

Review

The Relationship between Hereditary Predisposition and Epigenetic Mechanisms of Schizophrenia Development

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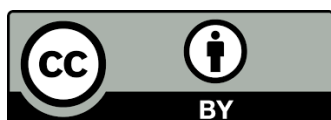
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Abstract

Schizophrenia is a multifactorial mental disorder associated with multiple SNPs in the human genome, located mainly outside the annotated protein-coding genes. These regions contain a large number of retroelements, which drive epigenetic regulation. Therefore, it is suggested that schizophrenia-associated SNPs exert their influence on the pathological functioning and activation of retroelements, which contribute to epigenetic imbalance in the brain with the development of pathological processes. A reflection of these changes is a shift in the expression of specific microRNAs, including those arising from retroelements and those that interact with them. Such microRNA changes disrupt the regulation of protein-coding genes in the brain. Retroelement expression products, both transcripts and proteins, drive immunopathological reactions in the brain that lead to inflammation. As a result, patients with schizophrenia develop progressive clinical symptoms. In addition, insertions of activated retroelements can disrupt gene regulation in the brain. An analysis of scientific literature was conducted, which presents data from experimental and clinical studies on the increased activity of HERV, LINE, and Alu retroelements in the brain in schizophrenia. Moreover, to prove the impact of these changes on the epigenetic imbalance in schizophrenia, 19 retroelement-derived microRNAs whose expression is impaired in the



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disease are described. The obtained results may form the basis for targeted therapy of schizophrenia using the described microRNAs as tools and targets for intervention.

Keywords

microRNA; polymorphisms; predisposition; retroelements; schizophrenia; epigenetic factors

1. Introduction

Schizophrenia is a multifactorial neuropsychiatric disorder with a global prevalence of 1% of the human population. Schizophrenia is characterized by executive dysfunction, disorganized speech, hallucinations, and delusions, and is one of the top 10 causes of disability worldwide [1]. Treatment resistance is characteristic of 33% [2] - 36.7% [3] of patients with schizophrenia. Therefore, new approaches to the development of schizophrenia therapy are critical, among which targeted therapy using epigenetic mechanisms of disease development, which are reversible, may be promising. The heritability of schizophrenia, according to twin research methods, is 73% [4] - 79% [5], which indicates a high potential for influencing this disease factor. Epigenetic factors play a vital role in the implementation of genetic information and its interaction with environmental factors in multifactorial diseases. Retroelements are drivers of epigenetic regulation [6], highly sensitive sensors of environmental influences [7], and key regulators of neurogenesis [8].

Epigenetic factors include DNA methylation, histone modifications, and the influence of non-coding RNAs (ncRNAs), such as long noncoding RNAs (lncRNAs) and microRNAs. According to an EWAS (epigenome-wide association study) meta-analysis, 1048 differentially methylated loci (DMLs) are associated with treatment-resistant schizophrenia [9]. This demonstrates the potential to target this factor using microRNA as a tool. Because microRNAs can function as guides for DNA methyltransferase in RNA-directed DNA methylation (RdDM) mechanisms [10], particularly at retroelement loci [11]. A recent meta-analysis showed that 213 VMPs (variably methylated positions) were associated with schizophrenia based on EWAS of genomic DNA samples from blood cells, some of which overlapped genes involved in neural function (S100P, KCNQ1, KCNK10, HTR2A, GRM2, GLRA1, ADBR3) [12]. Acceleration of biological aging in late life was also determined in patients with schizophrenia compared to healthy controls according to DNA methylation data [13]. It should be noted that the cause of impaired epigenetic regulation leading to schizophrenia may be changes in the activity of retroelements, given their role in neurogenesis [8] and the regulation of epigenetic factors in ontogenesis [6, 7].

According to a systematic review, several lncRNAs in the pathogenesis of schizophrenia have been determined: BDNF-AS, DISC-2, Gomafu, TUG1, and MEG3. These lncRNAs regulate synaptic plasticity, inflammation, and nervous system development. Changes in the expression of these lncRNAs have been determined in brain tissues and peripheral blood of schizophrenia patients [14]. A number of original studies have found associations between various lncRNAs and schizophrenia: AK096174, uc011dma.1, DB340248, EST00000509804-1 [15]. Also, a network was constructed among lncRNA, miRNA, and mRNA (ENSG00000251562 > miR-22-3p > SIRT1; ENSG00000251562 > miR-26a-5p > EZH2), whose expression is altered in exosomes of patients

with the first episode of schizophrenia, influencing the development of schizophrenia [16]. In patients with schizophrenia, a significant decrease in antisense lncRNA expression to the interferon gamma gene (IFNG-AS1) was found, with a significant correlation with the expression of the IFNG gene [17]. The relationships between lncRNAs HCP5 and ZNF883 and specific microRNAs miR-130b-5p, miR-520a-5p, miR-150-3p, and target mRNAs DFFA, DIABLO, DNAJC3, CYLD, and EGR3 in the regulation of apoptosis in schizophrenia were determined [18]. Increased levels of lncRNA NONHSAT089447, which regulates dopamine receptor expression, were detected in blood mononuclear cells of schizophrenia patients [19]. Reduced expression of lncRNA NEAT1, which is involved in the regulation of oligodendrocytes, was detected in cerebral cortex samples from patients with schizophrenia [20]. Changes in the expression of lncRNAs RP11-390F4.3, RP5-884C9.2, and RP1-135L22.1 were determined in peripheral mononuclear cells of patients with early-onset schizophrenia [21]. Therefore, the question of the probable role of retroelements in the development of schizophrenia, which are the most important sources of the emergence of lncRNAs and miRNAs, may be relevant. Currently, 405 retroelement-derived microRNAs and 23,379 lncRNA transcripts containing retroelement sequences have been described in humans [22].

Due to the significant role of heredity in the development of schizophrenia, GWAS (genome-wide association studies) were conducted to determine the impact of various polymorphisms on the disease. As a result, the association of many SNPs (single-nucleotide polymorphisms) and CNVs (copy number variations) with schizophrenia was determined. Thus, back in 2014, an analysis of GWAS results on large samples of patients with schizophrenia (36989) and controls (113075) showed the presence of 128 independent associations covering 108 specific conservative loci of the genome, of which 83 loci had not been previously described [23]. In 2018, a meta-analysis identified another 50 new loci associated with schizophrenia [24]. In 2025, 140 genes with differential polymorphisms associated with schizophrenia pathogenesis were identified from exome sequencing data [25]. In 2025, 218 genomic loci associated with schizophrenia were identified using T1 data, 138 loci using DTI (diffusion tensor imaging) data [26]. In order to correlate polymorphisms with epigenetic factors, I have proposed that many polymorphisms associated with schizophrenia, most of which are located in intergenic, intronic, and regulatory regions, exert their influence on the epigenetics of schizophrenia by changing the functioning and activity of retroelements. This is because retroelement genes are located in intergenic, intronic, and regulatory regions of the human genome [27]. Pathological activation of retroelements can result in epigenetic imbalance, which is expressed in observed changes in genome methylation [9, 12, 13] under the influence of impaired expression of microRNAs [10, 11] derived from retroelements [22].

Since retroelements are drivers of epigenetic regulation [6] and neurogenesis [8], their classification warrants further examination. Retroelements are specific DNA sequences that can move to a new locus by reverse transcription of their own RNAs with their integration. If retroelements encode their own enzymes for movement (reverse transcriptase and integrase), they are called autonomous. These include LTR (long terminal repeat)-containing retroelements and non-LTR elements LINEs (long interspersed nuclear elements). Non-autonomous retroelements that do not contain LTR include SINE (short interspersed nuclear elements), including Alu, and SVA (SINE-VNTR-Alu) [28]. Various retroelements are distributed across all chromosomes, making up a significant proportion of the genome (42.44%). Of these, LINEs

account for 20.67% (the most common are LINE1 – 16.77%, LINE2 – 3.4%), LTR-RE – 8.84% (mainly human endogenous retroviruses – HERVs), SINE – 12.78% (the most common are Alu – 10.1% and MIR – 2.65%), SVA – 0.15% [27]. It should be noted that numerous clinical and experimental studies have identified pathological activation of various retroelements.

