Section: Psychiatry

Original Research Article

GLOBAL DNA METHYLATION AND CLINICAL MANIFESTATIONS IN BIPOLAR DISORDER: INSIGHTS FROM DRUG-NAÏVE PATIENTS

Danish Hussain[1], Niharika Singh[2]

[1]*Consultant Psychiatrist, Sanctum Wellness and Healing Mental Health Establishment, New Delhi, India.*
[2]*Consultant Psychiatrist, Sanctum Wellness and Healing Mental Health Establishment New Delhi, India.*

Received *: 19/01/2025*
Received in revised form *: 03/03/2025*
Accepted *: 25/03/2025*

Corresponding Author:
Dr. Danish Hussain,
Consultant Psychiatrist, Sanctum Wellness and Healing Mental Health Establishment, New Delhi, India.
Email: drnikhilreddy@gmail.com

DOI: 10.70034/ijmedph.2025.3.278

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (3); 1514-1519

ABSTRACT

Background: Bipolar disorder (BD) is a chronic mood disorder characterized by episodic mood disturbances. Emerging evidence suggests that epigenetic mechanisms, particularly DNA methylation, may play a role in BD pathophysiology. This study investigates the correlation between global DNA methylation levels and symptom severity in drug-naïve BD patients.

Materials and Methods: This cross-sectional study included 98 drug-naïve BD patients and 99 age- and gender-matched healthy controls. Clinical assessments included the Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HDRS). Global DNA methylation was quantified using an enzyme-linked immunosorbent assay (ELISA)-based method. Correlations between DNA methylation levels and clinical variables were analyzed using Pearson's correlation and multiple linear regression.

Results: BD patients exhibited significantly lower global DNA methylation levels compared to controls (4.0 ± 1.0% vs. 5.1 ± 0.7%, $p<0.001$). Methylation levels decreased with increasing symptom severity, being highest in mild cases (4.5 ± 0.9%) and lowest in severe cases (3.5 ± 0.8%). Negative correlations were observed between DNA methylation and YMRS ($r = -0.462$, $p<0.001$), HDRS ($r = -0.523$, $p<0.001$), illness duration ($r = -0.339$, $p=0.004$), and number of mood episodes ($r = -0.419$, $p<0.001$). Childhood trauma and lower socioeconomic status were independent predictors of reduced methylation ($\beta = -0.29$, $p<0.001$ and $\beta = -0.15$, $p=0.032$, respectively). Sleep duration positively correlated with methylation levels ($r = 0.383$, $p<0.001$).

Conclusion: This study demonstrates a significant association between reduced global DNA methylation and BD symptom severity, suggesting an epigenetic contribution to disease progression. Environmental factors, including childhood trauma and sleep disturbances, may further influence methylation patterns. Future research should explore whether interventions targeting these modifiable factors can mitigate epigenetic alterations and improve clinical outcomes in BD patients.

Keywords: Bipolar disorder, DNA methylation, Epigenetics, Symptom severity, Childhood trauma.

INTRODUCTION

Bipolar disorder (BD) is a severe, chronic mood disorder affecting approximately 0.3–1.2% of the global population, with a higher prevalence of around 0.4–1.5% in India.[1] It is characterized by recurrent episodes of mania, hypomania, and depression, leading to substantial psychosocial impairment. The disorder has a strong genetic basis, with heritability estimates ranging between 60% and 85%.[2] However, genetic predisposition alone does not fully explain the variability in disease onset, progression, and symptom severity, highlighting the need to explore epigenetic mechanisms such as DNA methylation.

DNA methylation, a key epigenetic modification involving the addition of methyl groups to cytosine residues, plays a critical role in gene expression

regulation. Aberrant DNA methylation patterns have been implicated in BD, particularly in genes associated with neuroplasticity, stress response, and neurotransmitter function.[3] Studies have reported altered methylation levels in BD patients compared to healthy controls, with hypermethylation and hypomethylation affecting genes such as BDNF, NR3C1, and SLC6A4, which are involved in mood regulation and stress response.[4] Global DNA methylation levels, which provide an overall measure of genomic methylation status, have been found to differ significantly between BD patients and controls, suggesting potential biomarker utility.[5]

However, most existing research has been conducted on medicated BD patients, where the effects of psychotropic drugs such as mood stabilizers and antipsychotics on DNA methylation remain a confounding factor.[6] Lithium, a first-line treatment for BD, has been shown to modulate epigenetic mechanisms, including DNA methylation and histone modifications, complicating the interpretation of findings.[7] Investigating DNA methylation in drug-naïve BD patients provides a unique opportunity to assess epigenetic alterations independent of pharmacological influences, thereby offering clearer insights into the disease's underlying biological mechanisms.

