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Review

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A review of the relationship between the *SLC6A4* gene and mental disorders

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Abstract

The *SLC6A4* gene, which encodes the serotonin (5-hydroxytryptamine; 5-HT) transporter, plays an important role in the pathogenesis of mental disorders by regulating serotonin reuptake in the synaptic cleft. This review summarizes current evidence on the associations of *SLC6A4* polymorphisms, epigenetic modifications, and neuroimaging findings with schizophrenia (SCZ), major depressive disorder (MDD), bipolar disorder (BD), and other psychiatric conditions. Studies have shown that the impact of SLC6A4 polymorphisms varies across ethnic groups and populations. Epigenetic studies indicate that DNA methylation in the promoter and exon regions of SLC6A4 can inhibit gene expression and exacerbate imbalances in the 5-HT signaling pathway, which are closely related to negative symptoms in SCZ, childhood trauma, and gender-specific risks for MDD. Neuroimaging evidence further suggests that SLC6A4 polymorphisms and methylation status are significantly associated with brain structural and functional abnormalities, pointing to a multidimensional mechanism involving ontogeny, epigenetics, and neural networks. Moreover, alterations in *SLC6A4* have also been implicated in BD and attention-deficit/hyperactivity disorder. Despite significant progress, challenges remain, including ethnic biases in study

populations, discrepancies between epigenetic patterns in peripheral and central nervous systems, and unclear mechanisms underlying gene-environment interactions. Future research should integrate multi-omics approaches, large cross-ethnic cohorts, and gender-stratified analyses to elucidate the precise regulatory network of SLC6A4 in mental disorders.

Keywords: *SLC6A4* gene, serotonin transporter, epigenetic modification, mental disorders

INTRODUCTION

According to the latest World Mental Health Report by the World Health Organization (WHO), nearly 1 billion people worldwide suffer from mental disorders, representing more than 13% of the global population. These disorders are characterized by high incidence, substantial resource utilization, and significant disability rates[1,2]. They frequently co-occur, which increases the complexity of diagnosis and treatment[3-5]. Strong genetic correlations between psychiatric traits have also been reported, with multiple neurotransmitters, hormones, and neurotrophic factors directly implicated in the development of these conditions[6,7]. Research exploring the pathological mechanisms of mental disorders - spanning social, psychological, biochemical, genetic, and neuroimaging perspectives - has consistently concluded that they are multifactorial in origin, involving both genetic and environmental influences[2].

As research has progressed, several hypotheses have been proposed to explain the development of psychiatric disorders[8-10], among which the serotonin (5-hydroxytryptamine; 5-HT) hypothesis remains the most prominent. The 5-HT system, a core neuromodulatory network, regulates a wide range of behaviors including sleep, memory, emotion, and aggression. Dysregulation of this system has been linked to various psychiatric disorders[11], such as schizophrenia as well as alcohol and drug dependence[12-15].

Within the serotonergic system, the 5-hydroxytryptamine transporter (5-HTT) plays a critical role in controlling the intensity and duration of neural signaling by regulating the reuptake of 5-HT in the synaptic cleft. Reduced 5-HTT activity results in abnormally elevated 5-HT concentrations in the synaptic cleft and diminished neurotransmitter storage within neurons. This imbalance may lead to receptor desensitization or impair synaptic plasticity, ultimately contributing to the emergence of psychiatric symptoms[16].

The *SLC6A4* gene, located on chromosome 17q11.2, encodes the 5-HTT protein[17]. In recent years, numerous studies have investigated the relationship between *SLC6A4* and psychiatric disorders, focusing on its role in disease pathogenesis and clinical manifestations. Evidence suggests that *SLC6A4* is associated with several major psychiatric disorders, including schizophrenia, depression, and antisocial personality disorder[18-20]. Accordingly, this review synthesizes current evidence on the diverse roles of *SLC6A4* genetic variation and epigenetic regulation in the pathophysiology of major psychiatric disorders, highlighting insights from genetic, epigenetic, and neuroimaging studies.

METHODOLOGY

The literature search was conducted in PubMed (https://pubmed.ncbi.nlm.nih.gov/), PsycINFO (https://www.apa.org/pubs/databases/psycinfo/) and Web of Science (https://www.webofscience.com/). The search terms included "*SLC6A4*", "5-HTT", "serotonin transporter", "polymorphism", "methylation", "schizophrenia", "depression", and "bipolar disorder", among others. The search was limited to publications between January 1, 2000, and August 25, 2025.

A total of 278 records were identified in the initial search. After removing duplicates, 230 articles remained. Screening by title and abstract excluded 129 articles that did not meet the inclusion criteria. The full texts of the remaining 101 articles were reviewed for eligibility. Of these, 20 were excluded for the following reasons: non-human studies (n = 5), non-original research (e.g., reviews, case reports; n = 9), and duplicate publications (n = 6). Thus, 81 articles were included in the final review. An updated search in 2025 identified 15 additional records. After duplicate removal and title/abstract screening, 5 full-text articles were assessed, of which 3 met the inclusion criteria and were added to the review, bringing the total number of included studies to 84.

Inclusion criteria: (1) case-control or cohort studies; (2) patients diagnosed with confirmed mental disorders (e.g., schizophrenia, depression, bipolar disorder); and (3) studies analyzing the association between *SLC6A4* gene polymorphisms or methylation status and mental disorders. Exclusion criteria: (1) non-human studies; (2) non-original studies such as reviews or case reports; (3) duplicate publications. Based on these criteria, articles that did not meet the inclusion criteria were excluded from the initial 278 papers. The final 81 studies included in the review were published between 2000 and 2025 (see Tables 1-5 for details).