2. Review Framework

This article will cover the following sections:

1. Mechanisms of influence of schizophrenia-associated SNPs on retroelement function in disease pathogenesis. This section will examine several ways in which retroelements influence the development of schizophrenia, with examples. It will also demonstrate the mechanisms by which SNPs influence the dysfunction of non-coding RNAs associated with retroelements. The limitations of existing data on the influence of SNPs on retroelement function in schizophrenia pathogenesis will be discussed, along with possible ways to overcome them.
2. Evidence for retroelement activation in the development of schizophrenia. This section presents the results of clinical and experimental studies demonstrating significant activation of HERVs, LINEs, and Alus in patients with schizophrenia. Not only genetic predisposition (SNPs associated with schizophrenia cause retroelement dysfunction), but also viral infections are suggested as causes of pathological activation. Specific mechanisms of schizophrenia pathogenesis associated with the adverse effects of retroelement protein products on the brain are discussed. Possible pathways for influencing these mechanisms, along with their advantages and disadvantages, are identified.
3. Mechanisms of influence of retroelements on the etiopathogenesis of schizophrenia. This section sequentially outlines the pathways by which retroelements influence the schizophrenia development: insertional mutagenesis, protein-mediated neuroinflammation, direct interference with neurotransmission, and microRNA-mediated dysregulation.
4. Relationship between retroelements and epigenetic factors in schizophrenia development. This section examines the mechanisms by which retroelements contribute to the pathogenesis of schizophrenia through interactions with their derived microRNAs, DNA modification enzymes, and histone tails.

3. Mechanisms of Influence of Schizophrenia-Associated SNPs on Retroelement Function in Disease Pathogenesis

The influence of SNPs associated with schizophrenia [23-26] on retroelement function is mediated by several mechanisms (Figure 1). First, retroelement genes inserted near protein-coding genes become essential sources of binding sites for transcription factors [29, 30]. Secondly, retroelements are the evolutionary sources of enhancers, silencers, intronic regulatory sequences, insulators, and even the exons of protein-coding genes themselves [31]. Accordingly, any changes in the nucleotide sequences of retroelements can cause mediated dysregulation of specific genes. Third, retroelements have been a major source of genes for lncRNAs and microRNAs throughout evolution [22]. Therefore, retroelement transcripts can function as competitive endogenous RNAs (ceRNAs) that bind to non-coding RNAs derived from them via complementary nucleotide sequences (Figure 2). Furthermore, the ability of retroelement transcripts to function as lncRNAs

and lncRNA-like molecules has been described [32, 33]. Indeed, although retroelements identified by genome sequencing constitute 42.44% of the human genome [27], transposon-specific oligonucleotides constitute approximately 2/3 of the human genome [34]. This suggests a role for retroelements in the global distribution of non-coding RNA genes during evolution. MicroRNAs can influence gene expression, including retroelements, not only post-transcriptionally but also transcriptionally in AGO4-mediated RdDM. DNA gap, AGO4, SIRT1, and MGB1 have been found to colocalize in human cell nuclei. It was found that HMGB1 or Alu siRNA increased Alu methylation, whereas Alu siRNA could not methylate HMGB1-deficient cells [8]. Bioinformatics studies showed that microRNAs [35] and miRNAs [36] formed from retroelement transcripts can affect the retroelements expression through complementary interactions of sequences in the genome structure [10].

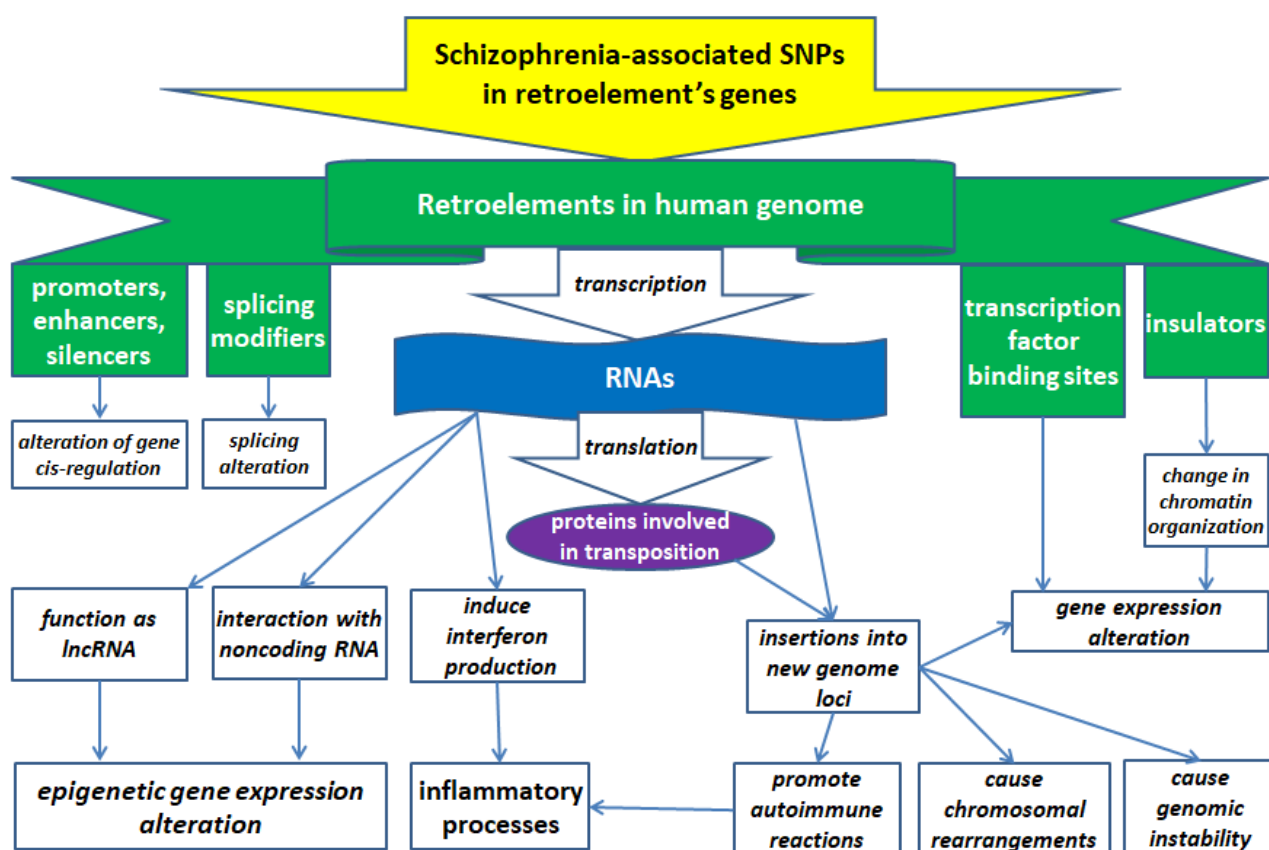


Figure 1 Scheme of the influence of schizophrenia-associated SNPs on various pathways of retroelement functioning in relation to the localization of such SNPs in the sequences of these retroelements.

