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Increased DNA Methylation of the *HTR1A* Gene Promoter in the Peripheral Blood Mononuclear Cells of Patients with Schizophrenia

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Abstract

Introduction: Schizophrenia (SCZ) is a chronic and complex mental disorder with poorly recognized basic characteristics. It is accompanied by numerous genetic and environmental factors, which has a significant impact on the response to treatment. Epigenetic mechanisms, such as DNA methylation, substantially contribute to the dysregulation of SCZ-associated genes. Thus, this study aimed to investigate the role of DNA methylation in the *5-HT1A* receptor gene and its potential collaboration with SCZ's etiology, focusing on how epigenetic alterations may influence serotonergic neurotransmission and lead to neurodevelopmental features of this disorder.

Methods: In the present study, the DNA methylation level of the *HTR1A* gene promoter (the 5-HT1A receptor) in the peripheral blood mononuclear cells (PBMCs) of 100 patients with SCZ and 100 healthy control subjects was assessed using the high-resolution melting (HRM) method. Genomic DNA was extracted from PBMCs, and following bisulfite conversion, the HRM method was used to quantify the methylation rates in the 5′ promoter region of the *HTR1A* gene.

Results: Based on the results, a significant increase was detected in mean methylation in individuals with SCZ ($P<0.001$). Moreover, the analysis of receiver operating characteristic curve demonstrated an area under the curve of 0.678, indicating the epigenetic dysregulation of serotonergic signaling in SCZ.

Conclusion: Our findings revealed higher DNA methylation in the *HTR1A* gene promoter region in SCZ patients' PBMCs compared to healthy controls. To discover the biological mechanisms and clinical significance of epigenetic alterations, future studies should concentrate on brain tissue and gene expression.

Keywords: Schizophrenia, *HTR1A* gene promoter methylation, 5-HT1A receptor, Serotonergic dysregulation, Epigenetics in psychosis

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Introduction

Schizophrenia (SCZ) is widely recognized as one of the most debilitating and persistent mental illnesses. There is an association between this syndrome and a number of medical complications, and it generally manifests in adolescence or early adulthood. Recent genetic studies, such as Psychiatric Genomics Consortium, underscore the crucial role of variations in genetics, the while gene-environment interactions are obviously of relevance to the process of neurodevelopment.[1,2] In spite of comprehensive reviews on SCZ over the past century, research in recent decades has demonstrated that it is a brain condition, with a considerable proportion of cases suffering from this neurodevelopmental disorder.

SCZ is identified by cognitive, positive, and negative symptoms, resulting in a chronic disorder. During the last ten years, there has been a marked improvement in researchers' awareness of the genetic makeup and high heritability rate of SCZ. The realization of such an advancement is chiefly due to both developments in the techniques of molecular genetics, promoting extensive genotyping and sequencing, and international collaborative integrated research specimens, as presented by the Psychiatric Genomics Consortium. The detection of numerous rare variations, copy number variations, and shared risk variants has been feasible by this integrated approach, highlighting significant novel insights into SCZ's biological foundation.[3,4]

A wide variety of physiological activities, including mood, movement, and cognitive functions, are regulated

by the serotonergic system, which has an integrated physiological role in the body. In addition, serotonin neurons (5-HT), located on the raphe nuclei, send their axons to limbic regions, the cerebral cortex, and other areas of the brain. Different 5HT receptors facilitate serotonergic neurotransmissions, which, based on their signaling mechanisms, are generally separated into seven categories (5HT1 to 5HT7) and 14 subtypes.[5-7]

The 5-HT1A receptors are located on serotonergic and postsynaptic neurons, and their significant therapeutic role in treatment with atypical antipsychotics is evident.[8-10] According to scientific and empirical evidence, the role of these receptors in SCZ's pharmacological treatment, motor regulation, and the modulation of dopamine neurotransmission is crucial. Many atypical antipsychotics are 5-HT1A receptor partial agonists, and this action is thought to contribute to their beneficial effects on negative symptoms in SCZ. Atypical antipsychotic medications cause fewer extrapyramidal symptoms or side effects. Moreover, they are efficient in the treatment of positive and negative symptoms, as well as cognitive deficiencies connected with SCZ.[11]

The role of DNA methylation, as an epigenetic DNA modification, has been implicated in the advancement of neurodevelopmental disorders. As a stable epigenetic process, it can regulate gene expression without altering the underlying DNA sequence.[12] This chemical alteration, which continues to exist after cell division, is inherited by offspring cells all over the subsequent mitoses.[13] Additionally, the accessibility of RNA polymerase and transcription components can be changed by the covalent modification of DNA, thereby altering the transcription of genes when they situate in the promoter region of a gene.[14]

