mental illness remains insufficiently acknowledged worldwide. The prevalence and economic impact of mental disorders continue to rise, contributing notably to increased disability rates. Schizophrenia, with a global lifetime prevalence of ~0.4%, is a leading cause of disability. Currently, revealing the pathological mechanisms of schizophrenia, exploring early objective diagnosis and individualized treatment prediction indicators, and developing more effective treatment technologies are still hotspots in research. Several studies highlight schizophrenia as a severe, multifactorial disorder that directly disrupts brain function and profoundly impacts daily life. This review provides an overview of recent advances in schizophrenia research, summarising current research on the mechanisms of its pathogenesis; both genetic and environmental factors exert a significant influence on schizophrenia. Furthermore, investigations into animal models for schizophrenia research aim to establish more precise models, which will facilitate further exploration of the disease's pathogenesis and therapeutic approaches.

Contents

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1. Introduction

Mental health, recognized as a fundamental human right, holds critical importance globally. However, mental illness is escalating worldwide (1). Major mental disorders, such as depressive disorders, anxiety disorders, bipolar disorder, schizophrenia and autism spectrum disorders, contribute significantly to this burden. The Global Burden of Diseases, Injuries and Risk Factors Study (GBD) 2019 highlights a substantial increase in the burden of non-communicable diseases, including mental health conditions, over the past three decades (1990-2019) (2,3). While diagnostic rates of mental disorders may appear higher in high-income countries due to better healthcare infrastructure and reporting, access to effective treatment and mental health services remains insufficient across both high- and low-income regions (4).

Schizophrenia, a severe mental disorder with a global lifetime prevalence of ~0.4%, stands as one of the leading causes of disability worldwide (5-7). Numerous affected individuals experience long-term functional impairment, with significant life-altering consequences such as social isolation, self-stigmatization and increased difficulty in forming relationships (8). Schizophrenia is not characterized by pathognomonic symptoms, but rather by a constellation of features typically categorized into positive, negative and cognitive domains (9). Positive symptoms reflect distortions of normal perception and behavior, including delusions, hallucinations and disorganized behavior. Negative symptoms involve diminished emotional expression and motivation, manifesting as avolition, asociality and affective flattening. Cognitive deficits, such as impairments in attention, working memory and executive functioning, are increasingly recognized as core features of the disorder (10,11). Some researchers argue that cognitive impairment is the primary determinant of long-term functional disability in schizophrenia (12). Diagnosing schizophrenia and evaluating treatment effectiveness remain challenging, primarily due to the absence of reliable, objective biomarkers (13). This review describes the potential pathogenesis of schizophrenia from environmental and genetic factors. Further summarising model studies of schizophrenia, this work integrates genetic, environmental and modelling perspectives to advance the understanding of the disorder from both holistic and cellular-molecular viewpoints. This approach yields significant benefits for research into

characteristic biomarkers, pathophysiology and aetiological mechanisms.

2. Methods

This is a narrative review aiming to summarise current research on the influence of genetic and environmental factors on schizophrenia, alongside studies concerning research models for schizophrenia. The primary themes are the pathogenesis of schizophrenia (genetic and environmental factors) and model studies (animal and cellular models). References were retrieved from the PubMed database {using the following search string: {[(schizophrenia) OR (psychosis)] AND [(pathogenesis) OR (mechanism) OR (gene) OR (environment); (schizophrenia) OR (psychosis)] AND [(model) OR (modeling) OR (animal model) OR (cell model)]}, encompassing reviews, randomised controlled trials, meta-analyses and experimental research data from the past decade. Based on this review, we have screened articles exploring the pathogenesis of schizophrenia from both genetic and environmental perspectives, as well as disease research methodologies utilising animal and cellular models. Studies incorporating schizophrenia diagnoses will be included. Research primarily consisting of review reports will be excluded. Model studies failing to explicitly state that relevant ethical approvals were obtained will be excluded.

