

Molecular Biology and Genetics Research on Schizophrenia

Chongwei Shi

Oral and Maxillofacial Surgery, University of Michigan, Michigan, 48109, USA

ABSTRACT

Schizophrenia is a severe mental disorder characterized by a complex etiology involving genetic, environmental, and neurobiological factors. Recent advances in molecular biology and genetics have provided crucial insights into the pathogenesis of schizophrenia. This paper reviews the fundamental concepts and etiological theories of schizophrenia, with a detailed examination of the applications of molecular biology and genetics in schizophrenia research, particularly focusing on the latest developments in genomics and genetic susceptibility studies. By analyzing the functions of known relevant genes and exploring gene-environment interactions, this paper reveals the complex molecular mechanisms underlying schizophrenia and discusses future research directions. Our research indicates that integrating modern molecular biology techniques and genetic methods will aid in early diagnosis and precise treatment of schizophrenia, advancing clinical applications and optimizing public health strategies.

KEYWORDS

Schizophrenia; Molecular Biology; Genetics; Genomics; Gene-Environment Interaction

1. INTRODUCTION

Schizophrenia is a multifaceted mental disorder characterized by disruptions in thought, perception, and behavior. Understanding its pathogenesis involves exploring both genetic and environmental factors. Recent research highlights the critical role of gene-environment interactions and epigenetic mechanisms in the disease's development. Genetic studies, including genome-wide association studies (GWAS), have identified several risk genes, while epigenetics reveals how environmental influences, such as prenatal stress or nutritional deficiencies, can modify gene expression and contribute to the disorder. This integrated approach provides valuable insights into the complex mechanisms underlying schizophrenia and informs strategies for early diagnosis and targeted interventions [1].

2. BASIC CONCEPTS OF SCHIZOPHRENIA

2.1. Definition and Symptoms of Schizophrenia

Schizophrenia is a chronic and severe mental disorder primarily characterized by severe distortions in perception of reality. This disease affects not only an individual's thoughts and emotions but also significantly impairs daily functioning and social adaptability. The definition of schizophrenia involves various abnormal symptoms experienced by patients, which are typically classified into three main categories: positive symptoms, negative symptoms, and cognitive symptoms. Positive symptoms refer to the addition or abnormality of normal thoughts and behaviors, including hallucinations and delusions. Among hallucinations, auditory hallucinations are the most common,

where patients may hear non-existent voices or conversations. Delusions are erroneous beliefs that do not align with reality, such as believing one is being followed or possessing special abilities. Thought disorder, where patients struggle with logical reasoning or maintaining coherent conversation, is also a positive symptom [2]. Negative symptoms involve a reduction or absence of normal functions, including emotional blunting, social withdrawal, and diminished motivation. Emotional blunting is characterized by reduced emotional responses to the environment and others. Social withdrawal manifests as reduced social activities and avoidance of contact with others. Diminished motivation leads to a lack of initiative and action willingness, affecting the ability to perform daily activities and self-care. Cognitive symptoms involve impairments in cognitive functions, including attention and memory issues, as well as executive function deficits. Patients may experience difficulties in concentrating and remembering, with executive function deficits affecting their ability to plan and organize tasks, impacting decision-making and problem-solving abilities. Symptoms of schizophrenia typically first appear in adolescence or early adulthood, and the severity and manifestations vary among individuals. Diagnosis relies on detailed clinical assessments and a comprehensive analysis of patient symptoms, while treatment usually combines medication and psychosocial interventions to help manage symptoms and improve quality of life.