As an epigenetic factor, DNA methylation contributes to the discordance between monozygotic twins for SCZ [15]; in other words, differences in identical twins suggest a role for epigenetics. The connection between DNA methylation and developmental processes like cell differentiation demonstrates its capacity for the advancement of neurodevelopmental diseases.[16] Maternal health, coupled with medications and nutritional factors, is continuously present throughout embryonic and fetal growth. A number of these variables are known to affect DNA methylation, causing slight differentiations in neural development and leading to syndrome detection.[17] A multitude of studies show that epigenetic alterations may contribute to the etiology of SCZ and some psychotic disorders.[18]

Although the majority of epigenetic studies have focused on DNA obtained from tumors or post-mortem brain tissues, particularly affected tissues, blood cells have also been productive in investigations into epimutation.[19,20] According to a recent study, DNA collected from peripheral blood mononuclear cells (PBMCs) can contribute to the detection of epigenetic changes occurred during the starting phases of embryogenesis.[21,22] Overall, while brain tissue is regarded ideal, PBMC-derived DNA can reveal initial epigenetic alterations.

Reliance on peripheral blood samples, the relatively modest receiver operating characteristic (ROC) analysis discriminatory power, the lack of direct HTR1A mRNA/protein expression evaluation, and no adjustment for confounders (e.g., smoking status, body mass index, illness duration, and antipsychotic medications) are among the limitations observed in this research.

Future examinations should prioritize longitudinal designs to keep track of epigenetic modifications over time, incorporate DNA methylation data with gene expression assessment, and underscore brain tissue studies in order to establish mechanistic relevance and confirm *HTR1A* methylation as a potential biomarker for SCZ.

The present study aims to explore DNA methylation's role within the *5-HT1A* receptor gene and its potential collaboration with SCZ's etiology, investigating how epigenetic alterations may affect serotonergic neurotransmission and result in the neurodevelopmental features of this disorder.

Methods

A structured clinical and diagnostic interview, based on the diagnostic criteria of the DSM-5, was performed with patients who were referred to the emergency room and inpatient units of Razi Psychiatric Hospital in Tabriz in 2023. After removing patients with acute psychoses, mood psychoses, and substance-induced psychoses, a total of 200 participants, with no post-hoc exclusion, were included in the final analysis. First, 100 patients diagnosed with SCZ were selected, and blood samples were collected after obtaining informed consent.

Then, 100 volunteers, whose general physical conditions were verified to be satisfactory and met the current study's age and gender criteria, were chosen from among a pool of healthy individuals who expressed their willingness to participate and served as a control group. Peripheral blood samples were extracted after the study's methodology was explained and consent was obtained from the legal guardians of these healthy participants, and the PBMCs were isolated employing Ficoll density gradient centrifugation.

Each vacutainer blood collection tube was used to collect and hold 4 mL of peripheral blood samples. After the blood was diluted with phosphate-buffered saline in a 1:1 ratio, it was transferred to the Ficoll tubes. Following centrifugation (at 1000x g for 20 minutes at room temperature), the PBMC-containing buffy coat was obtained and transferred to a 15-mL Falcon tube. After the PBMC was washed twice with 10 mL phosphate-buffered saline, it was centrifuged for 10 minutes at 250 g. The resulting precipitate was used to extract the whole DNA.

Based on the manufacturers' protocols, standard commercial kits, such as the Noegen blood isolation kit (CAT. 62600) and the EZ DNA MethylationTM Kit (Zymo Research, Irvine, CA, USA, D5001), were employed to extract genomic DNA from peripheral leukocytes and by bisulfite conversion. Previously published primers (Carrard et al., 2011) were used to conduct the polymerase chain reaction amplification of the bisulfite-converted

HTR1A gene's promoter region.

Moreover, the high-resolution melting (HRM) analysis performed with the Roche LightCycler instrument using standard temperature ramp settings was utilized to measure the levels of DNA methylation since HRM approach is highly sensitive and facilitates precise differentiation and rapid results. Each sample was tested twice. In this test, the HRM profile was employed to determine the percentage of methylation in the samples. In addition, commercial standards for methylation and unmethylated DNA (Chemicon, Temecula, CA) were used to estimate unknown substances. To increase the accuracy of the results, a subset of samples was verified using pyrosequencing.

The collected data were recorded into SPSS program checklists (version 23) that were developed, and the research findings were expressed as percentages of methylation. The Kolmogorov-Smirnov test was used to validate the normality of the data. Further, the Mann-Whitney U test and Chi-squared or Fisher's exact test were employed to compare the values of quantitative and qualitative data between the two groups, respectively. A *P*-value < 0.001 was considered statistically significant.