3. Mechanism of pathogenesis

The precise pathogenesis of schizophrenia remains to be fully elucidated. However, it is generally accepted that genetic, environmental and immunological factors are key contributors to the disorder (14,15). The causes of schizophrenia are multifactorial, typically arising from the complex interplay of these factors (Fig. 1) (16).

Genetic factors and schizophrenia. Genetic factors play a significant role in schizophrenia's etiology, with heritability estimates of ~80 and ~45% for monozygotic twins (17). Following the completion of the human genome sequencing in 2003, genetic research has expanded considerably (18). Approximately 70-80% of human genes are expressed in the brain, and numerous genes involved in synaptic transmission have been linked to psychiatric disorders (19). Schizophrenia exhibits familial aggregation, and studies involving adoption and twins suggest that genetic factors outweigh environmental influences (20,21). The 22q11.2 gene deletion was one of the first variants identified in relation to schizophrenia, but no single genetic mutation has been conclusively tied to the disorder (22,23). Individuals with a deletion in the glutathione S-transferase theta 1 gene within the 22q11.2 region exhibit an increased risk of developing schizophrenia (24). A genetic study encompassing 36,989 patients with schizophrenia and 113,075 controls revealed 108 independent loci strongly associated with the disorder. These include the gene encoding dopamine D2 receptor, the primary target of nearly all antipsychotic drugs, as well as genes involved in glutamatergic signaling and synaptic plasticity, such as glutamate ionotropic receptor α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid type subunit 1, glutamate ionotropic receptor noncompetitive malondialdehyde type subunit 2A and serine racemase, providing genetic support for existing hypotheses that implicate both dopaminergic and glutamatergic systems in schizophrenia (25-27). A separate study of 5,220 patients with schizophrenia and 18,823 controls identified 145 independent gene loci linked to the disorder (28). These risk variants primarily cluster in neuronal and synaptic gene sets, and ongoing research with larger sample sizes continues to enhance the understanding of schizophrenia's genetic underpinnings (29). Certain researchers proposed that common genetic variants account for 30-50% of schizophrenia's genetic liability, but the risk posed by any individual variant is limited (30).

Notably, several studies have identified new mutations clustered in loss-of-function genes in individuals with childhood-onset schizophrenia (31). These studies highlight that many of the mutations affect genes linked to neurodevelopmental disorders, including ATPase Na+/K+ transporting subunit alpha 3, Up-frameshift suppressor 3B, snf2 related CREBBP activator protein and polynucleotide kinase 3'-phosphatase (32-34).

Further research has underscored the role of epigenetic modifications in schizophrenia (35). Epigenetic processes, including histone modification, DNA methylation, chromatin remodeling and non-coding RNA expression, contribute to the regulation of gene expression. Guidotti *et al* (36) suggested that targeting the link between reduced Reelin expression in patients with schizophrenia and epigenetic dysregulation may offer a more promising therapeutic approach. A large-scale study by Jaffe *et al* (37) identified 2,104 methylated CpG sites in the forebrain cortex of schizophrenia cases, which differed significantly from controls. Additionally, histone deacetylase (HDAC) inhibitors have shown potential for improving clinical symptoms of schizophrenia (38). Evidence from brain samples of patients with schizophrenia indicates altered epigenetic markers, including elevated H3R17 methylation levels (39), increased cortical HDAC1 expression (40) and reduced cortical HDAC2 levels (41).

Environmental factors and schizophrenia. Environmental factors, once overlooked, are now widely acknowledged as significant contributors to the development of schizophrenia. It is increasingly recognized that a combination of biological, psychological and social environmental influences may play a critical role in the onset and progression of the disorder, as summarized in Table I (42-53).

Environmental factors (such as prenatal infections, childhood trauma and adolescent cannabis use) can shape schizophrenia risk across critical developmental windows, from early gestation to young adulthood, impacting both individuals and populations. These factors may play a more significant role in the onset of schizophrenia than common genetic variants identified in global genomic studies (54).

Schizophrenia's origins may be rooted in neurodevelopmental disruptions during the fetal stage. Research has shown that maternal exposure to infections or stress during pregnancy can increase the likelihood of schizophrenia in offspring (55-57). Early investigations into psychiatric disorders following in-utero infections primarily focused on schizophrenia (58). A significant amount of research has examined the effects of *Toxoplasma gondii* infection, though

Table I. Environmental factors and schizophrenia.