2.2. Etiological Theories of Schizophrenia

The etiological theories of schizophrenia encompass multiple factors, including genetic, neurobiological, and environmental influences. These theories aim to explain the complex pathogenesis of schizophrenia. Firstly, genetic theories suggest that schizophrenia has a notable genetic susceptibility. Family and twin studies have shown that the incidence of schizophrenia is higher among family members than in the general population, particularly in monozygotic twins, where the risk of developing the disorder is significantly increased if one twin is affected. These findings indicate that genetic factors play a crucial role in the onset of schizophrenia. Research has also identified several gene variations associated with schizophrenia, such as DISC1, COMT, and DTNBP1, which may influence brain neurodevelopment and function, thereby increasing the risk of schizophrenia. Secondly, neurobiological theories focus on the relationship between schizophrenia and abnormalities in brain structure and function. Studies have found that patients with schizophrenia often exhibit structural and functional abnormalities, such as reduced cortical thickness, enlarged ventricles, and neurotransmitter system dysregulation. The dopamine hypothesis, in particular, posits that positive symptoms of schizophrenia may be related to excessive activity in the dopamine system. Additionally, other neurotransmitter systems, such as glutamate and serotonin (5-HT), are also believed to play significant roles in the pathological mechanisms of schizophrenia. Environmental factors theories suggest that the occurrence of schizophrenia is influenced not only by genetic factors but also by environmental factors [3]. For instance, prenatal infections, malnutrition, psychosocial stress, and early life experiences may be associated with the risk of developing schizophrenia. Research has indicated that maternal influenza infection during pregnancy may be a potential risk factor for schizophrenia, and social environmental stressors, such as childhood trauma or social exclusion, may trigger or exacerbate the disease. Finally, gene-environment interaction theories emphasize that the development of schizophrenia results from the combined effects of genetic susceptibility and environmental factors. This theory suggests that genetic susceptibility may influence an individual's response to environmental stress, while environmental factors may impact the risk of developing schizophrenia by altering gene expression or brain development. For example, certain gene variations may make individuals more sensitive to environmental stress, thereby increasing the risk of schizophrenia. These etiological theories provide a multidimensional perspective for understanding schizophrenia, laying a crucial scientific foundation for developing effective prevention and treatment strategies.

3. MOLECULAR BIOLOGY FUNDAMENTALS

3.1. Overview of Genomics

Genomics is the science of studying the entire genome of organisms, including aspects such as gene structure, function, evolution, and interactions. In schizophrenia research, genomics provides a comprehensive framework for uncovering genetic factors and molecular mechanisms associated with the disorder. Key aspects of genomics include genome sequencing, gene expression analysis, and genome-wide association studies (GWAS). Genome sequencing technologies allow scientists to perform detailed analyses of entire genomes, revealing all genetic variations present. Since the completion of the Human Genome Project, genome sequencing technologies have significantly advanced, providing valuable data resources for schizophrenia research. These data not only help identify genes and variations associated with schizophrenia but also promote a deeper understanding of gene function and disease mechanisms. Gene expression analysis involves studying gene expression patterns under different physiological and pathological conditions [4]. In schizophrenia research, gene expression analysis helps identify specific changes in gene expression related to the disease, which may reflect dysregulation or functional abnormalities in neural networks within the brain. For instance, by comparing gene expression profiles between schizophrenia patients and healthy controls, researchers can identify biomarkers associated with schizophrenia and further explore their potential pathogenic mechanisms. Genome-wide association studies (GWAS) are another key genomics technique that identifies genetic variations associated with diseases through large-scale genome-wide screening. GWAS has successfully revealed multiple genetic variations related to schizophrenia, such as genes associated with the dopamine system and neurodevelopment. These findings not only contribute to understanding the genetic basis of schizophrenia but also provide theoretical support for personalized treatment and prevention strategies. Overall, the application of genomics in schizophrenia research has greatly advanced our understanding of the genetic mechanisms underlying the disorder. Through techniques such as genome sequencing, gene expression analysis, and GWAS, scientists are able to gain insights into the molecular mechanisms of schizophrenia, laying the groundwork for future diagnostic and therapeutic developments.

3.2. Discovery of Schizophrenia-Associated Genes

Research on schizophrenia has identified several genes associated with the disorder, providing important clues to understanding the genetic basis and pathogenesis of schizophrenia. Recently, advances in techniques such as genome-wide association studies (GWAS), whole-genome sequencing, and functional genomics have revealed key genes related to schizophrenia. These gene discoveries not only help elucidate the genetic background of schizophrenia but also offer potential targets for future diagnosis and treatment. Firstly, DISC1 (Disrupted in Schizophrenia 1) is an important schizophrenia-associated gene. Variations in the DISC1 gene are closely related to the occurrence of schizophrenia, with the gene playing a critical role in neurodevelopment and synaptic formation. Research has found that mutations or abnormal expression of DISC1 may lead to changes in brain structure and function, thereby increasing the risk of schizophrenia. Secondly, COMT (Catechol-O-Methyltransferase) is another important gene associated with schizophrenia. The enzyme encoded by the COMT gene plays a crucial role in dopamine metabolism. Different variations of this gene can affect dopamine levels, thereby influencing the manifestation of schizophrenia. Notably, the Val158Met polymorphism of COMT has been found to be related to susceptibility and severity of schizophrenia symptoms. Additionally, DTNBP1 (Dystrobrevin-binding Protein 1) is also associated with the risk of schizophrenia. The DTNBP1 gene is involved in the regulation of synaptic function and neurotransmission. Research indicates that variations in DTNBP1 may affect the normal function of neural circuits, thereby increasing the risk of schizophrenia. Other schizophrenia-associated genes include NRG1 (Neuregulin 1) and CACNA1C (Calcium Channel, Voltage-Dependent, L-Type, Alpha 1C Subunit). The NRG1 gene plays a role in neurodevelopment and