The severity of BD symptoms, often assessed using standardized scales such as the Young Mania Rating Scale (YMRS) for mania and the Hamilton Depression Rating Scale (HDRS) for depression, varies widely among individuals.[8,9,10] Understanding the relationship between global DNA methylation levels and symptom severity in drug-naïve BD patients may help identify epigenetic biomarkers associated with disease progression and treatment response. This study aimed to explore this correlation, contributing to the growing evidence on the role of epigenetics in BD and potentially guiding the development of targeted therapeutic strategies.

MATERIALS AND METHODS

Study Design and Setting

This cross-sectional study was conducted in the department of Psychiatry at a tertiary care center in North India, over a period of 2 years from July 2021 to June 2023. The study was approved by the Institutional Ethics Committee (IEC), and written informed consent was obtained from all participants prior to their enrollment in the study.

Study Population

The study included 98 drug-naïve patients diagnosed with bipolar disorder (BD) based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Participants were recruited from the psychiatry outpatient department following a comprehensive clinical evaluation. Eligible patients were aged between 18 and 60 years, with no prior exposure to psychiatric medications. Exclusion criteria included individuals with comorbid psychiatric disorders such as schizophrenia or major depressive disorder, chronic systemic diseases like diabetes or hypertension, neurological disorders, or substance use disorders. Additionally, a control group of age- and sex-matched healthy individuals (n = 99) was recruited from the general population, ensuring that none had a personal or family history of psychiatric illnesses.

Clinical Assessment

The severity of BD symptoms was assessed using the Young Mania Rating Scale (YMRS) for manic symptoms and the Hamilton Depression Rating Scale (HDRS) for depressive symptoms. Each participant underwent a structured clinical interview conducted by a trained psychiatrist, and scores were categorized into mild, moderate, and severe symptom severity groups based on established cut-off values. Alongside clinical assessments, demographic and clinical history, including duration of illness, number of previous episodes, family history of psychiatric disorders, and psychosocial factors, were documented using a structured proforma.

Sample Collection and DNA Extraction

Peripheral blood samples (5 mL) were collected from each participant using EDTA-coated tubes to prevent coagulation. The samples were immediately stored at -80°C until further analysis. Genomic DNA was extracted using the Qiagen DNeasy Blood & Tissue Kit following the manufacturer's standard protocol. The quality and purity of the extracted DNA were assessed using a Nanodrop 2000 spectrophotometer (Thermo Fisher Scientific, USA), and DNA concentration was measured in ng/µL using a Qubit fluorometer (Thermo Fisher Scientific, USA). Only samples with an A260/A280 ratio between 1.8 and 2.0 were considered for further analysis to ensure high-quality DNA.

Global DNA Methylation Analysis

Global DNA methylation levels were quantified using the MethylFlash Global DNA Methylation (5-mC) ELISA Kit (Epigentek, USA), which measures total 5-methylcytosine (5-mC) levels in genomic DNA. The assay was performed according to the manufacturer's protocol, wherein DNA samples were immobilized on a 96-well plate, followed by the addition of capture and detection antibodies specific to 5-mC. Absorbance readings were obtained at 450 nm using a BioTek Epoch 2 microplate reader. Methylation levels were calculated as a percentage of total DNA, based on the standard curve generated using methylated DNA standards provided in the kit.

Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Continuous variables, including age, symptom severity scores (YMRS and HDRS), and global DNA methylation levels, were presented as mean ± standard deviation (SD) and compared between BD patients and controls using the

independent t-test or Mann-Whitney U test based on data normality. Categorical variables, such as gender, socioeconomic status, and family history of psychiatric disorders, were expressed as frequencies and analyzed using the chi-square test. The relationship between global DNA methylation levels and symptom severity was assessed using Pearson's or Spearman's correlation, as appropriate. To adjust for potential confounders such as age, gender, BMI, and illness duration, multiple linear regression analysis was performed. A significance level of $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using SPSS version 20.0 (IBM Corp., USA).

Ethical Considerations

The study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki. All participants were assured of confidentiality, and their data were anonymized for analysis. No financial incentives were provided for participation, and individuals had the right to withdraw from the study at any time without any consequences to their medical care.

RESULTS

A total of 197 participants were enrolled in the study, comprising 98 drug-naïve BD patients and 99 age- and sex-matched healthy controls. In this study, BD patients (mean age: 34.9 ± 9.3 years) and controls (34.6 ± 8.5 years) had comparable demographic profiles, including gender distribution (p=0.821) and BMI (p=0.113). However, BD patients had significantly fewer years of education (9.5 ± 3.2 vs. 11.7 ± 2.7, p=0.008) and were more likely to belong to a low socioeconomic status (39.8% vs. 21.2%, p=0.027). Family history of BD (27.6% vs. 4.0%) and psychiatric disorders (37.8% vs. 9.1%) were significantly higher in BD patients (both p<0.001). The mean illness duration in BD patients was 6.7 ± 3.0 years, with an average of 2.4 ± 1.1 manic and 2.6 ± 1.0 depressive episodes. Psychotic symptoms were present in 25.5% of BD patients but absent in controls (p<0.001). BD patients had significantly higher symptom severity scores (YMRS: 24.1 ± 6.4 vs. 2.9 ± 1.0; HDRS: 19.7 ± 5.6 vs. 3.6 ± 1.2; both p<0.001), higher childhood trauma prevalence (41.8% vs. 10.1%, p<0.001), and shorter sleep duration (5.8 ± 1.5 vs. 7.3 ± 1.1 hours, p<0.001) (Table 1).

Table 1: Demographic and Clinical Characteristics of the Study Population

Variable	BD Patients (n=98)	Controls (n=99)	p-value
	Frequency (%)/Mean ± SD		
Age (years)	34.9 ± 9.3	34.6 ± 8.5	0.742
Gender			
Male	57 (58.2%)	56 (56.6%)	0.821
Female	41 (41.8%)	43 (43.4%)	
BMI (kg/m²)	23.1 ± 3.5	24.0 ± 2.8	0.113
Education Level (Years of Schooling)	9.5 ± 3.2	11.7 ± 2.7	0.008
Socioeconomic Status			
Low	39 (39.8%)	21 (21.2%)	0.027
Medium	46 (46.9%)	52 (52.5%)	
High	13 (13.3%)	26 (26.3%)	
Marital Status			
Married	54 (55.1%)	64 (64.6%)	0.231
Single	36 (36.7%)	30 (30.3%)	
Divorced	8 (8.2%)	5 (5.1%)	
Family History of BD	27 (27.6%)	4 (4.0%)	<0.001
Family History of Psychiatric Disorders	37 (37.8%)	9 (9.1%)	<0.001
Duration of Illness (years)	6.7 ± 3.0	—	—
Number of Manic Episodes	2.4 ± 1.1	—	—
Number of Depressive Episodes	2.6 ± 1.0	—	—
Presence of Psychotic Symptoms	25 (25.5%)	0 (0.0%)	<0.001
YMRS Score	24.1 ± 6.4	2.9 ± 1.0	<0.001
HDRS Score	19.7 ± 5.6	3.6 ± 1.2	<0.001
History of Childhood Trauma	41 (41.8%)	10 (10.1%)	<0.001
Sleep Duration (hours)	5.8 ± 1.5	7.3 ± 1.1	<0.001

Global DNA methylation levels were significantly lower in BD patients (4.0 ± 1.0%) compared to controls (5.1 ± 0.7%, p<0.001). Within the BD group, methylation levels varied with symptom severity, with the highest levels observed in patients with mild symptoms (4.5 ± 0.9%), followed by those with moderate symptoms (4.0 ± 1.0%), and the lowest levels in patients with severe symptoms (3.5 ± 0.8%) (Table 2).