Factors	Type	Mechanism	(Refs.)
Biological-infectious/immune-related factors	*Toxoplasma gondii*	Linked to neuroinflammation	(42)
	Cytomegalovirus	Linked to brain damage	(43,44)
	Herpes simplex viruses	Linked to brain damage	(45,46)
Psychological-early life psychological stressors	Early life stress	Linked to neurodevelopmental impairments	(47)
	Childhood adversity	Linked to neurodevelopmental impairments	(48)
Social-socio-environmental exposures	Psychosocial stress	Linked to mental stress	(49)
	Cannabis use	Linked to neuro-regulatory disorder	(50,51)
	Alcohol use	Linked to neuroinflammation	(52)
	Migration	Linked to mental stress	(53)

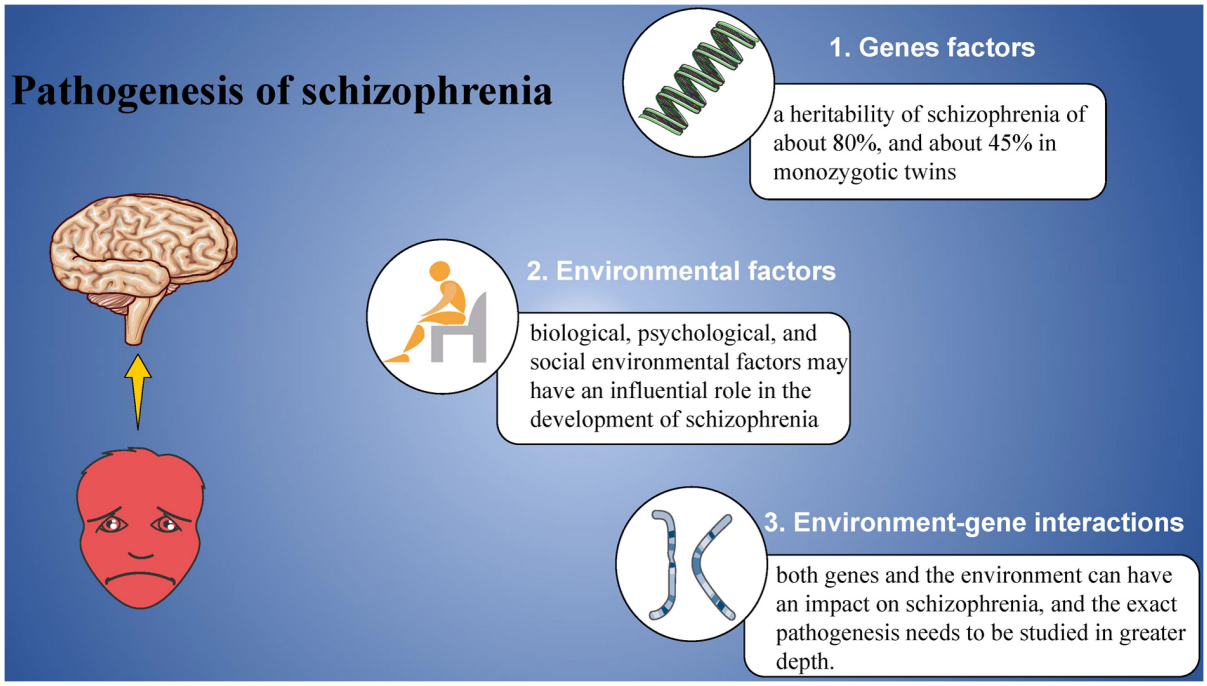

Figure 1. Pathogenesis of schizophrenia. This review mainly introduces three pathogeneses of schizophrenia, including: Gene factors, environmental factors and environment-gene interactions.