synaptic plasticity, with its variations associated with the risk of schizophrenia. The *CACNA1C* gene encodes a calcium channel involved in neuronal signal transmission, with variations in this gene also related to susceptibility to schizophrenia. These gene discoveries not only reveal the genetic basis of schizophrenia but also provide direction for further exploration of disease mechanisms and development of novel treatment strategies. By studying these relevant genes and their functions, scientists hope to identify more effective early diagnostic and personalized treatment methods, thereby improving the quality of life for individuals with schizophrenia [5].

4. ADVANCES IN GENETIC RESEARCH

4.1. Genetic Susceptibility Research

Genetic susceptibility research is a crucial area in uncovering the etiology of schizophrenia. By exploring genetic variations associated with the disease, it aids in identifying high-risk individuals and understanding the genetic basis of the illness. In recent years, advances in genomics technology have led to significant progress in genetic susceptibility research for schizophrenia. Firstly, large-scale Genome-Wide Association Studies (GWAS) have played a central role in studying genetic susceptibility to schizophrenia. GWAS identifies genetic markers associated with schizophrenia by scanning variations across the entire genome. Research has revealed that susceptibility genes for schizophrenia are distributed across multiple genomic regions, involving genes related to neurodevelopment, synaptic function, and neurotransmitter systems. For example, genes such as *MIR137*, *ZNF804A*, and *CACNA1C* have been closely linked to the risk of schizophrenia. These findings not only enhance our understanding of the genetic basis of schizophrenia but also provide a foundation for identifying potential therapeutic targets. Secondly, family studies and twin studies have provided important data for understanding the genetic susceptibility to schizophrenia [6]. Family studies show a higher incidence of schizophrenia among family members, indicating a certain degree of genetic susceptibility to the disease. Twin studies further confirm the impact of genetic factors on the development of schizophrenia, with a significantly increased risk of illness in the co-twin if one identical twin is affected. These results suggest that genetic factors play a crucial role in the development of schizophrenia, but susceptibility is not attributed to a single gene; rather, it results from the interplay of multiple genes and environmental factors. Moreover, the application of genomic sequencing technologies has achieved breakthroughs in genetic susceptibility research. Whole-genome sequencing enables researchers to identify rare genetic variations present in schizophrenia patients, which may have significant implications for the disease's occurrence. For instance, rare copy number variations (CNVs) associated with schizophrenia have been identified, which might lead to changes in gene dosage affecting brain development and function. Genetic susceptibility research also explores the interaction between genetic and environmental factors. Studies have found that genetic susceptibility may be modulated by environmental factors such as prenatal infections, early trauma, and social stress. These environmental factors may interact with genetic susceptibility to increase the risk of developing schizophrenia. Overall, genetic susceptibility research provides critical information for understanding the genetic basis of schizophrenia, revealing multiple genetic variations and mechanisms associated with the disease. These research findings help identify high-risk individuals, improve early diagnosis, and develop personalized treatment strategies, thus advancing the prevention and treatment of schizophrenia.

4.2. Genome-Wide Association Studies (GWAS)

Genome-Wide Association Studies (GWAS) are a powerful tool used to uncover genetic variations associated with complex diseases such as schizophrenia. GWAS systematically scans the entire genome to identify single nucleotide polymorphisms (SNPs) and other genetic markers related to disease risk, helping to identify potential susceptibility genes and pathological mechanisms. In schizophrenia research, GWAS has become a core method for understanding the genetic basis of the