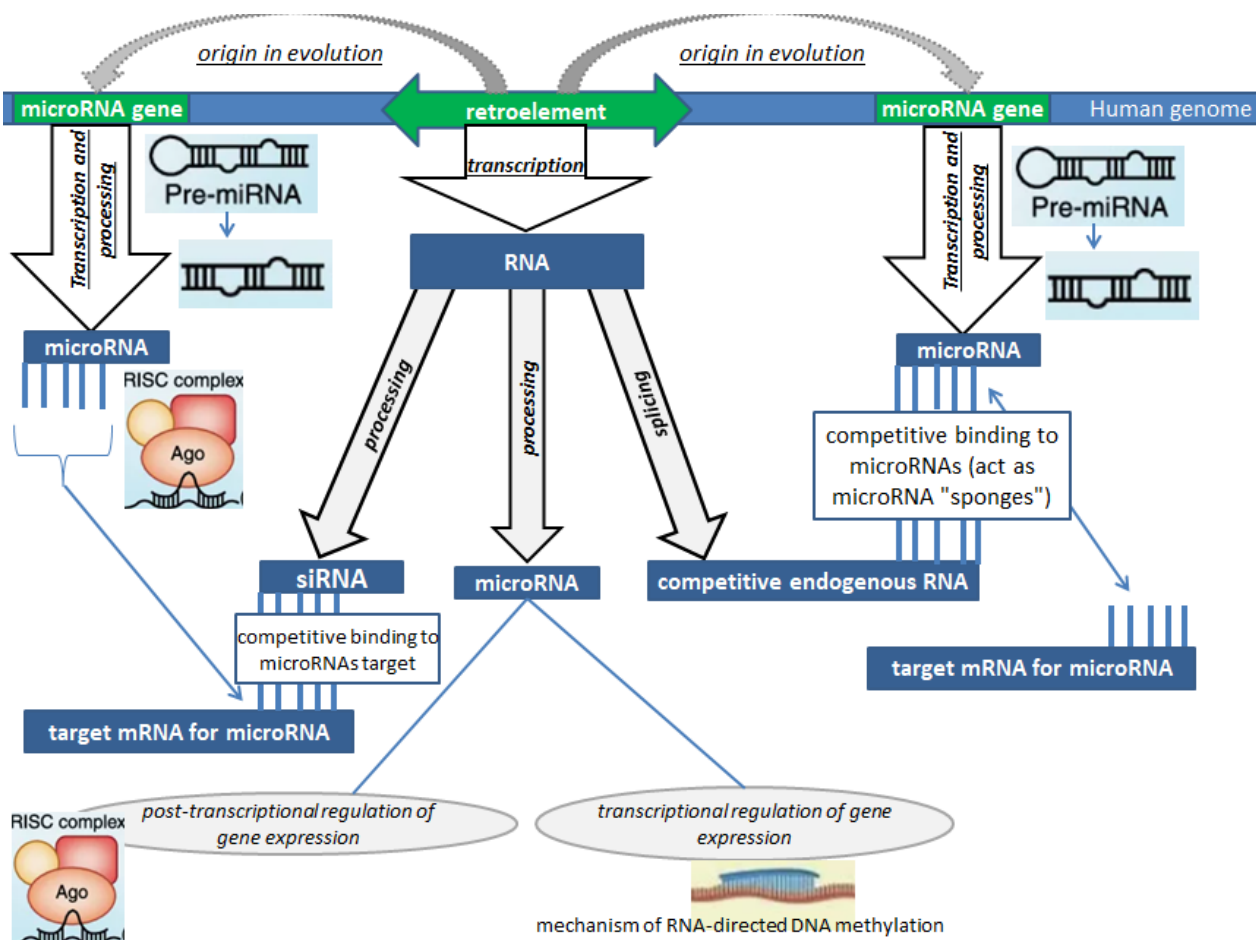


Figure 2 Mechanistic pathways of retroelement transcript influence on epigenetic regulation in the mechanisms of schizophrenia pathogenesis.

Also, SNPs associated with schizophrenia in GWAS data may be located in the regions of microRNA and lncRNA genes and affect their expression patterns and interactions with each other, with mRNA and protein-coding genes, and transcripts of retroelements. An example is miR-1307, located in a locus associated with schizophrenia according to GWAS data. In brain samples from patients with schizophrenia, miR-1307 expression was found to be 3-fold lower compared to healthy controls. At the same time, lncRNA AC005009.2, also located in the schizophrenia-associated locus, shows increased expression in the brains of patients and interaction with miR-1307 [37]. Another example is the lncRNA gene EU358092 and the miR-137 located at the schizophrenia-associated locus 1p21.3, whose expression changes in response to psychoactive drugs (valproate, cocaine) as determined in an experiment on the SH-SY5Y neuroblastoma cell line [38]. SNP located in the regulatory region of the LINC00461 gene is significantly associated with schizophrenia (rs410216). At the same time, people with rs410216 have a reduced hippocampus size, and LINC00461 expression is substantially lower in patients with newly diagnosed schizophrenia [39]. Polymorphisms located in the regions of ncRNA genes not only affect the nature of their expression, but can also disrupt their interactions with target molecules (for miRNAs, these are mRNAs of specific genes and retroelements, and for lncRNAs, these are particular miRNAs, various proteins, and chromatin regions). The influence of SNP in the miR-137 gene region (rs1625579) on the etiopathogenesis of schizophrenia was demonstrated by changes

in the regulation of protein-coding genes, whose polymorphisms also affect the development of the disease [40]. Thus, there are multifaceted pathways of interactions between schizophrenia-associated loci, retroelements, and epigenetic factors in the development of this pathology (Figure 3). In addition, even SNPs located in specific gene regions, especially those that do not cause changes in amino acid sequences but are associated with schizophrenia, can affect the development of the disease due to disruption of interactions with ncRNAs (changes in nucleotide sequences complementary to such ncRNAs) [28, 41].

