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Epigenetics of schizophrenia

Katherine Barraza [1], Daniela Parra [1], Ana Pérez [1,*], Alessandra Rangel [1] and Brissia Lazalde [2]

[1] *Faculty of Medicine and Nutrition, Universidad Juárez del Estado de Durango, Durango, Durango, Mexico.*
[2] *Department of Genetics, Faculty of Medicine and Nutrition, Universidad Juárez del Estado de Durango, Durango, Durango, Mexico.*

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Abstract

Schizophrenia is a severe mental illness characterized by a disconnection from reality, significantly impacting a person's ability to function and leading to substantial disability. While the exact causes of schizophrenia remain unclear, it is understood to result from a combination of genetic, neurochemical, and environmental factors. The heritability of schizophrenia is high, although it does not follow Mendelian patterns. The symptomatology includes both positive symptoms such as hallucinations, delusions, and psychotic episodes, and negative symptoms like apathy and speech difficulties, which fluctuate in severity over time. Environmental influences, including prenatal and perinatal factors, trauma, and lifestyle, also play a crucial role in its development. The prevalence of schizophrenia is approximately 12.1% globally, with incidence rates higher in males than females. Genetic studies have identified several associations that contribute to the disease's pathophysiology, including common variants and copy number variants. Epigenetic mechanisms, such as DNA methylation and histone modifications, further influence gene expression and disease manifestation. The interplay between genetic predisposition and environmental factors underscores the complexity of schizophrenia and the importance of a multifaceted approach to its study and treatment.

Keywords: Schizophrenia; Epigenetic; Gen; Mental disorder.

1. Introduction

Schizophrenia is a serious mental illness that affects the way a person behaves. They seem to be out of touch with reality, and their symptoms can make it difficult for them to participate in effective activities [1] that cause significant disability and are highly heritable. Recent studies have estimated a high degree of heritability although these are not due to Mendelian segregation [2,3].

According to the U.S. National Institute of Mental Health (NIMH) [4], a serious mental disorder is defined as "a heterogeneous group of persons with severe psychiatric disorders, who have mental disturbances of prolonged duration, involve a variable degree of disability and social dysfunction, and must be cared for through various social and health care resources of the psychiatric and social care network".

The causes of schizophrenia are not known but researchers believe that a combination of genetics, brain chemistry and environment contribute to the development of this mental disorder [5].

1.1. Symptomatology

This disorder is characterized by a general decline in mental abilities and emotional and behavioral regulation, leading to a disruption of all basic cognitive processes. Symptomatology includes positive signs such as fantasies, hallucinations,

* Corresponding author: Ana Pérez

delusions, psychotic outbursts, psychomotor agitation (also called subjective symptoms), and negative signs such as apathy, speech problems and those related to the reward system (also called life-limiting) [6 ,7, 8].

As time goes by, symptoms vary in severity and frequency. Males, compared to females, show symptoms in their early 20s [1].

1.2. Environmental factors

Epidemiological studies establish that the risk factors for schizophrenia occur from a very early period in brain development (during pregnancy), however, this does not exclude adulthood and adolescence from presenting manifestations [9].

The symptoms expressed may vary due to different factors (or origins of the disease) such as fetal life, nutritional status, paternal age, trauma, genetic susceptibility, environmental factors and the combination of all of them that generate a decrease in the normal functions of neurotransmitters and affect the normal development and maturation of the brain [8,10].

In addition to having a major impact on health, the disease also has a major social and occupational relevance and reduces life expectancy by 15 to 20 years compared to people without severe mental illness [7].

1.3. Heritability

The most important risk factor is family history, taking into account the most important elements: siblings, father and/or mother with schizophrenia [1].

A 2022 paper suggests that epigenetic information, independent of DNA, could be inherited over many generations, even in humans. This could indicate that epigenetics contributes to the phenotypic variation that leads to human evolution. [11] It explains that this inheritance can occur through direct replication or indirect reconstruction of a signal in younger generations [12].

1.4. Prevalence and incidence

Globally, schizophrenia has a prevalence rate of 12.1%[13]. The number of people affected has increased from 13.1 million in 1990 to 20.9 million in 2016. The incidence has been reported as 15.2/100 000 persons [14].

It appears in men between 15 years of age and in women between 25 and 35 years of age, appearing a greater number of times in men than in women with a ratio of 1.2 to 1.4. It is estimated that only in Mexico there are half a million affected [15, 16].

1.5. Mortality and morbidity

The comorbidity of schizophrenia represents a high medical pathology. Some studies say it affects 46-80% of inpatients and 23-43% of outpatients. It is associated with an excess of premature deaths since it decreases from 9 to 10 years. Many of the patients affected with this disorder are likely to have a higher pain tolerance, and their hygienic abilities make them more prone to chronic diseases [17].

People suffering from schizophrenia experience a 2 to 3 times higher risk of death, as they have a higher rate of suicides and accidents due to poor health behaviors, effects of their psychotic outbreaks, under-diagnosis or under-treatment of general disorders [14, 18, 19].

1.6. Genetic of schizophrenia

Recently, there has been much progress in human genetics of SCZ, concluding that there are three classes of genetic associations: common variants identified by genome-wide association studies; copy number variants, and uncommon coding variants identified by exome/genome. These last have a lot of impact and a strong individual risk for having the disease.

1.7. Common variants

With the genome-wide association studies in 2022, there was nominated approximately 120 genes associated with schizophrenia, which are concentrated in genes that codify for excitatory and inhibitory neurons in the central nervous system; besides they have an important participation in neuronal development and differentiation, synaptic

organization, and transmission. With this, it can be concluded that schizophrenia pathophysiology arises from modifications in neuronal aspects, such as their function, development and/or communication [20].

Gen SLC39A8 is one of the common genes in schizophrenia. When it presents a missense mutation (A391T) on it, it cannot synthesize for ZIP8, a zinc transporter. The lack of this gene in the brain affects proteins involved in glutamate and gamma-aminobutyric acid (GABA) neurotransmission, dopamine, and adhesion migration [21, 22].

The major histocompatibility complex locus has the most statistically significant association with SCZ in the European genetic ancestry meta-analysis, and it was related to the complement component 4 (C4), specially C4A which has more potent effects in men than in women, what is one of the genetic factors that explain the higher prevalence of schizophrenia in men than in women. [20]

1.8. Copy number variants.

The 22q11.2 microdeletion is one of the best-studied examples of these variants that increase the risk of developing schizophrenia because it includes the catechol-O-methyltransferase gene that plays a critical role in dopamine metabolism [22, 21].