the exact mechanism by which it contributes to schizophrenia remains elusive. *Toxoplasma gondii*, a unicellular eukaryote primarily hosted by felines but capable of infecting any warm-blooded animal, has been associated with behavioral alterations in humans (59). In healthy individuals, *Toxoplasma gondii* infection typically shows no overt clinical symptoms, but during pregnancy, it can be transmitted to the fetus via the placenta (60). Serological studies have revealed significantly higher serum levels of anti-*Toxoplasma* IgG and IgM in patients with schizophrenia compared to healthy controls (61-63). Current research indicates that *Toxoplasma* infection may disrupt central nervous system neurotransmitter regulation, the blood-brain barrier, immune stress responses and inflammatory reactions, factors closely associated with schizophrenia pathogenesis (64,65).

Childhood adversity is also known as childhood trauma, such as abuse, domestic violence and neglect (66). Individuals with schizophrenia who have experienced such adversity may exhibit earlier cognitive deficits, possibly due to neurodevelopmental impairments (67). There is substantial evidence linking childhood maltreatment to more severe psychotic symptoms, with those affected being more than four times as likely to develop a psychotic disorder following trauma (68,69). Additionally, such adversity is strongly associated with positive symptoms of schizophrenia, such as hallucinations and delusions (70).

Several studies have also highlighted the influence of the social environment on the onset of schizophrenia. Factors such as social adversity, discrimination, poverty and substance use-especially cannabis-have all been identified as potential contributors to schizophrenia development (71-75).

Environment-gene interactions and schizophrenia. As research has advanced, it has become increasingly evident that schizophrenia is a multifactorial disorder, prompting more studies focused on the interaction between genetic and environmental factors in its development. Epidemiological studies have established a clear link between infection and schizophrenia (76). Among the infectious agents, *Toxoplasma gondii* has been the most extensively studied, with substantial evidence supporting its association with schizophrenia. A meta-analysis by Wang *et al* (77) revealed that schizophrenia-associated genes were notably enriched in the *Toxoplasma gondii* IgG seropositive population, suggesting that *Toxoplasma* infection may influence the expression of genes related to schizophrenia. However, a more recent study by Lori *et al* (78) indicated that signs of *Toxoplasma* infection do not serve as reliable predictors of schizophrenia. As previously noted, *Toxoplasma gondii* infection exerts a significant influence on schizophrenia by affecting associated genetic loci. Additional studies have indicated that inflammatory environments and stress responses within the central nervous system may contribute to psychiatric disorders, including schizophrenia, by affecting the hypothalamic-pituitary-adrenal axis (79), with anti-inflammatory medications showing promise in alleviating certain schizophrenia symptoms (80). In the context of environment-gene interactions in schizophrenia, neuroinflammation driven by infectious agents has been recognized as a potential mechanism. Elevated peripheral inflammatory markers, such as C-reactive protein, have been observed in patients with schizophrenia (81). Furthermore, high levels of immune antibodies in infected mothers have been suggested as potential causes of neuropathological changes (82). Neuropathological alterations in offspring resulting from maternal infection with infectious viruses such as influenza and measles may increase the incidence rate by 1-20% (83).

Cannabis use interacts with genetic factors in the pathogenesis of schizophrenia (84). Further studies suggest that individuals with a genetic predisposition may be more susceptible to developing schizophrenia as a result of cannabis use (85). Cannabis use may influence the development of schizophrenia by affecting specific genetic loci, potentially alleviating symptoms of central nervous system disorders (86). A study on the catechol-o-methyltransferase (COMT) Val158Met polymorphism revealed that the COMT Val158Met Val allele is associated with an increased risk of psychosis following cannabis use (87). In a further study, Met allele homozygotes for the COMT Val158Met polymorphism were more sensitive to stress and exhibited a neurotic tendency in response to daily stressors (88). Additionally, research on specific alleles of the Protein Kinase B and fatty acid amide hydrolase genes has demonstrated that cannabis users with certain genetic variations are more susceptible to showing psychotic symptoms (89). However, the relationship between cannabis use and schizophrenia is complex and somewhat controversial. Cannabis is known to alleviate stress symptoms and individuals who have experienced high levels of stress or depression may be more inclined to use it (90). This highlights the intricate nature of the link between cannabis use and schizophrenia, further reinforcing the understanding that schizophrenia is a multifactorial mental illness.