Table 2: Global DNA Methylation Levels in BD Patients and Controls

Group	Global DNA Methylation (% 5-mC)	p-value
	Mean ± SD	
BD Patients (Overall) (n=98)	4.0 ± 1.0	<0.001
Mild symptoms (n=32)	4.5 ± 0.9	

Moderate symptoms (n=42)	4.0 ± 1.0	
Severe symptoms (n=24)	3.5 ± 0.8	
Controls (n=99)	5.1 ± 0.7	

Pearson's correlation analysis revealed a significant inverse correlation between global DNA methylation levels and symptom severity, as indicated by YMRS (r = -0.462, p<0.001) and HDRS scores (r = -0.523, p<0.001). A negative correlation was also observed with illness duration (r = -0.339, p=0.004), number of mood episodes (r = -0.419, p<0.001), and family history of BD (r = -0.376, p<0.001). Although age showed a weak negative correlation (r = -0.181, p=0.081), it was not statistically significant. Conversely, sleep duration exhibited a significant positive correlation with DNA methylation levels (r = 0.383, p<0.001), suggesting a potential association between sleep patterns and epigenetic alterations in BD (Table 3).

Table 3: Correlation Between Global DNA Methylation and Clinical Parameters

Variable	Pearson's Correlation Coefficient (r)	p-value
YMRS Score	-0.462	<0.001
HDRS Score	-0.523	<0.001
Age (in years)	-0.181	0.081
Duration of Illness (in years)	-0.339	0.004
Number of Episodes	-0.419	<0.001
Family History of BD	-0.376	<0.001
Sleep Duration (in hours)	0.383	<0.001

Lower global DNA methylation in BD patients was significantly associated with greater symptom severity (YMRS: β = -0.41, HDRS: β = -0.44, p<0.001), longer illness duration (β = -0.27, p<0.001), and a higher number of mood episodes (β = -0.30, p<0.001). Psychotic symptoms (β = -0.17, p=0.022), lower socioeconomic status (β = -0.15, p=0.032), female gender (β = -0.14, p=0.022), family history of BD (β = -0.35, p<0.001), and childhood trauma (β = -0.29, p<0.001) further contributed to methylation decline. In contrast, longer sleep duration correlated positively with methylation (β = 0.33, p<0.001). These findings highlight a strong link between disease severity, psychosocial factors, and epigenetic alterations in BD (Table 4).

Table 4: Multiple Linear Regression Analysis for Factors Associated with Global DNA Methylation

Predictor Variable	Beta Coefficient (β)	95% CI	p-value
Age (years)	-0.09	(-0.15, 0.02)	0.091
Gender			
Male (Reference)	—	—	—
Female	-0.14	(-0.24, -0.05)	0.022
BMI (kg/m²)	-0.05	(-0.12, 0.05)	0.181
Socioeconomic Status			
Low (Reference)	—	—	—
High	-0.15	(-0.27, -0.04)	0.032
YMRS Score	-0.41	(-0.50, -0.31)	<0.001
HDRS Score	-0.44	(-0.55, -0.33)	<0.001
Duration of Illness (years)	-0.27	(-0.38, -0.15)	<0.001
Number of Episodes (Manic/Depressive)	-0.3	(-0.40, -0.20)	<0.001
Presence of Psychotic Symptoms			
No (Reference)	—	—	—
Yes	-0.17	(-0.28, -0.07)	0.022
Family History of BD			
No (Reference)	—	—	—
Yes (n=27)	-0.35	(-0.46, -0.24)	<0.001
History of Childhood Trauma			
No (Reference)	—	—	—
Yes (n=41)	-0.29	(-0.41, -0.17)	<0.001
Sleep Duration (hours)	0.33	(0.21, 0.44)	<0.001

DISCUSSION

This study highlights a significant reduction in global DNA methylation in drug-naïve BD patients compared to healthy controls, with lower methylation levels correlating with greater symptom severity.