disease. The key steps in GWAS include selecting large case and control samples, conducting high-density genotyping of the entire genome, and performing statistical analyses to identify genetic markers significantly associated with the disease. Researchers use high-throughput genotyping chips to analyze samples and employ statistical methods such as linear regression and logistic regression to evaluate the association between each genetic variation and disease risk. These analyses help reveal genetic variations associated with schizophrenia and assess their contribution to disease risk. GWAS has successfully identified several genetic variations associated with schizophrenia [7]. For example, MIR137 and ZNF804A are two prominent susceptibility genes discovered in multiple independent GWAS, showing a significant association with schizophrenia risk. The MIR137 gene is involved in neurodevelopment and synaptic function, and its variations may impact brain structure and function, thereby increasing the risk of schizophrenia. The ZNF804A gene is related to the regulation of brain structure and function, with its variations being associated with cognitive dysfunction in schizophrenia. Additionally, the CACNA1C gene is another important gene identified in GWAS. The calcium channel encoded by CACNA1C plays a crucial role in neurotransmitter release and synaptic transmission. Variations in this gene have been linked to schizophrenia and other psychiatric disorders such as bipolar disorder, suggesting its potential key role in the disease's pathogenesis. GWAS has also identified some copy number variations (CNVs) associated with schizophrenia. These variations involve large segments of duplication or deletion in the genome, which may lead to changes in gene dosage affecting neurodevelopment and function. For instance, copy number variations in the 22q11.2 region have been shown to be associated with the occurrence of schizophrenia. The results from GWAS not only reveal the genetic basis of schizophrenia but also provide new biomarkers and potential therapeutic targets. By identifying genetic variations related to schizophrenia, scientists can better understand the disease's pathological mechanisms and explore treatment strategies targeting specific genes or genetic pathways. Additionally, GWAS provides a basis for personalized medicine, aiding in the development of preventive and therapeutic strategies tailored to different genetic backgrounds. Overall, genome-wide association studies have played a crucial role in the genetic research of schizophrenia, with their findings contributing to the advancement of early diagnosis, prevention, and personalized treatment of the disease.

5. MOLECULAR MECHANISMS

5.1. Gene-Environment Interactions

Gene-environment interactions offer a crucial perspective for understanding the pathogenesis of complex diseases such as schizophrenia. This theory posits that genetic susceptibility and environmental factors jointly influence the onset and progression of the disease. Research into gene-environment interactions reveals how environmental factors affect schizophrenia risk by modulating genetic susceptibility and how genetic susceptibility influences an individual's response to environmental stressors. Firstly, the sensitivity of genetic factors to environmental influences is central to gene-environment interactions. Certain genetic variants may make individuals more sensitive to environmental stressors, such as psychosocial stress and early-life trauma. For example, variations in the 5-HTTLPR gene are associated with stress response; individuals carrying the short allele exhibit a significantly increased risk of developing schizophrenia when exposed to negative life events. This suggests that environmental stress may affect disease onset through interactions with specific genetic susceptibilities. Environmental factors may also contribute to the pathogenesis of schizophrenia by influencing gene expression. Epigenetics is a critical field in studying gene-environment interactions, focusing on how environmental factors affect gene transcription and expression. Factors such as prenatal infection, malnutrition, or early stress might alter gene methylation or histone modifications, influencing neurodevelopment and increasing schizophrenia risk. For instance, prenatal infection is thought to affect fetal brain development by triggering maternal immune responses, thereby raising the risk of schizophrenia. Moreover, gene-environment

interactions can affect schizophrenia risk by influencing neurodevelopment and function. Environmental factors such as early-life stress and social isolation may alter brain development, particularly affecting neural circuit formation and synaptic plasticity, which in turn affects an individual's ability to adapt to the environment. For example, social isolation may disrupt the brain's stress response system, impacting emotional regulation and cognitive function, thus increasing schizophrenia risk. Research into gene-environment interactions underscores the importance of early intervention and personalized prevention. Understanding specific gene-environment interactions can help identify high-risk individuals and develop targeted prevention and intervention strategies. For example, early psychological support and stress coping training for individuals with high genetic susceptibility may help reduce the risk of schizophrenia. Overall, research on gene-environment interactions reveals the complexity of schizophrenia's pathogenesis, emphasizing the combined role of genetic susceptibility and environmental factors. This field of study not only deepens our understanding of the pathological mechanisms of schizophrenia but also provides new insights for early prevention and personalized intervention [8].