Another variant is the 2p16.3, which increases the risk more than 10 times, impacting the NRXN1 gene, which encodes neurexin-1, a presynaptic cell—adhesion molecule involved in synapse properties. When it is deleted, it can show a significantly impaired synaptic transmission, a disease phenotype observed in neurons of patients with schizophrenia.

1.9. Environmental factors involved in schizophrenia

It should be noted that the environment can have a strong impact on the developmental stages after childhood and even into adulthood [23]. The most frequently associated factors include obstetric complications, infections, addictions, and migration, among others[24]. Environmental factors account for 15% to 40% of the risk of schizophrenia. [25]

1.10. Time of birth

A higher incidence has been found in people born between the winter and spring seasons [26] which has been justified by the variation in viral exposure, immune system condition, exposure to sunlight or a combination of all these variables that lead to a change in the conformation of the product. Vitamin D deficiency is associated in winter, according to the data mentioned in the diet section. This area of research is still being explored, expecting it to apport future preventive and therapeutic strategies [24].

1.11. Diet

It has been proposed that the type and amount of food may accelerate disease manifestation in genetically compromised individuals [23].

Deficiencies of eicosapentaenoic and docosahexaenoic acids (omega-3 fatty acids) are crucial for the normal development of the nervous system and low levels of these acids are often associated with people with schizophrenia as they are involved in the regulation of neuronal function and inflammation that cause symptoms to become even more severe. Similarly, low levels of vitamin D, vitamin B12, and folic acid negatively impact overall mental health. Additionally, diets high in sugar, saturated fats, gluten, and casein exacerbate the symptoms of this mental disorder through associated inflammatory processes. Conversely, a diet rich in antioxidants has the opposite effect [27, 28].

1.12. Infections

Several viral, bacterial, and parasitic agents, including *Toxoplasma Gondii*, *Cytomegalovirus*, *Chlamydia Spp*, and various types of herpes viruses, have been shown through testing to be associated with schizophrenia developed during the prenatal and perinatal period. It is suggested that interaction with these pathogens triggers abnormal responses in susceptible individuals, which contribute to inflammation and oxidative stress that ultimately affect neurotransmission and synaptic plasticity. Infections can trigger an inflammatory mechanism that results in the release of cytokines and other molecules, which are implicated in altering DNA methylation in schizophrenia-related genes such as RELN [29].

1.13. Obstetric complications

It encompasses complications during pregnancy, delivery, growth and abnormal development of the fetus. Oxygen insufficiency has been a shared feature and a possible reason that triggers this mental disorder. Additionally, important factors have been mentioned regarding fetal development that affect individuals. These include maternal complications

such as diabetes, preeclampsia, and Rh incompatibility, as well as fetal factors like low birth weight and reduced head circumference, which can be directly related to maternal care.

Furthermore, we must highlight complications during childbirth, such as asphyxia, emergency cesarean sections, and uterine atony, which ultimately result in a lack of oxygen to the newborn and a predisposition to the disorder [24, 30].

1.14. Upbringing and family environment

Upbringing and family environment play a crucial role in mental health as they can have profound effects on neuropsychological development. It should be noted that environmental factors also include the child-rearing environment and child abuse, which are important triggers for psychosis in the future. Many of the most common issues that give rise to this serious disorder are divorce, death in the family, abuse, financial difficulties, among others. Family stress, parental conflict, abuse or neglect can activate epigenetic pathways related to schizophrenia, for example in childhood has been associated with alterations in the NR3C1 gene, which is crucial in the stress response [24].

1.15. Migration

Migration is an increasingly common phenomenon that can put individuals at a disadvantage. A greater relationship has been found between migrants and psychotic disorders, especially schizophrenia(38). It is suggested that this section is closely related to the stress experienced and also the social and environmental differences involved in a change of this magnitude. Migration brings with it a series of changes that can cause stress and various concerns, such as cultural adaptation, discrimination, language barriers, etc., which ultimately influence the gene-environment interaction and trigger the onset of this disease [24, 31].

1.16. Urbanity

Living in a more densely populated area causes the risk of developing schizophrenia to grow exponentially compared to people living in rural areas (all indirectly related to migration) [24, 32].

A review of 43 studies showed that schizophrenia conditions varied according to the region investigated; socioeconomic factors, migration status and social fragmentation were independently associated with the risk of developing schizophrenia. It has been shown that the reduction of green areas and pollution are elements that have a positive relationship with greater development of schizophrenia [33].

1.17. Cannabis use

Cannabis use is usually accompanied by the abuse of more addictive substances, which generally increase the risk of schizophrenia. This type of association may also bring with it a genetic predisposition that is likely to be a shared risk factor with their ancestry and offspring [34].

This environmental factor has been justified by the increased concentration of the active ingredient “tetrahydrocannabinol” and the early exposure to cannabis for the first time.

Cannabis itself can produce, in most of its users, psychotic outbreaks as well as mental health disorders [35].

1.18. Gene-environment interactions

Some gene-environment interactions have been identified, with the inconvenience that are difficult to detect, they have been widely studied and the findings are important. Among the most studied factors are cannabis use, stress, infections and difficulties in childhood [39].

1.19. Infection

The link between psychosis and infections has been demonstrated with several pathogens such as Toxoplasma in the prenatal period, rubella, herpes simplex and cytomegalovirus, which make the risk of damage to neurological development higher. Among them, Toxoplasma is the one that has the most evidence in the development of schizophrenia disorder [36].

A GWAS was shown to be susceptible to Toxo and resulted in an enrichment in genes associated with schizophrenia [37]. The metallopeptidase-9 polymorphism, which actively participates in neurological inflammation, has also been associated with schizophrenia, in the glutathione S-transferase Theta 1 polymorphism, which is related to the 22q11.2 locus that is relevant to schizophrenia [36].

Concerning herpes simplex, it has been shown that the gene that participates in the IL18 pathway, IL18RAP, has been related to herpes seropositivity in schizophrenia, however there are still many biases in this research on herpes and the genetics of schizophrenia [38].

Another of the viruses associated with psychosis is COVID-19, which although it is very recent has relevant studies on its relationship with schizophrenia, this virus results in an increase in cytokines and chemokines, which causes inflammation that can be a risk for developing schizophrenia, in the same way in the fetus the increase in IL-8 in the third trimester is a risk for the development of schizophrenia [39].