Our study cohort comprised 98 drug-naïve BD patients and 99 healthy controls matched for age (34.9 ± 9.3 vs. 34.6 ± 8.5 years, p=0.742) and gender distribution (male: 58.2% vs. 56.6%, p=0.821). Despite these similarities, BD patients had significantly lower educational attainment (9.5 ± 3.2 vs. 11.7 ± 2.7 years, p=0.008) and were more likely to belong to lower socioeconomic strata (low SES: 39.8% vs. 21.2%, p=0.027). These findings support prior studies demonstrating an association between lower educational and socioeconomic status and increased risk of BD.[11,12] Lower socioeconomic

conditions may contribute to increased psychological stress, poor health literacy, and reduced access to healthcare, exacerbating BD severity.[11,12]

Clinically, BD patients exhibited an average illness duration of 6.7 ± 3.0 years, with recurrent manic (2.4 ± 1.1) and depressive (2.6 ± 1.0) episodes. The presence of psychotic symptoms was observed in 25.5% of BD patients, consistent with literature indicating that psychotic features are common in BD and associated with greater illness severity.[13] Mood symptom severity was significantly higher in BD patients, as evidenced by elevated YMRS (24.1 ± 6.4 vs. 2.9 ± 1.0, $p<0.001$) and HDRS (19.7 ± 5.6 vs. 3.6 ± 1.2, $p<0.001$) scores. These results align with previous findings that symptom severity is heightened in early BD stages, particularly in drug-naïve patients.[14,15]

Global DNA methylation levels were significantly lower in BD patients than in controls (4.0 ± 1.0% vs. 5.1 ± 0.7%, $p<0.001$). Notably, methylation levels progressively declined with increasing symptom severity, being highest in mild cases (4.5 ± 0.9%), followed by moderate (4.0 ± 1.0%) and severe cases (3.5 ± 0.8%). Pearson's correlation analysis revealed significant negative associations between DNA methylation and YMRS ($r = -0.462$, $p<0.001$) and HDRS scores ($r = -0.523$, $p<0.001$), indicating that greater mood symptom severity corresponds to reduced methylation.

These findings are consistent with studies by D'Addario et al. (2019) and Fries et al. (2017), which reported significant reductions in global and gene-specific methylation in BD patients, particularly in genes regulating stress response and synaptic plasticity.[16,17] Lower methylation levels have been linked to increased expression of inflammatory cytokines and oxidative stress markers, further supporting the hypothesis that BD is characterized by chronic neuroinflammation and oxidative damage.[18]

The negative correlation between methylation and illness duration ($r = -0.339$, $p=0.004$) and the number of mood episodes ($r = -0.419$, $p<0.001$) suggests a cumulative effect of disease burden on epigenetic alterations. Wen et al., similarly reported that chronic BD patients exhibit progressive reductions in DNA methylation, particularly in genes regulating neurodevelopmental and immune pathways.[19] Longitudinal studies have further shown that repeated mood episodes contribute to neuronal damage and neuroinflammation, potentially driving the observed epigenetic changes.[20]

Our findings revealed significant sociodemographic influences on DNA methylation. Female BD patients exhibited lower methylation levels than males ($\beta = -0.14$, $p=0.022$), consistent with prior studies suggesting that gender-based epigenetic differences may contribute to BD heterogeneity.[21] Estrogen has been shown to regulate DNA methylation, potentially explaining sex-specific vulnerability to mood disorders.[22]

Patients from lower socioeconomic backgrounds exhibited greater methylation deficits than those from higher SES ($\beta = -0.15$, $p=0.032$), reinforcing the role of early-life stress and financial adversity in epigenetic modifications. Several studies have demonstrated that socioeconomic stressors can induce long-term changes in DNA methylation, particularly in genes associated with stress reactivity and mood regulation.[23,24]

Childhood trauma was strongly associated with reduced methylation levels ($\beta = -0.29$, $p<0.001$), consistent with previous research demonstrating long-term epigenetic consequences of early adversity. Studies by Jiang et al., and Peng et al., have shown that individuals with childhood trauma exhibit hypomethylation of stress-regulatory genes, such as NR3C1 (glucocorticoid receptor) and BDNF (brain-derived neurotrophic factor), which are implicated in BD pathophysiology.[25,26] These findings suggest that environmental exposures during critical neurodevelopmental periods may predispose individuals to BD through persistent epigenetic modifications.[26]