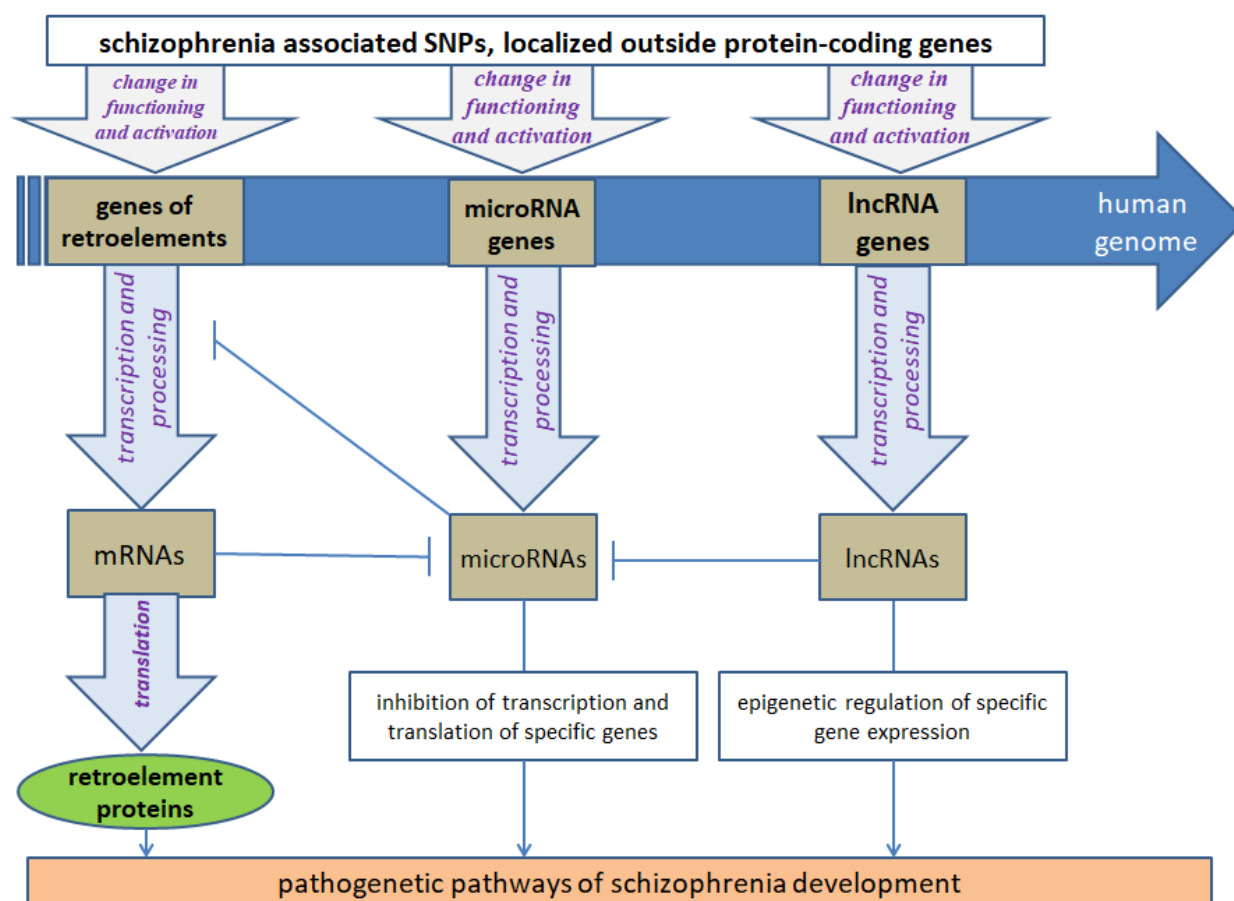


Figure 3 Influence of schizophrenia-associated polymorphisms on the development of pathology due to changes in the expression pattern of retroelements and epigenetic factors interacting with them.

The limitations of existing data on the influence of SNPs on retroelement function stem from the lack of precise genome maps of the retroelements' locations within intronic, intergenic, and regulatory regions. Accordingly, the experimental approach necessary to test this hypothesis involves bioinformatics studies to determine the localization of retroelement sequences within the area of SNPs associated with schizophrenia. Such bioinformatic studies are promising – it is essential to create a database on the physical distribution of retroelements in the genome relative to protein-coding genes and non-coding RNA genes, which can take epigenetics and genetics to a new level, explaining the etiopathogenesis of many idiopathic multifactorial diseases.

The impact of disease-associated SNPs on retroelement function and their relationship with microRNAs can be illustrated by a study of breast cancer. The evolutionary origin of miR-3144-3p

is LINE1 (suggesting its function as a competitive endogenous RNA for this microRNA) [22]. An SNP in the 3'UTR (untranslated region) of the *ERBB4* gene (referred to as rs1972820) disrupts miR-3144-3p binding to *ERBB4* mRNA, thereby affecting breast cancer pathogenesis [42]. Examples of how SNPs can influence the functionality of retroelements in the brain come from studies of autoimmune and neurodegenerative diseases. For instance, in multiple sclerosis, a SNP located in the intron of the *CD58* gene (designated rs1414273) is associated with the disease. This SNP alters the maturation of miR-348ac, which originates from the *Made1* transposon. This results in dysregulation of protein-coding genes involved in brain function [43]. Another example: SNPs in the LINE1 gene in ORF1p sequences lead to changes in the protein product of this gene. As a result, the altered LINE1 protein forms aggregates characteristic of neurodegeneration in the brain in amyotrophic lateral sclerosis [44].

4. Evidence for Retroelement Activation in the Development of Schizophrenia

The most tremendous significance among retroelements in the development of schizophrenia is given to HERVs. These retroelements were introduced into the germline genomes of placental mammals approximately 110 million years ago [45]. Back in 1999, a study of three pairs of monozygotic twins discordant for schizophrenia revealed an increased number of transcripts of schizophrenia-associated retroviruses called SZRV-1 (schizophrenia-associated retrovirus 1). This indicates the role of environmental factors in activating retroelements during disease development [46]. This is consistent with data on the role of retroelements as highly sensitive sensors of the genome to stress influences [7]. A possible reason for the discordance was the activation of retroelements in the brain by specific viruses. Similar mechanisms have been described in multiple sclerosis in relation to herpes viruses [47] and in neurodegenerative diseases about herpes viruses, HIV, hepatitis, and influenza [48]. At the same time, the development of schizophrenia is associated with infection with herpes viruses [49] and HIV (the incidence of schizophrenia in HIV-infected individuals is 6.3%) [50]. This may stimulate transcription of retroelements in the brain [48]. Other environmental factors, such as medications and foods, may also be involved. For example, valproate, a treatment for schizophrenia, has been shown to increase HERV-W expression in brain samples [51]. Caffeine has a similar effect, as shown in experiments on cell lines [52].

Increased expression of HERVs has been found in the cerebrospinal fluid [53] of schizophrenia patients compared to controls. In peripheral blood leukocytes of early-onset patients, an increased number of full-length HERV-K115 insertions capable of transposition was detected compared to healthy controls [54]. Also, significantly higher levels of HERV expression were determined in patients with schizophrenia compared to controls when studying RNA in samples of the cerebral cortex: HERV-W [55], HERV-K [56], ERV9 [51], HERV-H and HERV-W [57]; cerebrospinal fluid (HERV-W) [53], blood plasma: HERV-W [53, 58], ERV9 [59], HERV-W in blood mononuclear cells [60-63]. Transcriptomic association studies of postmortem brain samples identified 1238 HERVs with cis-regulatory expression, including 26 associated with mental disorders, including 2 HERV expression signatures specific to schizophrenia [64]. Interestingly, expression of HERV-W transcripts in the blood of schizophrenia patients correlates with elevated blood levels of proinflammatory cytokines [62].

Reliable data on the increased expression of HERVs in schizophrenia were obtained by studying the concentration of their protein products: in the brain, the enzyme reverse transcriptase [55] and the capsid protein gag [65], in the blood, reverse transcriptase [58], gag, and the retroviral envelope protein [66, 67]. Increased expression of the retroviral protein syncytin-1 has also been identified in patients with schizophrenia [68]. In humans, syncytin-1 protein is formed as a result of the processing of the HERV-W transcript [69]. A 2024 meta-analysis found the strongest association between elevated HERV-W RNA and envelope protein levels and the development of schizophrenia [70].

Although HERVs are obligate components of the human genome, their pathological activation induces antibody production. This contributes to autoimmune reactions, as has been shown in the etiopathogenesis of multiple sclerosis [71-73]. A potent activator of innate immunity is the env protein of the HERV-W retrovirus. It stimulates the production of Toll-like receptor 4 (TLR4), TNFA, interleukins six and 1 β by blood monocytes [74]. TLR4 stimulation, in turn, promotes brain neurodegeneration by affecting microglial phagocytosis and cytokine production [75]. Antiretroviral antibodies were detected in 52% of patients with schizophrenia compared to 25% of healthy controls [76]. Antibodies to pol ERV9 protein detected in HERV-positive schizophrenia patients [59]. Accordingly, the identification of these antibodies is promising for the diagnosis and targeted therapy of schizophrenia. However, the mixed and negative results of using Temelimab (GNbAC1) in targeted therapy for multiple sclerosis should be taken into account. This is due to the need for high drug doses to neutralize targets in the central nervous system optimally. As the dose increases, the likelihood of developing adverse reactions increases [73]. Furthermore, in clinical trials of 48-week administration of Temelimab to patients with multiple sclerosis, a slight reduction in brain atrophy was observed, which is insufficient for a complete cure of the disease. Temelimab also did not affect signs of acute inflammation [74], highlighting the complexity of multiple sclerosis pathogenesis and the need for comprehensive treatment, in which antibodies may be only one of many components. The same applies to the potential of this approach for the treatment of schizophrenia – the use of antibodies against pathogenic retroelement proteins may be just one component of a complex treatment for the disease.