1.20. Cannabis use

Cannabis use was related to schizophrenia after it was discovered that those who developed psychosis due to the use of this drug had a family history of schizophrenia, so there could be a genetic predisposition [40]. The gene mainly studied to investigate the relationship between cannabis and schizophrenia is COMT, which is also located on chromosome 22q11.1. The Val158Met polymorphism was found on this chromosome, which is important in moderating cannabis consumption and the development of schizophrenia. However, it is still being studied whether the relationship between this factor and schizophrenia is direct [41].

1.21. Childhood adversity and psychosocial stress

A factor directly related to psychosis is psychosocial stress. In genetic research, there were found interactions between COMT and stress. As mentioned before, COMT is associated with the relationship between cannabis and schizophrenia. It was mainly found that the allele COMT Val was present in individuals with susceptibility to stress. This allele was also found to be present in those who experienced childhood adversities such as bullying, abuse, or violence [42].

1.22. Sex influence on the development of schizophrenia

There is an important amount of information about the differences in schizophrenia, which is not surprising because of the importance of this topic in medicine, especially in a clinical way. It's known that both sexes have biological differences, including brain development, gene expression, and volume of different brain structures, among others that could guide us to a specific diagnosis for each gender. In Table 2 we had some differences between both sexes at distinct factors; the information was taken from [43, 44, 45] bibliography.

Table 1 Differences between both sexes with schizophrenia disease [43].

Factor	Differences
Schizophrenia rates.	Are higher in males than in females.
Genetic differences.	There is a relation between the catechol-O-methyltransferase and gamma aminobutyric acid (GABA) genes and the sex differences. The ZNF804A (encodes the zinc finger protein) and the SLC30A3 (encodes the protein zinc transporter) genes have a risk of schizophrenia in women. The dopamine, GABA and glutaminergic gene are a factor for the differences of treatment in both sexes.
Prenatal and perinatal risks	Davies *et.al.* [44] made a systematic review with 152 studies refereed to this factors, and the majority referred males to be more susceptible to develop abnormalities through the pregnancy then women, including bacterial infections, mother stress, premature rupture of the membranes, polyhydramnios, infant congenital malformations, physical challenges of labor and delivery, and another obstetric complications. [45]
Brain abnormalities	In most studies where are evaluated the structure of the brain in schizophrenia patients, the majority is from male, and it´s reported as having larger brain volumes of many tissues like amygdala, hippocampus, insula, white matter, cortex, pallidum, putamen and cerebellar cortex. Another aspect is that X-linked genes show high expression rates in the brain, what can influence in the variability involved.
Premorbility	Brain changes during adolescence are notable in females but not in males. These changes includes the volume of hippocampus and amygdala, and the increase of cerebral blood flow; another

	aspect is the action of female gonadal hormones at puberty that also delays onset of illness and provide a better initial course of illness.

1.23. Genetic and Environmental Influences on Schizophrenia: Analysis of Twin and Family Studies.

Schizophrenia is a complex mental disorder that has been extensively investigated to understand its causes and risk factors. The following are key findings from family and twin studies of schizophrenia, highlighting the influence of genetic and environmental factors that have been investigated over time.

Gottesman (1987) compiled results from about 40 European family studies conducted between 1920 and 1987 [46]. These studies showed that the risk of schizophrenia in relatives of schizophrenic individuals increases with the degree of genetic relatedness, proving once again that schizophrenia is a highly heritable disease due to the genetic component of developing schizophrenia[47].

Table 2 The risks

Third-degree relatives (cousins, nieces, nephews, grandchildren):	2%
Second-degree relatives (aunts, uncles, nieces, nephews, grandparents):	4 to 6%
First-degree relatives (parents, siblings, children)	9% to 13%.
Identical twins or offspring of double marriages:	46%.

Several studies have found that monozygotic twins have a higher probability of developing schizophrenia compared to dizygotic twins [47].

A descriptive study conducted in Santiago de Cuba in 2007 examined 24 pairs of twins diagnosed with schizophrenia. It found that 62% of the monozygotic twins suffered from schizophrenia, in contrast to 18% of the dizygotic twins. The study also investigated the age of symptom onset, finding that 50% of the monozygotic twins had symptoms before the age of 20, while in the dizygotic twins, symptoms appeared around the age of 23. The study also confirmed that susceptibility to schizophrenia is greater the closer the family relationship is to the first generation [48].

The results also supported the hypothesis that environmental factors, such as obstetric complications and viral infections during the intrauterine period, may interact with genetic vulnerability in the development of schizophrenia. In conclusion, family and twin studies highlight the relevance of genetic and environmental factors in the development of schizophrenia.

1.24. Epigenetic of Schizophrenia

Epigenetics focuses primarily on transformations in how genes are expressed without changing the DNA sequence, but by altering the organization and activity of chromatin. These changes, susceptible to environmental influences such as chemicals, stress or diet, can have long-lasting effects on gene regulation over time. Epigenetic regulation is essential in development and myelination, which, as we recall, is of paramount importance throughout our brain development because of the many functions it is responsible for in neuronal communication. During oligodendrocyte maturation, changes in chromatin structure occur due to histone modifications and DNA methylation [49]. Abnormal regulation of oligodendrocyte and myelin-related factors has been observed in mental illness. Several studies in psychiatric cohorts have concurred and identified changes in epigenetic regulators such as histone modifiers, methylation enzymes and microRNAs in schizophrenia [50].

A 2005 study suggests that epigenetic abnormalities in schizophrenia are partly linked to abnormal regulation of the enzyme GAD67. This enzyme synthesizes the inhibitory neurotransmitter GABA, the protein reelin, and the GABA membrane transporter (GAT1). The study observed a significant reduction in GAD67 activity, which is crucial as GABA is the main inhibitory neurotransmitter in the central nervous system. Additionally, a decrease in spider-like GABA interneurons has been associated with the lack of cortical coordination and deficits in working memory characteristic of schizophrenia [51].

1.25. Metilation

Multiple investigations have discovered DNA methylations in gene promoter regions, specifically in oligodendrocytes, which could indicate abnormalities in myelin development in psychiatric disorders like schizophrenia. Methylation changes in the BDNF gene at its promoter may contribute to the development of this disease, as well as the potential impact of peripheral BDNF production on brain activity. Individuals diagnosed with schizophrenia and bipolar disorder exhibit common alterations in the microstructure of white matter in the limbic system and the connections between neocortical regions. These changes, such as in the fornix, cingulum, and uncinate fasciculus, are unique features of schizophrenia. Reductions in white matter are associated with an increased genetic risk of developing the disease, while alterations in cortical gray matter seem influenced by environmental factors. Research involving neuroimaging, genetics, molecular biology, and anatomy has revealed irregularities in myelin development in various psychiatric illnesses, including schizophrenia [52, 53, 54].