An important finding in our study was the positive correlation between sleep duration and DNA methylation ($r = 0.383$, $p<0.001$). BD patients had significantly shorter sleep duration than controls (5.8 ± 1.5 vs. 7.3 ± 1.1 hours, $p<0.001$), and regression analysis confirmed that reduced sleep was an independent predictor of lower methylation ($\beta = 0.33$, $p<0.001$). These findings align with research by Niu et al., which demonstrated that chronic sleep deprivation leads to alterations in DNA methylation of circadian rhythm genes, contributing to mood instability and cognitive dysfunction in BD.[27]

Sleep disturbances are well-documented in BD and have been proposed as both a symptom and a causal factor in disease progression. Epigenetic studies suggest that sleep deprivation can induce widespread changes in DNA methylation, particularly in genes involved in synaptic plasticity, neuronal excitability, and stress response pathways.[28,29] Improving sleep patterns through behavioral or pharmacological interventions may therefore represent a potential strategy for stabilizing epigenetic alterations in BD.[29]

CONCLUSION

Our findings provide strong evidence that global DNA hypomethylation is associated with BD symptom severity, with progressive reductions in methylation linked to greater illness burden, recurrent episodes, and environmental stressors. The observed correlations with sleep duration, childhood trauma, and socioeconomic status highlight the complex interplay between genetic, epigenetic, and environmental factors in BD. These results support

the hypothesis that BD is an epigenetically mediated disorder influenced by cumulative life experiences. Future research should explore whether interventions targeting sleep, stress reduction, or pharmacological epigenetic modulation can mitigate these methylation deficits and improve clinical outcomes in BD patients.