Typically, during brain development, LINE1 retrotranspositions cause somatic mosaicism due to insertional mutagenesis, promoting neuronal differentiation [8] and memory formation [77]. However, compared with healthy individuals, a higher number of deleterious LINE1 insertions in the expressed genes of neurons in the dorsolateral prefrontal cortex was detected in schizophrenia [78, 79]. A study of LINE1 methylation levels in white blood cells showed that schizophrenia patients with a history of childhood trauma had significantly lower LINE1 methylation levels compared to healthy controls [80]. In addition to pathological insertions in the brain, the development of schizophrenia may be influenced by the distribution of LINE1 in the genome of all human cells. Many polymorphic human-specific LINE1s are not annotated in the current version of the genome and are therefore called “non-reference LINE1s”. Using NGS of DNA isolated from blood cells, such insertions were analyzed in patients with schizophrenia. As a result, 110 non-reference polymorphic LINE1 loci with Mendelian inheritance were identified. A significant portion of these loci was located within the open reading frames (ORFs) of protein-coding genes involved in pathways related to schizophrenia pathogenesis [81]. Using quantitative assessment of the expression of specific retroelements in the human brain, 4687 such retroelements specific to the dorsolateral prefrontal cortex were identified, of which 1689

retroelements (1484 of them localized in introns of 1137 protein-coding genes) were differentially expressed in patients with schizophrenia compared with healthy controls. Most of these retroelements are primate-specific, that is, evolutionarily younger [82]. Subsequently, 38 non-reference retroelement insertions (32 Alu, 3 LINE1, and 3 SVA) absent in healthy controls were identified in the dorsolateral prefrontal cortex genomes of patients with schizophrenia. Functional in silico studies showed that 9 of these 38 retroelements act as expression or alternative splicing loci for quantitative traits in the brain [28].

In addition to LINEs, a role for Alu in the development of schizophrenia has been identified. Hypomethylation of A3 CpG sites of AluY was detected in peripheral blood samples from patients with schizophrenia compared to healthy controls [83]. Alu insertion polymorphism at locus 10q24.32 with a length of 339 bp (rs71389983) is associated with schizophrenia [84]. Increased levels of Alu were found in the serum of patients with schizophrenia compared to healthy controls and patients with other mental illnesses (major depressive disorder and acute depressive disorder). This suggests that this indicator can be used for differential diagnosis. A positive relationship was also found between Alu and IL-1 β , and between Alu and IL-18 [85]. Analysis of the effect of insertional polymorphism showed a negative association of the Alu allele in the *TPA* gene with the development of schizophrenia [86].

5. Mechanisms of Influence of Retroelements on the Etiopathogenesis of Schizophrenia

Pathological activation and dysfunction of retroelements influence the pathogenesis of schizophrenia through specific pathways that can be divided into distinct mechanisms: insertional mutagenesis, protein-mediated neuroinflammation, direct interference with neurotransmission, and microRNA-mediated dysregulation (Figure 4). Indeed, activated retroelements are characterized by their ability to transpose into new genomic loci. To do this, autonomous retroelements (LINEs and HERVs) use their own enzymes (reverse transcriptase, endonuclease) encoded in their genes, while non-autonomous retroelements (SINEs) utilize the enzymes of autonomous LINEs. The role of activated LINEs and SINEs may be related to their insertions into new loci of the genome, disrupting the expression of genes essential for brain function, as well as by changing the levels of LINE- and SINE-derived specific microRNAs [48].

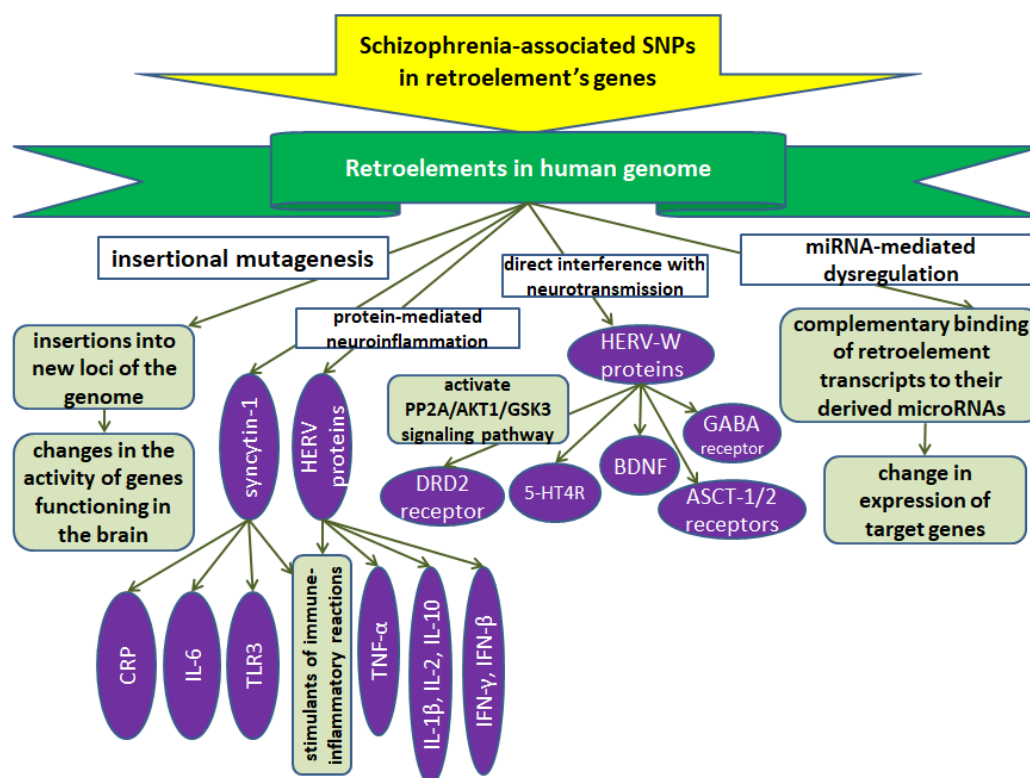


Figure 4 Mechanisms of influence of retroelements on the pathogenesis of schizophrenia.

How HERV retroviruses influence the pathogenesis of schizophrenia by stimulating immune responses and inflammation in the brain has been studied [71-75], as evidenced by the data on the identified antibodies to HERV proteins [59, 76]. Activated HERVs in the brain may cause pathology through activating inflammatory processes. This is consistent with GWAS data on the association between schizophrenia and allelic variants of genes involved in inflammation and immune responses [87]. Syncytin-1, which is expressed in schizophrenia, contributes to increased levels of C-reactive protein (CRP), TLR3, and IL-6 in microglia and astrocytes in the brain. Cellular colocalization and direct interaction between syncytin-1 and TLR3 have been identified, which contribute to inflammatory responses [68]. Other HERV protein products are also stimulants of immune-inflammatory reactions, which is typical for patients with schizophrenia [66]. The highest association of elevated CRP levels was found in patients with schizophrenia and cognitive deficits [88].

Clinical studies have shown that in patients with schizophrenia, increased HERV-W expression is accompanied by increased serum levels of TNF- α , IL-10, IFN- γ , and IL-2 compared with healthy controls [63]. Increased serum IFN- γ levels in patients with schizophrenia are due to the stimulating effect of the env HERV-W protein, which stimulates the expression of cyclic GMP-AMP synthase (cGAS) and the interferon gene stimulator protein (STING), and also promotes the phosphorylation of interferon regulatory factor 3 (IRF3) in neurons. At the same time, cGAS interacts with env HERV-W, triggering IFN- β expression and neuronal apoptosis induced by the env protein [89]. Increased serum IL-1 β levels in schizophrenia are a characteristic feature of pyroptosis, a pro-inflammatory programmed cell death. A positive correlation was found between the expression of env HERV-W and the levels of the protein products of *CASP1*, *GSDMD*, and *IL1B*

genes involved in pyroptosis in patients with schizophrenia. In experiments, it was confirmed that env HERV-W promotes caspase-1 activation and the cleavage of gasdermin D, thereby stimulating IL-1 β production [90]. Examining the influence of retroelements and epigenetic factors on inflammatory processes that contribute to the development of schizophrenia holds promise for cross-system studies. This approach allows for the interaction between inflammation and epigenetics to be considered a common therapeutic target in various diseases, as demonstrated in the case of the heart-brain axis. Here, inflammatory responses and epigenetic regulation were examined, jointly mediating the bidirectional relationship between cardiovascular disease and mood disorders [91].