In recent research on schizophrenia, increased levels of H3K9 have been noted globally in the parietal cortex in patients with schizophrenia. This increase is linked to a rise in the activities of GLP and SETDB1 enzymes, which facilitate its formation. In addition, men with schizophrenia have been found to show elevated levels of H3K9 di-methylation along with increased expression of SETDB1-associated G9α methyltransferase, suggesting a higher prevalence of this disease in men than in women [55, 56]. A connection has been established between DNA methylation in the SOX10 gene and oligodendrocyte dysfunction in schizophrenia. This suggests that epigenetic mechanisms contributing to risk gene dysfunction may increase the predisposition to oligodendrocyte dysfunction during the disease [57].

1.26. Histone alteration

Histone modification is present in a variety of psychiatric disorders. In recent research, decreased levels of one active chromatin mark, known as H3K4 trimethylation, and increased levels of another repressive mark, H3K27 trimethylation, were identified in the prefrontal cortex of individuals with schizophrenia in postmortem studies [58].

In addition, reduced levels of H3K4 methylation at the promoter of the GAD67 gene were found in the brains of women with schizophrenia, resulting in decreased expression of this gene. This finding suggests an important role of histone modifications in gene regulation associated with schizophrenia, especially in the context of GABA neurotransmitter function in the brain.

Histone alteration is present in a variety of psychiatric disorders. In one investigation, reduced levels of one active chromatin mark called H3K4 trimethylation, and increased levels of another repressive mark, H3K27 trimethylation, were found in the prefrontal cortex of people with schizophrenia postmortem. In addition, reduced levels of H3K4 methylation at the GAD67 promoter have been found in the brains of women with schizophrenia, resulting in decreased expression of this gene [59].

1.27. Noncoding ARNs

Non-coding RNAs are a kind of RNA that was identified in eukaryotic genomes, whose essential characteristic is that they do not translate into proteins; these molecules have a critical role in the occurrence and development of many diseases, including mental disorders. They consist of short sequences (approximately 18-25 nucleotides) that cause repression of the translation process or mRNA degradation causing the gene silencing process. It´s important to mention that microRNAs are the most related kind of ncRNAs to mental disorders. [60, 61]

The reason why different studies of schizophrenia are focused on miARN is the microdeletion at chromosome 22q11.2, which is related to a high risk of schizophrenia in humans for containing the gene (DGCR8) that transcribes a miRNA processing protein [62, 63]

Different kinds of miRNA are related to schizophrenia, those in different parts of the brain, especially cortical and subcortical zones; Perkins *et. al.* [64] cited by [60][62][65][66][67]were the first to identify these miRNA in postmortem patients with schizophrenia, obtaining various altered molecules such as mir130, mir181b, mir497, mir185, mir9, mir195, mir301a, mir132, mir1307, mir137, and others. Of all of them, mi137 is special for being a strongly predicted earlier psychosis in schizophrenia, being linked to it in many genome-wide association studies. This miRNA is significant for brain development and functions, as well as axon guidance signaling, ephrin receptor signaling, synaptic activity and reduced integrity of white matter [68, 69, 60, 63]

On the other hand, Studies have shown an elevation and reduction of miRNAs in peripheral blood, also used as identification factors; one of the most important miRNAs, 223, is expressed at the beginning of the disease. [70, 60]

1.28. Epigenetic modifications by drugs as a therapeutic approach

Studies on epigenetic treatment for schizophrenia are still developing; however, some important foundations for this treatment are presented in this section.

As previously mentioned, epigenetic modifications have a greater effect on gene expression; however, they are reversible, an important aspect for pharmacological therapy. The idea of this treatment is to correct the epigenetic abnormalities that are associated with the disease.

There are two main types of epigenetic treatment, DNA methyltransferase (DNMT) inhibitors, which reduce DNA methylation, potentially reactivating genes that have been abnormally silenced, and histone deacetylase (HDAC) inhibitors, which increase DNA acetylation. histones, which can lead to increased gene expression. An important mechanism for the therapy of schizophrenia is based on histone acetylation, as the inhibition of histone acetylation readers of a BET protein causes transcriptional defects to improve in neurons, thus making it an effective treatment for schizophrenia. In this process, the patient's age and the age at which SZ appeared also influence the outcome [71].

It has been observed that both basic and non-basic antipsychotics can affect DNA methylation [72]. In human research, a significant reduction in global methylation levels has been found in those who had schizophrenia, and it has been observed that the methylation of certain genes increases in patients with this disorder, DNA methylation very commonly causes a decrease in expressed genes, while changes in histones can either increase or decrease gene expression [73]. Furthermore, it has been reported that patients not treated with antipsychotics show different methylation patterns than those who have received treatment, suggesting that antipsychotic drugs could influence DNA methylation in patients with schizophrenia [74, 75].

Some antipsychotic drugs such as risperidone and clozapine, after being administered, cause epigenetic regulation through histone deacetylation of chromatin at the metabotropic glutamate 2 (mGlu2) receptors [76] However, clozapine is not approved for the treatment of schizophrenia, since it has important adverse effects such as seizures, agranulocytosis or cardiomyopathies [36].

The drug Valproate, an HDAC histone inhibitor (that also has a demethylating effect) is used in addition to antipsychotic therapy (such as clozapine or sulpiride) that shows a greater demethylation. This is related to Valproate's ability to increase the potency of antipsychotic drugs, even so, adding this drug is not of great advantage since it causes dizziness and sedation [77, 78].

The drug haloperidol causes changes in methylation, although this demonstration was carried out in rats, it is a basis for evidencing the effects of haloperidol on epigenetic regulation. This is related to the fact that the degree of methylation is linked to sex, which in turn is associated with the differences found in the degree of schizophrenia between genders, despite this, haloperidol should be indicated only if its benefit outweighs the debilitating adverse effects [79, 80].

Butyrate regulates gene expression by inhibiting HDACs. This compound, which belongs to the SCFAs, exerts a significant influence on microglial homeostasis, according to recent studies [81]. Microglia, essential in various pathways related to psychiatric disorders such as schizophrenia, play a crucial role as immune defense in the central nervous system, constantly detecting abnormalities such as plaques, neuronal damage, and infectious diseases [75].

The continued use of antipsychotics was inversely related to methylation in a specific region of DNA near the MEK1 protein gene, indicating once again the demethylating effect of these drugs. A strong correlation was found between methylation at the CpG13 site and treatment response in the negative symptoms of schizophrenia, where a decrease in methylation was associated with a less favorable response [82, 78]

Although the mechanism is not yet fully understood, this finding highlights the importance of the serotonin type 1 receptor in the action of antipsychotics and the potential impact that a single methylation site can have on the treatment response of this disease [78].