5.2. Epigenetics and Schizophrenia

Epigenetics is the study of gene expression regulation without changes in the DNA sequence itself, involving mechanisms such as DNA methylation, histone modification, and non-coding RNA functions. Recently, epigenetics has played a significant role in schizophrenia research, revealing how environmental factors influence the pathogenesis of schizophrenia by modulating gene expression. Firstly, DNA methylation is a crucial epigenetic modification that affects gene transcriptional activity. Abnormal DNA methylation patterns commonly observed in schizophrenia patients suggest that altered methylation states may be related to the disease's onset. Studies have found abnormal methylation patterns in certain gene regions of schizophrenia patients, which could lead to dysregulation of critical genes involved in neurodevelopment. For instance, abnormal methylation of the *DISC1* gene might disrupt its normal function, impacting brain development and increasing schizophrenia risk. Secondly, histone modifications are also key mechanisms of epigenetic regulation. Modifications such as acetylation and methylation of histones can influence gene openness and transcriptional activity. Research has shown abnormal histone modification patterns in the brains of schizophrenia patients, which may lead to dysregulation of neurodevelopment-related genes. For example, demethylation of histone H3K27me3 might lead to the derepression of inhibitory genes, affecting neurodevelopment and function. Non-coding RNAs, particularly long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), also play significant roles in the epigenetic regulation of schizophrenia. lncRNAs can regulate gene transcription and epigenetic modifications, affecting neurodevelopment and function. Abnormal expression levels of certain lncRNAs in schizophrenia patients are associated with disease onset and progression. miRNAs regulate gene expression by targeting mRNA stability and translation processes. Studies have found significant changes in the levels of specific miRNAs in schizophrenia patients, which may impact neuronal development and function, thereby relating to the disease's pathology. Environmental factors, such as prenatal infection, nutritional deficiencies, and social stress, also influence schizophrenia risk through epigenetic mechanisms. These environmental factors can alter DNA methylation, histone modifications, and non-coding RNA expression, affecting neurodevelopment and function. For example, prenatal infection might change the epigenetic state of the fetal brain, influencing schizophrenia susceptibility. In summary, epigenetics provides new perspectives for understanding the pathogenesis of schizophrenia. By revealing how epigenetic modifications affect gene expression, scientists gain insights into how environmental factors and genetic susceptibility interact to influence schizophrenia risk. These research findings not only offer new targets for early diagnosis and personalized treatment but also provide important theoretical foundations for developing new intervention strategies.

6. CONCLUSION

Schizophrenia is a complex mental disorder involving multiple genetic and environmental factors. Genetic research, particularly genome-wide association studies (GWAS), has identified several genetic variations associated with schizophrenia, providing crucial information about the disease's genetic basis. Epigenetic research further reveals how environmental factors influence disease risk by modulating gene expression, highlighting the importance of gene-environment interactions in schizophrenia's pathogenesis. In conclusion, research on schizophrenia not only enhances our understanding of the disease's genetic and epigenetic mechanisms but also offers new insights for early diagnosis and personalized treatment. Future research should continue exploring the complex interactions between genetic and environmental factors to advance more effective prevention and treatment strategies.

REFERENCES

- [1] Indonesia Schizophrenia Consortium, et al. "Mapping genomic loci implicates genes and synaptic biology in schizophrenia." *Nature* 604.7906 (2022): 502-508.
- [2] Kato, Hidekazu, et al. "The genetic architecture of schizophrenia: review of large-scale genetic studies." *Journal of Human Genetics* 68.3 (2023): 175-182.
- [3] Farsi, Zohreh, and Morgan Sheng. "Molecular mechanisms of schizophrenia: Insights from human genetics." *Current Opinion in Neurobiology* 81 (2023): 102731.
- [4] Mealer, Robert G., et al. "Glycobiology and schizophrenia: a biological hypothesis emerging from genomic research." *Molecular Psychiatry* 25.12 (2020): 3129-3139.
- [5] Tiihonen, Jari, et al. "Molecular signaling pathways underlying schizophrenia." *Schizophrenia Research* 232 (2021): 33-41.
- [6] Nakamura, Takumi, and Atsushi Takata. "The molecular pathology of schizophrenia: An overview of existing knowledge and new directions for future research." *Molecular Psychiatry* 28.5 (2023): 1868-1889.
- [7] Trifu, Simona Corina, et al. "Genetics of schizophrenia." *Experimental and therapeutic medicine* 20.4 (2020): 3462-3468.
- [8] McCutcheon, Robert A., Tiago Reis Marques, and Oliver D. Howes. "Schizophrenia—an overview." *JAMA psychiatry* 77.2 (2020): 201-210.