Direct intervention of retroelements in neurotransmission can be described. A high concentration of env HERV-W protein in the brain of patients with schizophrenia contributes to a significant increase in dopamine levels and the induction of DRD2 receptor expression. The cellular colocalization of env HERV-W with DRD2 and their direct interaction (enhancing sodium influx through DRD2) have also been identified. Moreover, by influencing DRD2, env protein activates the PP2A/AKT1/GSK3 signaling pathway [92]. The ability of the env HERV-W protein to stimulate pathological expression of BDNF [58], which is associated with schizophrenia, has also been shown [93]. HERV-activated proteins can also stimulate specific receptors in the brain. In patients with schizophrenia, the env protein of HERV-W binds to ASCT-1/2 receptors, leading to decreased amino acid consumption necessary for normal neuronal activity [94]. HERV-W, located in the regulatory region of GABA receptors-1, can also affect the development of schizophrenia by changing their transcription [95]. The expression of schizophrenia-associated allelic variants of the *C4A* and *C4B* genes is influenced by polymorphic HERV (C4-HERV) insertions in intron 9. Accordingly, long (with HERV insertion) and short forms of these genes are distinguished [96]. 5-hydroxytryptamine (5-HT) receptors play an important role in the pathogenesis of schizophrenia. A negative correlation has been found between 5-HT₄R and env HERV-W in schizophrenia. Increased expression of env HERV-W reduces 5-HT₄R protein levels and interacts with this protein [97]. Thus, the pathological activation of retroelements in schizophrenia contributes to the pathology both by disrupting the expression of brain-specific genes due to insertion mutagenesis and by stimulating immune-inflammatory responses and altering the activity of neurotransmitter receptors. Additionally, the epigenetic effects of activated retroelements on the development of schizophrenia should be considered, as retroelements are drivers of epigenetic regulation [6].

The influence of microRNA-mediated dysregulation of retroelements stems from the origin of microRNAs from retroelements, which determines the complementarity of their sequences [22]. As a consequence, retroelement transcripts can function as competitive endogenous RNAs (see Figure 2). Therefore, it is of interest to examine the role of retroelement-derived microRNAs involved in the pathogenesis of schizophrenia by dysregulating the expression of target mRNAs of brain-specific genes.

6. Relationship between Retroelements and Epigenetic Factors in Schizophrenia Development

In addition to the direct detection of retroelement expression products in various tissues of patients with schizophrenia, there is evidence of retroelement activation at the epigenetic level. These changes are reversible and can be corrected using specific microRNAs that can inhibit retroelement expression at the transcriptional and post-transcriptional levels due to the presence

of complementary sequences, as has been shown in the analysis of neurodegenerative diseases [48]. The specificity of these interactions is due to the origin of microRNAs from retroelements in evolution [22]. Methylation levels of HERV-K sequences in peripheral leukocytes are significantly lower in patients with first-episode schizophrenia compared to healthy controls [98]. In peripheral blood, patients with schizophrenia showed reduced methylation of CpG LINE1 sites compared to healthy controls, leading to activation of these retroelements [99]. A particularly pronounced decrease in LINE1 methylation was found in patients with paranoid schizophrenia [100]. Activation of LINE1 in patients with schizophrenia may be caused by impaired expression of DNA methyltransferase DNMT1, which was shown in a study of patients and confirmed in mouse experiments [101].

To suppress the pathological activity of retroelements that lead to the development and progression of schizophrenia, a selective monoclonal antibody against env HERV, which is effective in the treatment of multiple sclerosis, is being used in the treatment of schizophrenia [92]. Indeed, in multiple sclerosis, like in schizophrenia [74], elevated levels of antibodies against HERV-W proteins are also detected, with the highest levels in progressive forms of the disease [102]. In the second phase of clinical trials, a monoclonal antibody, GNBAC1 (temelimumab), targeting env HERV-W was shown to be effective in the treatment of multiple sclerosis in a randomized, placebo-controlled trial [71-73]. In mouse experiments, artificial enhancement of human-specific env HERV-W expression disrupted repetitive behavior, sensorimotor gating, and social and object recognition memory. According to whole-genome RNA sequencing of hippocampal tissues, these changes are caused by transgenic expression of env HERV-W, which reduces transcription of schizophrenia-associated genes such as *Ank3*, *Cacna1g*, *Setd1a*, *Shank3*, and the Set1-like histone methyltransferase family. As a result, lysine-specific demethylase-1 (LSD1) activity increased, with increased H3K4 monomethylation and decreased H3K4 di- and trimethylation in the hippocampus. Pharmacological inhibition of LSD1 by oral administration of ORY-1001 eliminated abnormal H3K4 methylation and normalized cognitive and behavioral defects in mice [103]. It is also possible to use reverse transcriptase inhibitors to suppress insertion mutagenesis in schizophrenia, as these drugs are effective in amyotrophic lateral sclerosis, which is also caused by pathological activation of HERV [104].

However, the evolutionarily programmed activation of retroelements in hippocampal neural stem cells is necessary for neural maturation and differentiation [8] and for memory formation [77]. Therefore, it is most expedient to act only on those retroelements that are of importance in the pathogenesis of schizophrenia. Since the pathological activation of retroelements is reflected in the expression of specific microRNAs that have evolved from them in evolution due to the role of retroelement transcripts as competitive endogenous RNAs [22], the scientific literature on the pathological expression of microRNAs in this disease has been analyzed to determine the ways of targeted action on specific retroelements in schizophrenia. Based on the analysis, articles were selected that reported changes only in microRNAs derived from retroelements, according to the MDTE [22].

However, such one-sided approaches using reverse transcriptase inhibitors and monoclonal antibodies may be ineffective. This is because inhibition of only pathologically activated and dysfunctional retroelements involved in the pathogenesis of schizophrenia is necessary. At the same time, inhibition of retroelements involved in normal neurogenesis [8] may have negative consequences. Accordingly, epigenetic intervention strategies such as microRNA-based targeted

therapy are needed. The use of DNA demethylating agents involved in base excision repair (BER) to restore neurotransmitter expression in the brain also holds promise [105]. Indeed, in schizophrenia, accumulation of 5-methylcytosine and 5-hydroxymethylcytosine has been identified proximally in the regulatory domains of genes expressed in telencephalic GABAergic and glutamatergic neurons. This results in decreased expression of BDNF, reelin, and GAD67. Therefore, pharmacological strategies using a histone deacetylase inhibitor (valproate), which promotes chromatin remodeling and restores the expression of regulatory genes in the brain, may potentially be successful in the treatment of schizophrenia [106]. This approach is promising, but it is one-sided, focusing primarily on the regulation of neurotransmitter systems, without taking into account the complex pathogenesis of schizophrenia. Accordingly, demethylating agents can be used as part of the complex treatment of the disease.

It should be noted that microRNA-based therapy is challenging to deliver to the brain and can cause off-target effects. Delivery to the brain is dependent on the blood-brain barrier, which requires specialized nanocarriers to overcome. This approach has been demonstrated in *in vivo* models of glioblastoma [107]. The off-target effects of microRNAs are due to their pleiotropic effects—the same microRNA can bind to multiple target mRNAs. Accordingly, when planning targeted therapy using microRNAs as tools for suppressing pathological activation of retroelements involved in the development of schizophrenia, bioinformatic approaches to determine the selectivity of the effect are necessary. In this regard, the use of antisense oligonucleotides may be a promising potential strategy, as has been predicted for the treatment of multiple sclerosis [108] and progeroid syndromes [109].