The identification of less invasive biomarkers, such as blood or saliva, multiple studies search for the relationship between DNA methylation levels in these peripheral samples and the brain in neurological and psychiatric diseases. Evidence suggests that some changes in DNA methylation in peripheral samples may reflect relevant changes in the brain. Support has been found for using DNA methylation as a biomarker in peripheral blood to predict treatment response in schizophrenia [83].

2. Conclusion

Schizophrenia, a serious and complex disease, remains a great challenge for medicine and science. Despite its rarity, the impact of schizophrenia on sufferers, their families and society as a whole is enormous. Understanding many biological factors, including genetic, epigenetic and environmental aspects, has advanced significantly in recent years, revealing complex interactions between genetic predisposition and environmental influences.

Recent genetic discoveries have opened new avenues for the treatment of schizophrenia. What has made the development of new epigenetic treatments possible is, in part, the ability to reverse epigenetic modifications, which makes it possible to control these different genetic changes through appropriate treatment, thus complementing or even eliminating the biases that exist in current treatments.

Identifying the different environmental factors that tend to modify the presentation of schizophrenia makes it important to implement long-term prevention and intervention methods. A better understanding of how factors such as intrauterine stress, infections and drug use can interact with genetic damage may allow the development of more effective health programs to reduce the incidence of this pathology.

The combination of genetic, epigenetic and environmental techniques promises not only a better understanding of schizophrenia but also the creation of more personalized and effective treatments. To improve therapeutic options and quality of life for those living with schizophrenia, this multidisciplinary strategy is required. To achieve these goals and give hope to the millions of people affected by this complex disease, continued research and collaboration in this field is necessary.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Reference

[1] National Institute of Mental Health (NIH) - La esquizofrenia. [Internet]. NIH[cited April 29, 2024]. Available in: https://www.nimh.nih.gov/sites/default/files/health/publications/espanol/la-esquizofrenia/la-esquizofrenia.pdf

[2] Raventós Vorst H. Bases genéticas de la esquizofrenia: "Nurture vrs Nature". Actual Psicología [Internet]. 2011;19(106):131–8. Available in: http://dx.doi.org/10.15517/ap.v19i106.52

[3] Hannon E, Dempster E, Viana J, Burrage J, Smith AR, Macdonald R, et al. An integrated genetic-epigenetic analysis of schizophrenia: evidence for co-localization of genetic associations and differential DNA methylation. Genome Biol [Internet]. 2016;17(1). Available in: http://dx.doi.org/10.1186/s13059-016-1041-x

[4] National Institute of Mental Health (NIMH) - Transforming the understanding and treatment of mental illnesses [Internet]. Nih.gov. [cited April 29, 2024]. Available in: https://www.nimh.nih.gov/

[5] Esquizofrenia [Internet]. Mayoclinic.org. 2021 [cited May 29, 2024]. Available in:https://www.mayoclinic.org/es/diseases-conditions/schizophrenia/symptoms-causes/syc-20354443

[6] Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet [Internet]. 2016;388(10039):86–97. Available in: http://dx.doi.org/10.1016/s0140-6736(15)01121-6

[7] Escamilla-Orozco RI, Becerra-Palars C, Armendáriz-Vázquez Y, Corlay-Noriega ISY, Herrera-Estrella MA, Llamas-Núñez RE, et al. Gac Med Mex [Internet]. 2023;157(94). Available in: http://dx.doi.org/10.24875/gmm.m21000501

[8] Richetto J, Meyer U. Epigenetic modifications in schizophrenia and related disorders: Molecular scars of environmental exposures and source of phenotypic variability. Biol Psychiatry [Internet]. 2021;89(3):215–26. Available in: http://dx.doi.org/10.1016/j.biopsych.2020.03.008

[9] Gejman PV, Sanders AR. La etiología de la esquizofrenia. Medicina (B Aires) [Internet]. 2012 [cited may 29, 2024];72(3):227–34. Available in: http://www.scielo.org.ar/scielo.php?pid=s0025-76802012000300007&script=sci_arttext

[10] Seeman MV. Esquizofrenia 2023. 2022; Available in: http://dx.doi.org/10.34810/PSICOSOMPSIQUIATRNUM230801

[11] Fitz-James MH, Cavalli G. Molecular mechanisms of transgenerational epigenetic inheritance. Nat Rev Genet. 2022 Jun;23(6):325-341. https://doi:10.1038/s41576-021-00438-5 Epub 2022 Jan 4. PMID: 34983971.

[12] Ulloa-Moreno S, Suárez-López A, Porras-Enriquez M. La función epigenética en la salud mental y las enfermedades neurodegenerativas. Revista Cubana de Investigaciones Biomédicas [Internet]. 2023. Available in: https://revibiomedica.sld.cu/index.php/ibi/article/view/2951

[13] Cheng Y, Fang Y, Zheng J, Guan S, Wang M, Hong W. The burden of depression, anxiety and schizophrenia among the older population in ageing and aged countries: an analysis of the Global Burden of Disease Study 2019. Gen Psychiatry [Internet]. 2024;37(1):e101078. Available in: http://dx.doi.org/10.1136/gpsych-2023-101078

[14] Legge SE, Santoro ML, Periyasamy S, Okewole A, Arsalan A, Kowalec K. Genetic architecture of schizophrenia: a review of major advancements. Psychol Med [Internet]. 2021;51(13):2168–77. Available in: http://dx.doi.org/10.1017/s0033291720005334

[15] Hay medio millón de esquizofrénicos en México, la mitad no recibe tratamiento adecuado [Internet]. Unam.mx. [cited may, 2024]. Available in: https://www.dgcs.unam.mx/boletin/bdboletin/2013_655.html

[16] Secretaría de Salud. En México más de un millón de personas padece esquizofrenia [Internet]. gob.mx. [cited may 29, 2024]. Available in: https://www.gob.mx/salud/articulos/en-mexico-mas-de-un-millon-de-personas-padece-esquizofrenia

[17] Touriño R, García Lourdes. Esquizofrenia, comorbilidad con enfermedades médicas y mortalidad. [Internet]. 1970. Available in: https://www.researchgate.net/profile/Rafael-Tourino/publication/264877661_ESQUIZOFRENIA_COMORBILIDAD_CON_ENFERMEDADES_MEDICAS_Y_MORTALIDAD/links/53fc6eee0cf22f21c2f3d7a5/ESQUIZOFRENIA-COMORBILIDAD-CON-ENFERMEDADES-MEDICAS-Y-MORTALIDAD.pdf