Results

The final analysis included a total of 100 SCZ patients and 100 age-matched and gender- matched healthy controls. Bisulfite treatment and succeeding HRM were applied to measure the methylation level of the *HTR1A* receptor gene promoter. Furthermore, the ROC curve test ($P < 0.05$) was utilized to validate the sensitivity and specificity of the tests. The comparison of HTR1A promoter methylation levels between SCZ patients and healthy controls is presented in Table 1, and the results indicating the methylation rates are shown in Figure 1.

ROC analysis yielded an AUC of 0.678, suggesting a restricted discriminatory power ($P = 0.0056$). The median rates of methylation were 35% (within a range of 10–100; interquartile range [IQR]: 25–60) for controls and 52.5 (within a range of 20–100; IQR 40–75) for patients. The Mann-Whitney U test was used to perform group comparisons (U = 3336.0, $P < 0.001$, rank-biserial r = 0.29). Based on the Mann-Whitney U test (U = 3336.0), $P < 0.001$ was considered statistically significant.

The ROC curve analysis ($P < 0.05$) was employed to rate the specificity, precision, and sensitivity of the tests. The AUC was 0.678 ($P = 0.0056$, Figure 2).

Discussion

The present study investigated the DNA methylation status of the *HTR1A* gene promoter in PBMCs collected from individuals with SCZ and healthy control subjects. The results demonstrated an increase in promoter methylation in SCZ patients, which is statistically significant, suggesting the existence of epigenetic changes related to this psychotic disorder. Likewise, the potential biological relevance and clinical significance of the results are highlighted due to the magnitude of the observed difference corresponding to the medium effect size (rank-biserial r = 0.29).

Earlier studies have identified alterations in the expression and binding of the 5-HT1A receptor in SCZ and other related psychiatric disorders, showing a significant decrease in mRNA expression.[23,24] Our research supports these findings by demonstrating a rise in gene methylation levels in SCZ. Accordingly, this rise might lead to a decline in the expression of 5HT1A receptors.[25] There is a connection between increased promoter methylation and transcriptional repression; however, the association between DNA methylation and gene expression is context-sensitive and needs direct assessment.

This study analyzed a promoter region that comprises the *HTR1A* gene's transcription start site, where an increase in methylation may interfere with the interaction of the gene with transcription elements or RNA polymerase II, which may change how genes are expressed. In other words, epigenetic modifications may affect RNA polymerase II recruitment and transcription factor binding. It is noteworthy that the methylation percentage increased in this location for the SCZ group. Consequently, instead of definite alterations in gene expression, the observed rise in methylation indicated a change in regulatory control.

A rise in the methylation of the *5HT1A* receptor

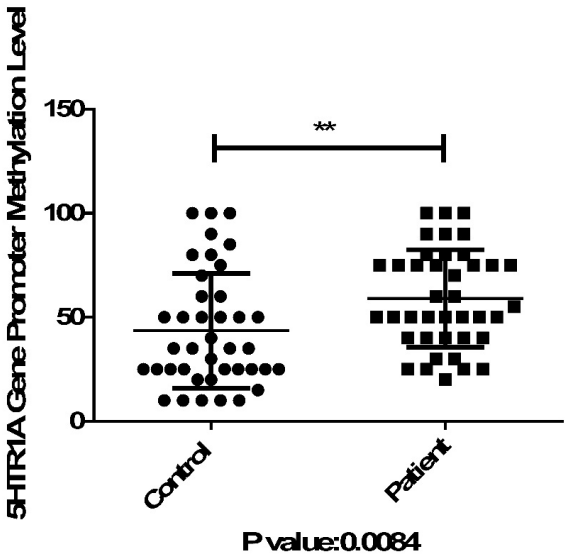

Figure 1. The *HTR1A* Receptor Gene Promoter Methylation Level

Table 1. Comparison of *HTR1A* Promoter Methylation Levels Between Schizophrenia Patients and Healthy Controls

Variable	Controls (n = 100)	SCZ Patients (n = 100)	Statistical Test	*P*-Value	Effect Size
HTR1A promoter methylation (%)	35 (25-60)	52.5 (40-75)	Mann-Whitney U = 3336	$P < 0.001$	R = 0.29* Cliff's δ = 0.33&

Note. Data are presented as medians (interquartile ranges). Mann-Whitney U test was used to compare the groups. *Rank-biserial correlation coefficient (medium effect size). &Cliff's delta (medium effect size; a positive value indicates higher methylation in schizophrenia patients).