In blood mononuclear cells from patients with schizophrenia, miR-181c (derived from LINE-BovB [22]) was found to be significantly more highly expressed compared to healthy controls [110]. In the postmortem brain tissue of patients with schizophrenia, a decrease in the expression of miR-342-5p was determined (source is LINE-BoVB [22]) [111]. The expression of ERVL-MaLR-derived miR-585 is reduced in the amygdala of patients with schizophrenia compared to healthy controls [37]. miR-619-5p derived from SINE-Alu is characterized by increased levels in serum exosomes in patients with schizophrenia [112]. LINE2-derived miR-708-3p targets LNPEP and JARID2 (whose protein products promote neuronal differentiation and enhance synapse formation) and disrupts the growth of neuronal axons. Compared to healthy controls, miR-708-3p expression is increased in peripheral blood mononuclear cells of patients with early-onset schizophrenia [113].

ERVL-MaLR-derived miR-1246 is elevated in serum in schizophrenia patients compared with healthy controls [114, 115]. In peripheral blood mononuclear cells of patients with schizophrenia, compared with healthy controls, increased expression of miR-885-3p (derived from SINE-MIR [22]), miR-1303 (SINE-Alu [22]), miR-3617 (SINE-MIR [22]), miR-3937 (ERVL-MaLR [22]), miR-4506 (from SINE-MIR [22]), miR-4753-3p (from LINE1 [22]) was determined [114]. Using high-throughput sequencing, it was found that miR-1271-5p (derived from LINE2 [22]) levels were reduced in blood mononuclear cells [116]. Overexpression of miR-1271-5p suppresses mRNA expression in neurons involved in a wide range of cellular functions, including cytoskeletal dynamics and cell junctions. MiR-1271-5p is expressed in the human forebrain and regulates the expression of neuronal signaling genes [117].

LTR-ERV1 originated [22]. miR-4428 expression was elevated in plasma samples from patients with schizophrenia [114]. Reduced expression of miR-4772 (derived from LINE1 [22]) was detected in peripheral blood in patients with schizophrenia [118]. In peripheral blood mononuclear cells of

patients with schizophrenia, an increase in the expression of miR-1587, derived from ERVL-MaLR [22], and a decrease in the expression of miR-3194, derived from SINE-MIR [22], were also determined [118]. SINE-MIR-derived miR-5100 is characterized by increased expression in schizophrenia patients compared to controls in serum [115]. Table 1 presents data on retroelement-derived microRNAs associated with schizophrenia. These microRNAs may be used for targeted therapy of schizophrenia.

Table 1 MicroRNAs derived from retroelements whose expression changes in schizophrenia.

miRNA name	changes in microRNA * [source]	tissue where microRNA expression is determined [source]	mRNA targets for microRNA	collective biological functions of target genes	RE-source of microRNAs [22]
miR-181c-5p (miR-181c)	↑ [110]	blood mononuclear cells [110]	<i>CREBRF, C2CD5, ZNF594, ZNF268, ZNF439, DDX3X, ZNF781, PRTG, TRIM2, SESN3, TNPO1, ZFP90, ZNF37A, ZNF780B, KMT2A, FIGN</i>	regulation of metabolism, transcription, and neurogenesis	LINE-BovB
miR-342-5p	↓ [111]	brain [111]	<i>EFNA2, CCAR2, CPLX2, LIMD2, SYNGAP1, TDRD10, PTPRN2</i>	regulation of neurogenesis, metabolism, and synaptic transmission	LINE-BoVB
miR-585	↓ [37]	brain [37]	<i>PI15, SOCS5, TMEM38B, SLC20A1, CREBZE, TMEM134</i>	regulation of neurogenesis, cytokine signals	ERV-L-MaLR
miR-619-5p	↑ [112]	blood serum exosomes [112]	<i>NAA50, CORO1C, GPATCH8, CYP20A1, COPG2, CPEB1, ETS1</i>	regulation of the cell cycle, splicing, metabolism	SINE-Alu
miR-708-3p	↑ [113]	blood mononuclear cells [113]	<i>SCAMP1, JARID2, TRAF3, VIM, BAZ1B, SPRED1, HSPA4L, CATSPERB, PPP1R15B, DDHD2</i>	promote neuronal differentiation and enhance synapse formation	LINE2
miR-885-3p	↑ [114]	blood mononuclear cells [114]	<i>RGS8, GPCPD1, RAVR2, SOCS6, SPATS2L, RARG, ARMH3, NAT8L, SLC45A3, IGF1R, ARMCM3, PFN2</i>	regulation of neurotransmitters, catabolism, splicing	SINE-MIR
miR-1246	↑ [114, 115]	blood serum [114, 115]	<i>FAM53C, C12orf71, GLRB, FPGT, CREBL2, QTRT2</i>	regulation of transcription and neurotransmission	ERV-L-MaLR

miR-1271-5p	↓ [116, 117]	blood mononuclear cells [116], brain [117]	<i>ADCY6, LRCH2, NEXMIF, PLPR4, FRS2, HAS2, SH3BP5, ATXN1, OXSR1, SLC1A1</i>	regulation of catabolism and neurogenesis	LINE2
miR-1303	↑ [114]	blood mononuclear cells [114]	<i>OGFRL1, TMEM108, TASOR, AGMO, SLC35G1, RSBN1, AVL9, EXOC6B, NR3C1, TMEM151B</i>	regulation of neurotransmission, neurogenesis, and transposons	SINE-Alu
miR-1587	↑ [118]	blood mononuclear cells [118]	<i>ZSWIM5, NCOR1, SDC3, STK40, NIPSNAP1, ZIC4, NPY, TAGLN, KCNH5</i>	regulation of mitochondrial dynamics and transcription	ERV1-MaLR
miR-3194-5p (miR-3194)	↓ [118]	blood mononuclear cells [118]	<i>EBPL, ATPAF2, LAMP5, SYBU, IRF5, TRAF1, MEAF6, TMSB4X, TNRC6B</i>	regulation of metabolism, mitochondrial function, and synaptic plasticity	SINE-MIR
miR-3617-5p (miR-3617)	↑ [114]	blood mononuclear cells [114]	<i>CNTN1, RFX7, SRP72, SOX6, SECISBP2L, MAPK10, DTWD2</i>	regulation of neurogenesis, transcription, and translation	SINE-MIR
miR-3937	↑ [114]	blood mononuclear cells [114]	<i>NPW, GRM4, PSMB6, USP9X, GPR17, WDFY1, DCAF12L2, GFRA2, TAP2</i>	regulation of neurogenesis, neurotransmission, inflammation, and the functioning of the immune system	ERV1-MaLR
miR-4428	↑ [114]	blood plasma [114]	<i>EPHB1, ADAR, RELN, CCT8, KLF9, NCBP1, ST8SIA6</i>	regulation of cell differentiation and immunity	LTR-ERV1
miR-4433a	↓ [118]	blood mononuclear cells [118]	<i>PTPN12, AGPAT4, TM9SF3, MAPK10, CENPN, GRID2, STRN3</i>	regulation of the cell cycle, mitochondria, and neurotransmission	LINE2
miR-4506	↑ [114]	blood mononuclear cells [114]	<i>SYNJ1, ZNF680, JAZF1, SIGLEC14, PHF2, TFDP1</i>	regulation of synapses, transcription, and inflammation	SINE-MIR

miR-4753	↑ [114]	blood mononuclear cells [114]	<i>SPTLC2, LHX6, CNOT7, ATP5IF1, ZBTB20, NUFIP2, SLC25A36</i>	regulation of synapses, neurogenesis, and immune responses	LINE1
miR-4772	↓ [118]	blood [118]	<i>PHACTR3, APP, IQSEC2, F8, KLHDC10</i>	regulation of neuronal function and development	LINE1
miR-5100	↑ [115]	blood serum [115]	<i>MOXD1, SMARCA2, MOSPD2, CSNK1G3, HTR2C, CPSF6</i>	regulation of neurotransmission, chromatin remodeling	SINE-MIR

*Increased – is ↑, decreased – is ↓.