REFERENCES

1. Vajawat B, Suhas S, Moirangthem S, et al. Bipolar affective disorder in India: A multi-site population-based cross-sectional study. Indian J Psychiatry. 2023;65(12):1230-1237.
2. Manjunatha N, Jayasankar P, Suhas S, et al. Prevalence and its correlates of anxiety disorders from India's National Mental Health Survey 2016. Indian J Psychiatry. 2022;64(2):138-142.
3. Li L, Chen R, Zhang H, et al. The epigenetic modification of DNA methylation in neurological diseases. Front Immunol. 2024; 15:1401962.
4. Rasmi Y, Shokati A, Hassan A, et al. The role of DNA methylation in progression of neurological disorders and neurodegenerative diseases as well as the prospect of using DNA methylation inhibitors as therapeutic agents for such disorders. IBRO Neurosci Rep. 2022; 14:28-37.
5. Milicic L, Porter T, Vacher M, Laws SM. Utility of DNA Methylation as a Biomarker in Aging and Alzheimer's Disease. J Alzheimers Dis Rep. 2023;7(1):475-503.
6. Reyes-Mata MP, Mireles-Ramírez MA, Griñán-Ferré C, et al. Global DNA Methylation and Hydroxymethylation Levels in PBMCs Are Altered in RRMS Patients Treated with IFN-β and GA-A Preliminary Study. Int J Mol Sci. 2023;24(10):9074.
7. Zafrilla-López M, Acosta-Díez M, Mitjans M, et al. Lithium response in bipolar disorder: Epigenome-wide DNA methylation signatures and epigenetic aging. Eur Neuropsychopharmacol. 2024; 85:23-31.
8. Goud Alladi C, Etain B, Bellivier F, Marie-Claire C. DNA Methylation as a Biomarker of Treatment Response Variability in Serious Mental Illnesses: A Systematic Review Focused on Bipolar Disorder, Schizophrenia, and Major Depressive Disorder. Int J Mol Sci. 2018;19(10):3026.
9. Busk J, Faurholt-Jepsen M, Frost M, Bardram JE, Kessing LV, Winther O. Daily estimates of clinical severity of symptoms in bipolar disorder from smartphone-based self-assessments. Transl Psychiatry. 2020;10(1):194.
10. Marino P, Schulberg HC, Gildengers AG, et al. Assessing bipolar disorder in the older adult: the GERI-BD toolbox. Int J Geriatr Psychiatry. 2018;33(1):e150-e157.
11. Eid L, Heim K, Doucette S, McCloskey S, Duffy A, Grof P. Bipolar disorder and socioeconomic status: what is the nature of this relationship? Int J Bipolar Disord. 2013; 1:9.
12. Karanti A, Bublik L, Kardell M, et al. Patient educational level and management of bipolar disorder. BJPsych Open. 2021;7(2):e63.
13. Chakrabarti S, Singh N. Psychotic symptoms in bipolar disorder and their impact on the illness: A systematic review. World J Psychiatry. 2022;12(9):1204-1232.
14. Shalev A, Merranko J, Gill MK, et al. Longitudinal course and risk factors associated with psychosis in bipolar youths. Bipolar Disord. 2020;22(2):139-154.
15. Dell'Osso B, Camuri G, Cremaschi L, Dobrea C, Buoli M, Ketter TA, Altamura AC. Lifetime presence of psychotic symptoms in bipolar disorder is associated with less favorable socio-demographic and certain clinical features. Compr Psychiatry. 2017; 76:169-176.
16. D'Addario C, Dell'Osso B, Palazzo MC, et al. Selective DNA methylation of BDNF promoter in bipolar disorder: differences among patients with BDI and BDII. Neuropsychopharmacology. 2012;37(7):1647-1655.
17. D'Addario C, Palazzo MC, Benatti B, et al. Regulation of gene transcription in bipolar disorders: Role of DNA methylation in the relationship between prodynorphin and brain derived neurotrophic factor. Prog Neuropsychopharmacol Biol Psychiatry. 2018; 82:314-321.
18. Rasmi Y, Shokati A, Hassan A, et al. The role of DNA methylation in progression of neurological disorders and neurodegenerative diseases as well as the prospect of using DNA methylation inhibitors as therapeutic agents for such disorders. IBRO Neurosci Rep. 2022; 14:28-37.
19. Wen KX, Miliç J, El-Khodor B, et al. The Role of DNA Methylation and Histone Modifications in Neurodegenerative Diseases: A Systematic Review. PLoS One. 2016;11(12):e0167201.
20. Mohd Murshid N, Aminullah Lubis F, Makpol S. Epigenetic Changes and Its Intervention in Age-Related Neurodegenerative Diseases. Cell Mol Neurobiol. 2022;42(3):577-595.
21. Abdolmaleky HM, Gower AC, Wong CK, et al. Aberrant transcriptomes and DNA methylomes define pathways that drive pathogenesis and loss of brain laterality/asymmetry in schizophrenia and bipolar disorder. Am J Med Genet B Neuropsychiatr Genet. 2019;180(2):138-149.
22. Wang T, Zhang J, Xu Y. Epigenetic Basis of Lead-Induced Neurological Disorders. Int J Environ Res Public Health. 2020;17(13):4878.
23. Cunliffe VT. The epigenetic impacts of social stress: how does social adversity become biologically embedded? Epigenomics. 2016;8(12):1653-1669.
24. Zhou A, Ryan J. Biological Embedding of Early-Life Adversity and a Scoping Review of the Evidence for Intergenerational Epigenetic Transmission of Stress and Trauma in Humans. Genes (Basel). 2023;14(8):1639.
25. Jiang S, Postovit L, Cattaneo A, Binder EB, Aitchison KJ. Epigenetic Modifications in Stress Response Genes Associated with Childhood Trauma. Front Psychiatry. 2019; 10:808.
26. Peng H, Zhu Y, Strachan E, et al. Childhood Trauma, DNA Methylation of Stress-Related Genes, and Depression: Findings from Two Monozygotic Twin Studies. Psychosom Med. 2018;80(7):599-608.
27. Niu L, Zhang F, Xu X, et al. Chronic sleep deprivation altered the expression of circadian clock genes and aggravated Alzheimer's disease neuropathology. Brain Pathol. 2022;32(3):e13028.
28. Gaine ME, Chatterjee S, Abel T. Sleep Deprivation and the Epigenome. Front Neural Circuits. 2018; 12:14.
29. Trivedi MS, Holger D, Bui AT, Craddock TJA, Tartar JL. Short-term sleep deprivation leads to decreased systemic redox metabolites and altered epigenetic status. PLoS One. 2017;12(7):e0181978.