[18] McGrath J, Saha S, Chant D, Welham J. Schizophrenia: A concise overview of incidence, prevalence, and mortality. Epidemiol Rev [Internet]. 2008;30(1):67–76. Available in: http://dx.doi.org/10.1093/epirev/mxn001

[19] Bitter I, Czobor P, Borsi A, Fehér L, Nagy BZ, Bacskai M, et al. Mortality and the relationship of somatic comorbidities to mortality in schizophrenia. A nationwide matched-cohort study. Eur Psychiatry [Internet]. 2017;45:97–103. Available in: http://dx.doi.org/10.1016/j.eurpsy.2017.05.022

[20] Farsi Z, Sheng M. Molecular mechanisms of schizophrenia: Insights from human genetics. Curr Opin Neurobiol [Internet]. 2023;81(102731):102731. Available in: http://dx.doi.org/10.1016/j.conb.2023.102731

[21] Trifu S, Kohn B, Vlasie A, Patrichi B-E. Genetics of schizophrenia (review). Exp Ther Med [Internet]. 2020; Available in: http://dx.doi.org/10.3892/etm.2020.8973

[22] Mealer RG, Williams SE, Noel M, Yang B, D'Souza AK, Nakata T, et al. The schizophrenia-associated variant in SLC39A8 alters protein glycosylation in the mouse brain. Mol Psychiatry [Internet]. 2022;27(3):1405–15. Available in: http://dx.doi.org/10.1038/s41380-022-01490-1

[23] Casavilca-Zambrano S, Cancino-Maldonado K, Jaramillo-Valverde L, Guio H. Epigenética: la relación del medio ambiente con el genoma y su influencia en la salud mental. Rev Neuropsiquiatr [Internet]. 2019;82(4):266–73. Available in: http://dx.doi.org/10.20453/rnp.v82i4.3648

[24] Robinson N, Bergen SE. Environmental risk factors for schizophrenia and bipolar disorder and their relationship to genetic risk: Current knowledge and future directions. Front Genet [Internet]. 2021;12.Available in: http://dx.doi.org/10.3389/fgene.2021.686666

[25] Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. Arch Gen Psychiatry [Internet]. 2003;60(12):1187.Available in: http://dx.doi.org/10.1001/archpsyc.60.12.1187

[26] Fuller Torrey E, Miller J, Rawlings R, Yolken RH. Seasonality of births in schizophrenia and bipolar disorder: A review of the literature. Schizophr Res [Internet]. 1997;24(1–2):260.Available in: http://dx.doi.org/10.1016/s0920-9964(97)82751-x

[27] Ketogenic Diet in People With Schizophrenia [Internet]. Clinicaltrials.gov. [cited May 18,2024]. Available in: https://classic.clinicaltrials.gov/ct2/show/NCT05968638

[28] Bai N. Pilot study shows ketogenic diet improves severe mental illness [Internet]. News Center. [cited May 18, de 2024]. Available in: https://med.stanford.edu/news/all-news/2024/04/keto-diet-mental-illness.html

[29] Arias I, Sorlozano A, Villegas E, de Dios Luna J, McKenney K, Cervilla J, et al. Infectious agents associated with schizophrenia: a meta-analysis. Schizophr Res [Internet]. 2012;136(1–3):128–36.Available in: http://dx.doi.org/10.1016/j.schres.2011.10.026

[30] Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: Historical and meta-analytic review. Am J Psychiatry [Internet]. 2002;159(7):1080–92.Available in: http://dx.doi.org/10.1176/appi.ajp.159.7.1080

[31] Cantor-Graae E, Pedersen CB. Full spectrum of psychiatric disorders related to foreign migration: a Danish population-based cohort study: A danish population-based cohort study. JAMA Psychiatry [Internet]. 2013;70(4):427–35.Available in: http://dx.doi.org/10.1001/jamapsychiatry.2013.441

[32] Vassos E, Pedersen CB, Murray RM, Collier DA, Lewis CM. Meta-analysis of the association of urbanicity with schizophrenia. Schizophr Bull [Internet]. 2012;38(6):1118–23.Available in: http://dx.doi.org/10.1093/schbul/sbs096

[33] Grover S, Varadharajan N, Venu S. Urbanization and psychosis: an update of recent evidence. Curr Opin Psychiatry [Internet]. 2024;37(3):191–201. Available in: http://dx.doi.org/10.1097/yco.0000000000000931

[34] Khokhar JY, Dwiel LL, Henricks AM, Doucette WT, Green AI. The link between schizophrenia and substance use disorder: A unifying hypothesis. Schizophr Res [Internet]. 2018;194:78–85.Available in: http://dx.doi.org/10.1016/j.schres.2017.04.016

[35] Casadio P, Fernandes C, Murray RM, Di Forti M. Cannabis use in young people: The risk for schizophrenia. Neurosci Biobehav Rev [Internet]. 2011;35(8):1779–87.Available in Available in: http://dx.doi.org/10.1016/j.neubiorev.2011.04.007

[36] Wahbeh MH, Avramopoulos D. Gene-environment interactions in schizophrenia: A literature review. Genes (Basel). [Internet] 2021;12(12):1850. Available in: http://dx.doi.org/10.3390/genes12121850

[37] Wang AW, Avramopoulos D, Lori A, Mulle J, Conneely K, Powers A, et al. Genome-wide association study in two populations to determine genetic variants associated with Toxoplasma gondii infection and relationship to schizophrenia risk. Progress in Neuro-Psychopharmacology and Biological Psychiatry. [Internet] 2019;92:133–47. Available in: http://dx.doi.org/10.1016/j.pnpbp.2018.12.019

[38] Shirts BH, Wood J, Yolken RH, Nimgaonkar VL. Comprehensive evaluation of positional candidates in the IL-18 pathway reveals suggestive associations with schizophrenia and herpes virus seropositivity. Am J Med Genet B Neuropsychiatr Genet. [Internet] 2008;147B(3):343–50. Available in: http://dx.doi.org/10.1002/ajmg.b.30603

[39] Moni MA, Lin P-I, Quinn JMW, Eapen V. COVID-19 patient transcriptomic and genomic profiling reveals comorbidity interactions with psychiatric disorders. Transl Psychiatry. [Internet] 2021;11(1). Available in: http://dx.doi.org/10.1038/s41398-020-01151-3