Extensive evidence indicates that both genetic and environmental factors contribute to schizophrenia, although the exact pathogenesis remains elusive. More comprehensive studies exploring the interaction between genes and the environment could offer valuable insights into the causes, pathology and potential treatment options for schizophrenia.

4. Schizophrenia modeling studies

Constructing an appropriate model is a powerful approach to understanding how a disease affects an organism. The schizophrenia model, described here from both an animal and cellular perspective, provides a key example.

Animal models. The unique complexity of the human brain in both function and structure poses challenges for schizophrenia research. Studies of the living patient's brain primarily rely on neuroimaging and cognitive testing, while direct analysis of brain tissue is restricted to post-mortem investigations. Factors such as ongoing environmental stress, genetic influences and drug effects in patients complicate research, necessitating the development of reliable animal models. An effective model should encompass three core characteristics: Face validity, construct validity and predictive validity (91). Face validity requires that the model replicates the symptoms of schizophrenia, while construct validity ensures the model mimics the structural and functional abnormalities observed in the disease. Predictive validity ensures that therapeutic interventions can reverse the disease-like phenotype. Animal models, including both invertebrates and vertebrates, such as non-human primates, offer valuable tools for investigating the mechanisms underlying schizophrenia risk. The MATRICS program, developed by the National Institute of Mental Health, identified seven domains relevant to schizophrenia and proposed corresponding rodent-based assays (92).

Established high-risk factors, such as maternal infections and early neurodevelopmental disorders, play a critical role in the pathophysiology of schizophrenia. Animal models addressing these factors often involve perinatal and/or early postnatal environmental manipulation, or the administration of medications, followed by longitudinal studies of offspring development. One of the earliest approaches to modeling schizophrenia in animals involved inducing ventral hippocampal lesions in rats through localized toxin injections on postnatal day 7. Another widely used model is the administration of methylazomethanol (MAM) to pregnant rats (93), which induces neuroanatomical, electrophysiological and behavioral alterations in offspring, with the timing of MAM exposure-particularly on gestational day 17-being a critical determinant of model fidelity (94).

Inducing maternal immune activation (MIA) in pregnant rodents is another widely used strategy for constructing schizophrenia models. Strong evidence suggests that rodents and primates subjected to MIA during gestation produce offspring exhibiting anatomical, neurochemical, electrophysiological and behavioral alterations consistent with schizophrenia (95). Using this model, Steullet *et al* (96) demonstrated that changes in parasympathetic interneurons and their associated perineuronal networks (extracellular matrix structures critical for structural and synaptic plasticity) in the prefrontal cortex

and hippocampal formation were linked to cognitive deficits, findings aligning with autopsy reports from patients with schizophrenia (97).

The most commonly utilized pharmacological agents in animal models of schizophrenia are dopamine enhancers and noncompetitive malondialdehyde (NMDA) receptor antagonists. Amphetamine, a dopamine-enhancing agent known to induce psychosis in humans, does not cause social impairment in rodents with continuous administration, although it does affect certain forebrain-associated cognitive functions (98). Studies have shown that amphetamine impairs cholinergic basal neurons in rat cerebral cortical projections, suggesting that dysregulation of this activity is related to attentional dysfunction (99-101). Wearne *et al* (102) identified 96 differentially expressed proteins in the prefrontal cortex of methamphetamine-treated rats, with 20% linked to schizophrenia pathogenesis. Additionally, certain dopamine enhancers are known to elevate tumor necrosis factor α (TNFα) and MDA, signaling increased inflammation and oxidative stress (103). NMDA receptor antagonists are often used in rodents to simulate the hypofunction of NMDA glutamate receptors observed in patients with schizophrenia (104). The NMDA receptor antagonist pentachlorophenol (PCP) induces hallucinations, delusions, speech impoverishment and cognitive deficits in humans, while in rodents, PCP causes social withdrawal and cognitive impairments.