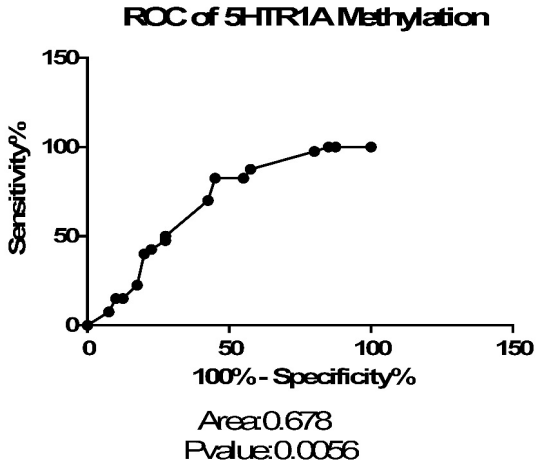

Figure 2. ROC of *HTR1A* Receptor Gene Methylation
Note. ROC: Receiver operating characteristic

gene promoter region has recently been detected in the frontal brain of major depressive disorder patients.[26] Scientists concluded that this high level of methylation demonstrates reduced prefrontal cortex 5HT1A receptor expression. Nevertheless, there is disagreement over the decline in the density of 5HT1a receptors, and some researchers have observed a rise or no alteration in the protein concentrations.[27,28] As stated by Gray et al, these inconsistencies are likely the result of different methods and heterogeneities in SCZ patient populations.[24]

Our results support the assertion that serotonergic genes undergo epigenetic dysregulation in psychiatric conditions. However, heterogeneity concerning receptor density and expression, found across studies, highlights that serotonergic regulation in SCZ has a complicated nature, which may be confirmed through variations observed in methodology, clinical characteristics, and drug exposure.

Although brain tissue remains an ideal source for neuropsychiatric epigenetic studies, lymphocyte DNA was employed in this investigation. Moreover, PBMCs offer easier access and an applicable preference and may reflect systematic epigenetic alterations identified throughout early development. However, their correlation with brain methylation patterns should be the focus of additional studies. Further, several lines of evidence indicate that blood cells can consecutively be utilized for epigenetic research. An earlier study compared the epigenetic differences between monozygotic twins that were different for SCZ using blood cells.[29] Since then, other research centers have employed blood cells to study the whole or local DNA methylation in mental diseases.[30]

According to previous arguments, blood leukocytes may help identify epigenetic alterations brought on by early embryogenesis and even emphasize hereditary epigenetic deviations.[21] Nevertheless, further research is needed to correlate DNA methylation information from particular brain areas and blood sources before making any definitive conclusions. These results should, therefore, be viewed as preliminary research and confirmed on brain tissue.

Additionally, the gene region used for this research was not heavily methylated. All these factors may, thus, affect positive findings. Nonetheless, the above-mentioned outcomes are intriguing and novel, as they help demonstrate the role of the epigenome in the psychopathology of the SCZ. This is due to an increased attention to DNA methylation in mental illnesses.

Based on the evidence, our findings revealed that *HTR1A* promoter methylation levels in the PBMCs of SCZ patients are higher than the controls, underscoring the role of epigenetic mechanisms in this mental disorder. Furthermore, a lower amount of 5HT1A receptor expression in this illness, compared to previous observations and changes to the serotoninergic system, could result from elevated levels of methylation.

Further studies utilizing bisulfite sequencing or an integrative method incorporating transcriptomic, epigenetic, and neurobiological data are warranted to elucidate the observations' functional mechanisms and clinical implications. Moreover, the semi-quantitative nature of HRM is considered a limitation, and researchers should include site-specific resolution in their studies. Finally, Due to the biomarker's restricted diagnostic ability (AUC = 0.678), clinical practices should be recommended with caution.

Conclusion

The findings of this study indicated higher DNA methylation in the *HTR1A* gene promoter region in the PBMCs of SCZ patients compared to healthy controls, aligning with the results of prior studies on epigenetic alterations in serotonergic pathway genes connected with psychotic disorders. Although *HTR1A* mRNA or protein expression was not directly assessed, a decline in gene transcription is commonly responsible for a rise in promoter methylation, potentially indicating systemic or developmental regulatory changes or modulations integral to SCZ's pathophysiology. It is noteworthy that this research advances existing findings by uniquely targeting SCZ with a larger sample and incorporating ROC analysis, though results remain preliminary due to modest discriminatory power and reliance on peripheral blood samples. To verify *HTR1A* methylation as a biomarker and clarify its mechanistic relevance, future examinations should utilize longitudinal designs, study brain tissues, integrate DNA methylation with gene expression data, and include confounders, such as smoking status, body mass index, illness duration, and antipsychotic medications.

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Authors' Contribution

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Competing Interests

The authors declare that they have no conflict of interests.

Ethical Approval

This study followed the Ethical Principles of the Declaration of Helsinki for Medical Research involving human subjects and was approved by the Ethics Committee of Razi Psychiatric Hospital, Tabriz. All patients and healthy subjects (or their legal guardians) provided written informed consent for inclusion before participation in the study. Moreover, the privacy and confidentiality of participants' information were strictly maintained.

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