[40] Henquet C, Di Forti M, Morrison P, Kuepper R, Murray RM. Gene-environment interplay between cannabis and psychosis. Schizophr Bull[Internet]. 2008;34(6):1111–21.Available in Available in: http://dx.doi.org/10.1093/schbul/sbn108

[41] Henquet C, Rosa A, Krabbendam L, Papiol S, Fañanás L, Drukker M, et al. An experimental study of catechol-O-methyltransferase Val158Met moderation of Δ-9-tetrahydrocannabinol-induced effects on psychosis and cognition. Neuropsychopharmacology. [Internet] 2006;31(12):2748–57. Available in: http://dx.doi.org/10.1038/sj.npp.1301197

[42] Debost J-C, Debost M, Grove J, Mors O, Hougaard DM, Børglum AD, et al. COMT Val158Met and MTHFR C677T moderate risk of schizophrenia in response to childhood adversity. Acta Psychiatr Scand. [Internet] 2017;136(1):85–95. Available in: http://dx.doi.org/10.1111/acps.12761

[43] Seeman MV. Sex differences in schizophrenia relevant to clinical care. Expert Rev Neurother [Internet]. 2021;21(4):443–53. Available in: http://dx.doi.org/10.1080/14737175.2021.1898947

[44] Davies C, Segre G, Estradé A, Radua J, De Micheli A, Provenzani U, et al. Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. Lancet Psychiatry [Internet]. 2020;7(5):399–410.Available in: http://dx.doi.org/10.1016/s2215-0366(20)30057-2

[45] Pietro JA, Voegtline KM. The gestational foundation of sex differences in development and vulnerability. Neuroscience. 2017;342:4–20.

[46] Gottesman, I.I., Gottesman, I.L., Wolfgram, D. Schizophrenia Genesis. Nueva York, NY, United States.: W.H. Freeman; 1991.

[47] McDonald, C., & Murphy, K. C. (2003). The new genetics of schizophrenia. The Psychiatric Clinics of North America, 26(1), 41–63. https://doi.org/10.1016/s0193-953x(02)00030-8

[48] Juan Carlos Rodríguez Chang MACNC. Caracterización de gemelos con esquizofrenia en el municipio de Santiago de Cuba. MEDISAN [Internet]. 1/ene-9/feb 2010; Available in: Available inhttp://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1029-30192010000100009

[49] Nielsen JA. Nuclear organization in differentiating oligodendrocytes. J Cell Sci [Internet]. 2002;115(21):4071–9.Available in: http://dx.doi.org/10.1242/jcs.00103

[50] Nestler EJ, Peña CJ, Kundakovic M, Mitchell A, Akbarian S. Epigenetic basis of mental illness. Neuroscientist [Internet]. 2016;22(5):447–63.Available in: http://dx.doi.org/10.1177/1073858415608147

[51] Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci [Internet]. 2005;6(4):312–24.Available in: http://dx.doi.org/10.1038/nrn1648

[52] Bartzokis G. Neuroglialpharmacology: white matter pathophysiologies and psychiatric treatments. Front Biosci [Internet]. 2011 [citado el 29 de abril de 2024];16(1):2695.Available in: https://pubmed.ncbi.nlm.nih.gov/21622204/

[53] Chen X, Duan H, Xiao L, Gan J. Genetic and epigenetic alterations underlie oligodendroglia susceptibility and white matter etiology in psychiatric disorders. Front Genet [Internet]. 2018;9.Available in: http://dx.doi.org/10.3389/fgene.2018.00565

[54] Fukunaga M, Okada N, Morita K, Nemoto K, Usui K, Yamamori H, et al. White matter microstructural alterations across four major psychiatric disorders: mega-analysis study in 2937 individuals Daisuke. COCOROShow authors Molecular Psychiatry. 2020;25:883–95

[55] Chase KA, Gavin DP, Guidotti A, Rajiv P. Sharma Publication, editores. Histone methylation at H3K9: Evidence for a restrictive epigenome in schizophrenia Author. En: Schizophrenia Research Publisher. Elsevier; 2013.

[56] Chase KA, Rosen C, Rubin LH, Feiner B, Bodapati AS, Gin H, et al. Evidence of a sex-dependent restrictive epigenome in schizophrenia. J Psychiatr Res [Internet]. 2015;65:87–94.Available in: http://dx.doi.org/10.1016/j.jpsychires.2015.04.005

[57] Iwamoto K, Bundo M, Yamada K, Takao H, Iwayama-Shigeno Y, Yoshikawa T, et al. DNA methylation status ofSOX10correlates with its downregulation and oligodendrocyte dysfunction in schizophrenia. J Neurosci [Internet]. 2005;25(22):5376–81.Available in: http://www.jneurosci.org/content/25/22/5376.abstract

[58] Li M, Xiao L, Chen X. Histone Acetylation and Methylation Underlie Oligodendroglial and Myelin Susceptibility in Schizophrenia. Front Cell Neurosci [Internet]. 2022;16.Available in: http://dx.doi.org/10.3389/fncel.2022.823708

[59] Huang H-S, Matevossian A, Whittle C, Kim SY, Schumacher A, Baker SP, et al. Prefrontal dysfunction in schizophrenia involves mixed-lineage leukemia 1-regulated histone methylation at GABAergic gene promoters. J Neurosci [Internet]. 2007;27(42):11254–62.Available in: http://dx.doi.org/10.1523/jneurosci.3272-07.2007

[60] Chen Q, Li D, Jin W, Shi Y, Li Z, Ma P, et al. Research progress on the correlation between epigenetics and schizophrenia. Front Neurosci [Internet]. 2021;15.Available in: http://dx.doi.org/10.3389/fnins.2021.688727

[61] Krichevsky AM, King KS, Donahue CP, Khrapko K, Kosik KS. A microRNA array reveals extensive regulation of microRNAs during brain development. RNA [Internet]. 2003;9(10):1274–81.Available in: http://dx.doi.org/10.1261/rna.5980303

[62] Richetto J, Meyer U. Epigenetic modifications in schizophrenia and related disorders: Molecular scars of environmental exposures and source of phenotypic variability. Biol Psychiatry [Internet]. 2021;89(3):215–26.Available in: http://dx.doi.org/10.1016/j.biopsych.2020.03.008

[63] Van L, Boot E, Bassett AS (2017): Update on the 22q11.2 deletion syndrome and its relevance to schizophrenia. Curr Opin Psychiatry 30:191–196.