Advances in human genome-wide studies have recently revealed a growing list of schizophrenia-associated and candidate genes (105), emphasizing the importance of genetic factors in the development of animal models. The identification of these candidate genes has significantly contributed to refining and enhancing schizophrenia model systems (106,107). Certainly, animal models used in modern research must obtain approval from the Animal Research Ethics Committee and comply with the animal experiment guidelines or directives formulated by relevant institutions.

Cellular models. In the post-genome-wide era of schizophrenia, the development of cellular models incorporating schizophrenia-associated variants has become a crucial tool for understanding the disease. Both autopsy and *in vivo* neuroimaging studies have highlighted neuronal and glial cell abnormalities as prominent features of schizophrenia.

SH-SY5Y neuroblastoma cells are widely used as an *in vitro* model for neuropsychiatric research due to their low cost, ease of culture and reproducibility (108). These cells resemble immature neurons, and human-derived SH-SY5Y neuroblastoma cells can differentiate into neuronal cells when exposed to various substances, with both undifferentiated and differentiated SH-SY5Y cells capable of secreting dopamine (109). While some current research questions the maturity of SH-SY5Y-derived neurons, they express well-established neuronal maturation markers, including neuronal nuclei, high-molecular-weight neurofilament, microtubule-associated protein 2 and growth-associated protein 43 (110,111). Furthermore, there is substantial evidence supporting the suitability of SH-SY5Y-derived neurons as functional and morphological neuronal models.

Artificially manipulating SH-SY5Y cells to construct cellular models greatly benefits research into schizophrenia at the cellular and molecular levels. SH-SY5Y cells treated with the NMDA antagonist MK-801 are commonly used to model neuronal damage seen in patients with schizophrenia. MK-801 downregulates the sirtuin 1/microRNA (miRNA)-134 signaling pathway and Ca^{2+} influx, replicating dysfunction in the prefrontal cortex (112). Additionally, SH-SY5Y cells are utilized to investigate the molecular mechanisms underlying reduced neurite spines, a known susceptibility factor for schizophrenia that is also observed in postmortem brain samples from patients (113). Lentiviral infection of SH-SY5Y cells with short hairpin RNA targeting the schizophrenia susceptibility gene DISC1 results in mitochondrial fragmentation and respiratory defects. Studies on DISC1 in SH-SY5Y cells suggest that DISC1-depleted cells fail to maintain proper mitochondrial oxidative phosphorylation complex function, and mitochondrial abnormalities may have a role in the onset of schizophrenia (114). SHANK2, a gene encoding a protein essential for the formation and development of glutamatergic synapses, has also been implicated in schizophrenia pathogenesis (115). Mutations in SHANK2 in SH-SY5Y cells impair early neuronal differentiation, alter cell growth properties and reduce both pre- and post-synaptic protein expression (116). Collectively, these studies strongly support the use of SH-SY5Y cells as a reliable model for investigating schizophrenia. Additionally, SH-SY5Y cells have proven valuable as a screening platform for potential antipsychotic drugs (117).

Induced pluripotent stem cells (iPSCs) were initially utilized to model diseases linked to highly penetrant genetic variants with significant phenotypic effects, and more recently, iPSC-derived neurons have been employed to construct models of psychiatric disorders. Although iPSCs are not commonly used to model schizophrenia-related processes directly, genetic variants associated with schizophrenia can substantially affect iPSCs. For instance, the 22q11.2 deletion has been shown to reduce the proliferation rate of iPSCs in culture (118). Furthermore, the study of patient-derived iPSCs enables the screening of genetic variants that may not be detectable through human genome-wide studies, while also shedding light on the roles of relevant candidate variants. Although the reproducibility of iPSC models remains a subject of debate, careful selection of iPSC lines for reprogramming, as well as thoughtful consideration of subjects and controls, can mitigate many of their limitations (119).