In addition to changes in the expression of specific microRNAs, changes in the sequences of their genes may influence the development of schizophrenia. This supports the hypothesis proposed in this article that multiple SNPs and CNVs associated with schizophrenia may influence hereditary predisposition by changing the activity of retroelements. Since microRNAs are involved in the epigenetic regulation of retroelements [11], changes in microRNA gene sequences may also influence schizophrenia development. It is interesting to note that microRNA genes are also distributed mainly in intergenic regions, where most polymorphisms associated with multifactorial diseases are localized [119]. Accordingly, retroelement-derived microRNAs are most likely to exert an effect on retroelements due to the complementarity of their nucleotide sequences and thus exert the effect of schizophrenia-associated polymorphisms on the development of pathology (Figure 5). An example is the identified association of CNV in the miR-640 gene (derived from SINE-MIR [22]) with the development of schizophrenia. The targets of miR-640 are the genes GSR (encodes glutathione reductase, a central enzyme in the antioxidant defense of cells), FXN (encodes the mitochondrial protein frataxin, which protects neurons from iron-catalyzed oxidative stress), and ATCAY (encodes kaitaxin, involved in postnatal maturation of the cerebellar cortex) [120]. To determine the relationship between microRNA and schizophrenia, a Mendelian randomization study of genetic variants associated with microRNA was conducted. The results were obtained using GWAS. As a result, the role of LINE RTE-BovB [22] miR-130a in the development of schizophrenia was determined [121].

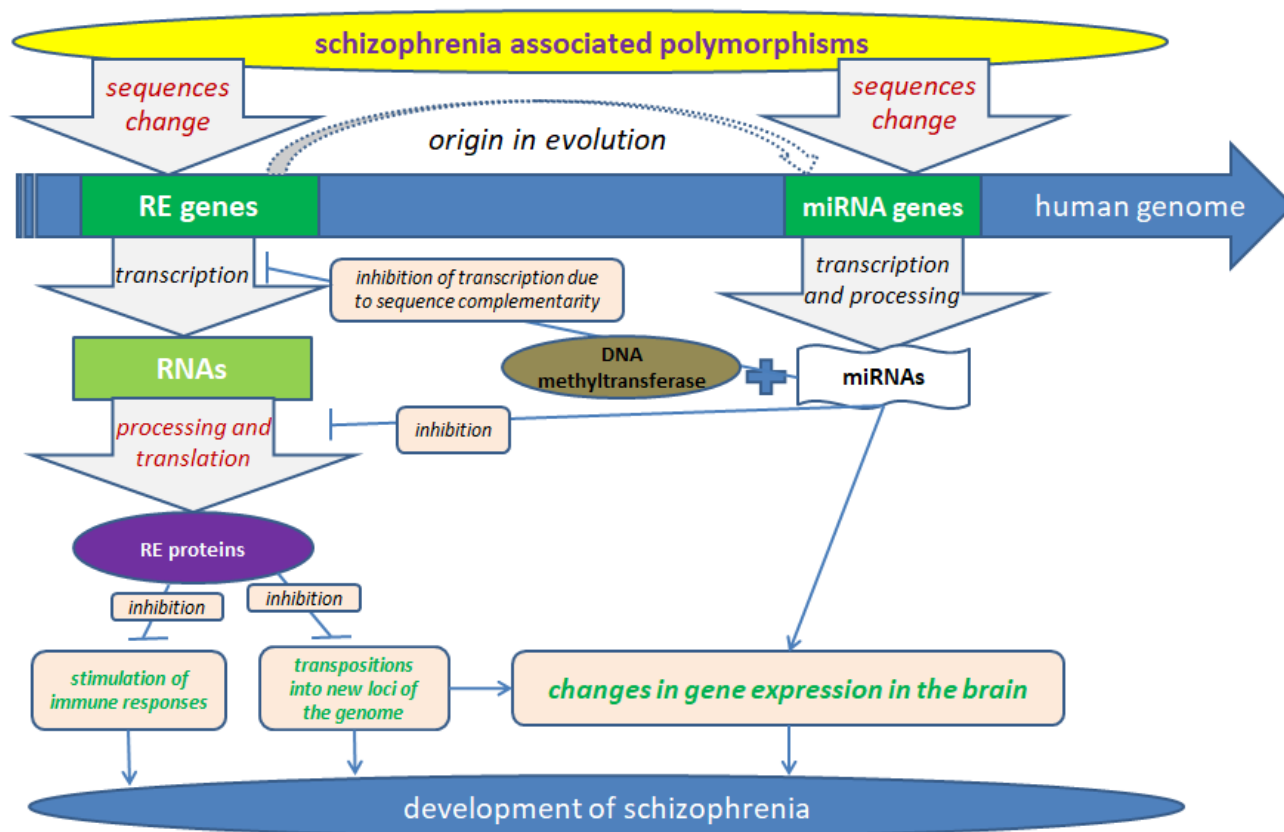


Figure 5 Mechanisms of influence of retroelement-derived microRNAs on the development of schizophrenia.

7. Conclusion

There are numerous articles published in the scientific literature demonstrating that schizophrenia patients have reliably pathologically increased expression of HERVs, LINEs, and Alus. The transcription products and proteins of these retroelements are found not only in brain samples of deceased schizophrenia patients, but also in the cerebrospinal fluid, blood plasma, and blood mononuclear cells of patients. The mechanisms of influence of these molecules on the development of brain pathology leading to the development of schizophrenia have been described. These molecules promote immune reactions, inflammation, and neurodegenerative processes in the brain. In addition, activated retroelements insert into new genomic loci in neurons and neuroglia, disrupting their normal function and differentiation. The influence of the distribution features of LINE1s and Alus in the human genome on schizophrenia development has also been determined, which suggests the possibility of using this feature to predict predisposition to the disease and differential diagnosis with other mental illnesses. Due to the regulatory role of retroelements in the expression of protein-coding genes, pathological activation of HERV contributes to the disruption of the synthesis of dopamine, amino acid neurotransmitters, GABA receptors, and 5-hydroxytryptamine. The association of multiple SNPs with schizophrenia may be related to the location of retroelement genes and non-coding RNAs interacting with them in the regions surrounding these SNPs. This contributes to the pathological functioning and activation of retroelements, especially under the influence of viral infections caused by HIV and herpes viruses. In connection with the proven role of retroelements in the development of schizophrenia and their relationship with epigenetic factors, it is possible to propose the use of targeted therapy in the complex treatment of schizophrenia. Specific microRNAs complementary to retroelements that are pathologically activated in schizophrenia can be used for this purpose, since total retroelement inhibition is inappropriate given their evolutionarily programmed role in neurogenesis. An analysis of the scientific literature identified and described 19 microRNAs derived from retroelements whose expression is impaired in schizophrenia.

Abbreviations

CNVs	copy number variations
DMLs	differentially methylated loci
DTI	diffusion tensor imaging
ERVL-MaLR	endogenous retrovirus-Mammalian-apparent Long-terminal Repeat
EWAS	epigenome-wide association study
GWAS	genome-wide association studies
HERVs	human endogenous retroviruses
IFNG-AS1	antisense lncRNA to the interferon gamma gene
lncRNAs	long noncoding RNAs
LINE	long interspersed nuclear elements
LTR	long terminal repeat
ncRNAs	non-coding RNAs
RdDM	RNA-directed DNA methylation
SINE	short interspersed nuclear elements
SINE-MIR	short interspersed nuclear elements-Mammalian-wide Interspersed Repeat

SNPs	single nucleotide polymorphisms
SVA	SINE-VNTR-Alu
UTR	untranslated region
VMPs	variably methylated positions

Author Contributions

The author did all the research work for this study.

Competing Interests

The author declares no conflict of interest.

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