[64] Perkins DO, Jeffries CD, Jarskog LF, Thomson JM, Woods K, Newman MA, et al. microRNA expression in the prefrontal cortex of individuals with schizophrenia and schizoaffective disorder. Genome Biol [Internet]. 2007;8(2):R27. Available in: http://dx.doi.org/10.1186/gb-2007-8-2-r27

[65] Trifu S, Kohn B, Vlasie A, Patrichi B-E. Genetics of schizophrenia (review). Exp Ther Med [Internet]. 2020;Available in: http://dx.doi.org/10.3892/etm.2020.8973

[66] Khavari B, Cairns MJ. Epigenomic dysregulation in schizophrenia: In search of disease etiology and biomarkers. Cells [Internet]. 2020;9(8):1837.Available in: http://dx.doi.org/10.3390/cells9081837

[67] Lett TA, Chakavarty MM, Felsky D, Brandl EJ, Tiwari AK, Gonçalves VF, et al. The genome-wide supported microRNA-137 variant predicts phenotypic heterogeneity within schizophrenia. Mol Psychiatry [Internet]. 2013;18(4):443–50.Available in: http://dx.doi.org/10.1038/mp.2013.17

[68] Wright C, Calhoun VD, Ehrlich S, Wang L, Turner JA, Bizzozero NIP-. Meta gene set enrichment analyses link miR-137-regulated pathways with schizophrenia risk. Front Genet [Internet]. 2015;6:147. Available in: http://dx.doi.org/10.3389/fgene.2015.00147

[69] Collins AL, Kim Y, Bloom RJ, Kelada SN, Sethupathy P, Sullivan PF. Transcriptional targets of the schizophrenia risk gene MIR137. Transl Psychiatry [Internet]. 2014;4(7):e404. Available in: http://dx.doi.org/10.1038/tp.2014.42

[70] Zhao Z, Jinde S, Koike S, Tada M, Satomura Y, Yoshikawa A, et al. Altered expression of microRNA-223 in the plasma of patients with first-episode schizophrenia and its possible relation to neuronal migration-related genes. Transl Psychiatry [Internet]. 2019;9(1). Available in: http://dx.doi.org/10.1038/s41398-019-0609-0

[71] Wawrzczak-Bargieła, A.; Bilecki, W.; Maćkowiak, M. Epigenetic Targets in Schizophrenia Development and Therapy. Brain Sci. [Internet]. 2023; 13 (3): 426. Available in: https://doi.org/10.3390/brainsci13030426

[72] Goud Alladi, C., Etain, B., Bellivier, F., Marie-Claire, C. DNA methylation as a bio marker of treatment response variability in serious mental illnesses: a systematic review focused on bipolar disorder, schizophrenia, and major depressive disorder. Int. J. Mol. Sci. [Internet]. 2018; 19 (10): e3026 Available in: https://doi.org/10.3390/ijms19103026

[73] Melka, M.G. Castellani, C.A., Laufer, B.I. et al. Olanzapine induced DNA methylation changes support the dopamine hypothesis of psychosis. J Mol Psychiatr. [Internet]. 2013; 1 (19) Available in: https://doi.org/10.1186/2049-9256-1-19

[74] Abdolmaleky, H.M., Pajouhanfar, S., Faghankhani, M., Joghataei, M.T., Mostafavi, A., Thiagalingam, S. Antipsychotic drugs attenuate aberrant DNA methylation of DTNBP1 (dysbindin) promoter in saliva and post-mortem brain of patients with schizophrenia and psychotic bipolar disorder. Am. J. Med. Genet. B Neuropsychiatr. Genet. [Internet]. 2015; 168 (8): 687–696. Available in: https://doi.org/10.1002/ajmg.b.32361

[75] Amanda J. Lisoway, Cheng C. Chen, Clement C. Zai, Arun K. Tiwari, James L. Kennedy, Toward personalized medicine in schizophrenia: Genetics and epigenetics of antipsychotic treatment, Schizophrenia Research. [Internet]. 2021; 232: 112-124 Available in: https://doi.org/10.1016/j.schres.2021.05.010.

[76] Kurita, M., Holloway, T., Garcia-Bea, A., Kozlenkov, A., Friedman, A.K., Moreno, J.L., et al. HDAC2 regulates atypical antipsychotic responses through the modulation of mGlu2 promoter activity. Nat. Neurosci. [Internet]. 2012; 15 (9), 1245-1254.

[77] Costa, E., Davis, J., Pesold, C., Tueting, P., Guidotti, A. The heterozygote reeler mouse as a model for the development of a new generation of antipsychotics. Curr. Opin. Pharmacol. [Internet]. 2002; 2 (1): 56–62. Available in: https://doi.org/10.1016/S1471-4892(01)00121-7

[78] Ellen S. Ovenden, Nathaniel W. McGregor, Robin A. Emsley, Louise Warnich , DNA methylation and antipsychotic treatment mechanisms in schizophrenia: Progress and future directions. Prog Neuropsychopharmacol Biol Psychiatry. 2017; 81: 38-49. Available in: https://doi.org/10.1016/j.pnpbp.2017.10.004

[79] Eranti, S. V, MacCabe, J.H., Bundy, H., Murray, R.M. Gender difference in age at onset of schizophrenia: a metaanalysis. Psychol. Med. [Internet]. 2013;43(1):155-167. Available in: https://doi.org/10.1017/S003329171200089X

[80] Shimabukuro, M., Jinno, Y., Fuke, C., Okazaki, Y. Haloperidol treatment induces tissue- and sex-specific changes in DNA methylation: a control study using rats. Behav. brain Funct. [Internet]. 2006; 2 (37). Available in: https://doi.org/10.1186/1744-9081-2-37

[81] Erny D, Hrabe de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, Keren-Shaul H, Mahlakoiv T, Jakobshagen K, Buch T, et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nat Neurosci. [Internet]. 2015; 18: 965–977. Available in: https://doi.org/10.1038/nn.4030

[82] Tang, H., Dalton, C.F., Srisaw at, U., Zhang, Z.J., Reynolds, G.P. Methylation at a transcription factor-binding site on the 5-HT1A receptor gene correlates with negative symptom treatment response in first episode schizophrenia. Interrnational J. Neuropsychopharmacol. [Internet]. 2014; 17 (4): 645–649. Available in: https://doi.org/10.1017/S1461145713001442

[83] Edgar, R.D., Jones, M.J., Meaney, M.J., Turecki, G., Kobor, M.S. BECon: a tool for interpreting DNA methylation findings from blood in the context of brain. Transl. Psychiatry. [Internet]. 2017; 7 (8): e1187 Available in: https://doi.org/10.1038/tp.2017.171