iPSC-derived neurons mainly include neural progenitor cells (NPCs), glutamatergic neurons, dopaminergic (DAergic) neurons and γ-aminobutyric acid-secreting (GABAergic) neurons. Studies involving NPCs have broadened the understanding of schizophrenia, highlighting its complexity as a neurodevelopmental disorder. The glutamatergic neurons model is based on the glutamatergic hypothesis, where SNP-4bp mutations in DISC1 in glutamatergic neurons result in reduced presynaptic labeling and defective neurotransmitter release. Notably, the mutant phenotype can be reversed by restoring the DISC1 sequence, thereby demonstrating how synaptic defects contribute to schizophrenia (120). The DAergic neurons model is linked to the dopaminergic dysfunction hypothesis, which remains central to schizophrenia research, supported by both animal models and human studies (121). The iPSC-derived DAergic neurons model helps elucidate the molecular mechanisms underlying the relationship between genetic variants

and dopaminergic dysfunction in patients with schizophrenia. While most studies on iPSC-derived GABAergic neurons have focused on Huntington's disease, research has indicated the downregulation of key GABA pathway genes in GABAergic neurons derived from patients with schizophrenia, suggesting there is still significant room for further exploration of GABAergic neurons in schizophrenia (122).

Non-neuronal cells can be reprogrammed into neuronal cells or used directly as cell models. It has been demonstrated that fibroblasts can be directly converted into patient-specific inducible neurons, such as glutamatergic and GABAergic neurons, through transcription factor overexpression and the addition of miRNAs (123). Non-neuronal cells, like HEK293 cells, can also serve as models for studying genes and proteins associated with schizophrenia. The primate-specific mutant isoform Kv11.1-3.1 of the brain voltage-gated potassium channel exhibits aberrant folding and impaired migration to the plasma membrane, which correlates with prolonged neuronal action potentials observed in patients with schizophrenia. Researchers have developed a platform for screening drugs that restore Kv11.1-3.1 function using HEK293 cells (124). Studies on the DPYSL2 isoform in HEK293 cells have shown that alterations in risk alleles can lead to changes in cellular morphology, affecting synaptic transmission and correlating with schizophrenia susceptibility (125,126).

In vitro models informed by human genome-wide studies offer significant insights into the brain pathology of schizophrenia and its underlying molecular mechanisms. Additionally, these models provide valuable tools for screening potential novel antipsychotic drugs and validating therapeutic candidates. As schizophrenia models continue to evolve, their role in advancing research and drug development will become more pivotal.

5. Limitations

However, current research on schizophrenia largely focuses on relatively narrow perspectives and the symptoms of schizophrenia exhibit significant individual variation. Such individual variations pose significant challenges to the establishment of disease models and the conduct of more in-depth research. Furthermore, differing hypotheses exist regarding the pathogenesis of schizophrenia, and genetic outcomes also vary across different populations. This review primarily employed broad keywords in its literature search (such as schizophrenia, mental illness, model studies, animal models, cellular models, environment, genes and epigenetics), and consequently may have overlooked certain publications. Advancing the translation of findings from animal/cell model research into human pathology facilitates researchers' deeper understanding of schizophrenia and aids in drug screening and validation.

6. Conclusion

The causes of schizophrenia are unknown and include complex genetic inheritance, the environment and the interaction of the two. Current findings suggest that schizophrenia involves a number of different neurotransmitters, including dopamine, glutamate and serotonin. More research related to schizophrenia remains to be done, and the construction of more accurate models will facilitate further exploration of the pathogenesis of schizophrenia as well as its treatment.

At present, mental disorders pose considerable challenges both in diagnosis and treatment. Schizophrenia lacks precise biomarkers or pathological criteria for diagnosis, and psychiatric disorders frequently co-occur with it, presenting symptoms that vary significantly among individuals. The current mainstream medications for treating schizophrenia carry significant side effects, resulting in a markedly reduced quality of life for patients. Whether through human genomics research or more complex and precise biological modelling, the aim is to gain deeper insights into schizophrenia, uncover its precise mechanisms, and identify therapeutic drugs with enhanced efficacy and reduced side effects. In the current state of mental health, research into mechanisms and therapeutic drug development is of considerable value and significance.

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Competing interests

The authors declare that they have no competing interests.

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