Data extraction included the following: study characteristics (author, year, country), participant characteristics (sample size, diagnosis), genetic variation data (polymorphic loci, genotype frequencies), methylation data (CpG sites), and statistical results (e.g., odds ratios, *P* values).

RESULTS

The *SLC6A4* gene and schizophrenia

Schizophrenia (SCZ) is a chronic mental disorder affecting approximately 1% of the global population[21]. Its symptoms can be divided into three categories: positive symptoms, including hallucinations, delusions, and speech disorders; negative symptoms, such as social withdrawal, affective flattening, lack of initiative, and anergia; and cognitive deficits[22]. The pathophysiology mechanisms of schizophrenia may involve genetic and epigenetic abnormalities, as well as changes in neurotransmitter structure or function[23].

In recent years, numerous studies have investigated the correlation between *SLC6A4* and SCZ, examining its association with schizophrenia pathogenesis, clinical manifestations, and treatment response. Key findings are summarized below.

SLC6A4 gene polymorphism and schizophrenia

Polymorphisms in the *SLC6A4* gene, particularly the linked polymorphic region in the promoter (5-HTTLPR) and the intron 2 variable number tandem repeat sequence (Intron 2 VNTR), have received widespread attention for their potential role in SCZ susceptibility. Several studies indicate that *SLC6A4* polymorphisms are differentially associated with SCZ risk across different populations. For example, studies in Tatar and Russian populations have found that the association of the 5-HTTLPR polymorphism with SCZ varies significantly by ethnicity: the L/L genotype is strongly associated with persistent schizophrenia in Russians, whereas the S/S genotype is less frequent among individuals with intermittent schizophrenia in Tatars. These findings suggest that genetic background may modulate disease susceptibility[24]. A study of outpatients and inpatients at Shanghai Mental Health Center in China showed that polymorphisms in the *SLC6A4* promoter region and the rs25531 locus were associated with SCZ susceptibility. Specifically, the S/XLA and G/XLA genotypes were identified as risk factors[25]. Similar or differing associations have been reported in populations from Iran[26], South India[27], East China[28], central China[29], and Xi'an (China)[30], further supporting a role for *SLC6A4* in SCZ risk. However, not all studies have confirmed this association.

Table 1. Studies on *SLC6A4* gene polymorphisms and SCZ

Author	Year	Journal	Biological material	Sample size	*SLC6A4* region	Main findings
Zainullina *et al.*[24]	2003	Molekulyarnaya Biologiya	Human peripheral blood cells	Nscz = 214, NNC = 197	5-HTTLPR	Association of *SLC6A4* polymorphisms with SCZ differs significantly between Tatar and Russian populations
Ikeda *et al.*[31]	2006	Journal of Neural Transmission	Human peripheral blood cells	Nscz = 383, NNC = 351	All exons, introns, promoter regions, 3' UTR	No significant association between *SLC6A4* polymorphisms and SCZ in Japanese patients
Pae *et al.*[32]	2006	Journal of Neural Transmission	Human peripheral blood cells	Nscz = 152, NNC = 152	5-HTTLPR	No significant association between *SLC6A4* polymorphisms and SCZ in Korean patients
Güzey *et al.*[103]	2007	European Journal of Clinical Pharmacology	Human peripheral blood cells	Nscz = 119, NNC = 56	5-HTTLPR	No significant association between *SLC6A4* polymorphisms and antipsychotic-induced extrapyramidal symptoms
Vijayan *et al.*[27]	2009	Journal of Human Genetics	Human peripheral blood cells	Nscz = 243, NNC = 243	5'end region	Polymorphisms in the 5' end region of *SLC6A4* are significantly associated with SCZ in South Indian populations
Lin *et al.*[28]	2009	Neuroscience Letters	Human peripheral blood cells	Nscz = 329, NNC = 288	Intron 2 STin2 VNTR, three intron-tagged SNPs (rs2054847, rs140700, rs2020942)	Two haplotypes (A-G-10, A-G-12) containing STin2 VNTR are significantly associated with SCZ
Vázquez-Bourgon *et al.*[39]	2010	Psychiatry Research	Human peripheral blood cells	Nscz = 147	5-HTTLPR	L/S polymorphisms are significantly associated with early negative symptoms in first-episode psychosis
Kohlrausch *et al.*[37]	2010	Journal of Psychiatric Research	Human peripheral blood cells	Nscz = 116	5-HTTLPR, Intron 2 STin2 VNTR	The rs25531 locus of *SLC6A4* may influence clozapine efficacy
Hung *et al.*[34]	2011	Neuroscience Letters	Human peripheral blood cells	Nscz = 168, NNC = 302	5-HTTLPR	The LA allele of 5-HTTLPR is significantly associated with suicide attempts in Chinese Han Chinese SCZ patients, particularly males
Božina *et al.*[104]	2012	Journal of Psychiatric Research	Human peripheral blood cells	Nscz = 519, NNC = 184	5-HTTLPR, Intron 2 VNTR	Suicide Attempters and Suicidal Ideators Differ from Controls in Depressive Symptoms and 5-HTTLPR/rs25531 Haplotype Distribution
Li *et al.*[29]	2013	Progress in Neuro-Psychopharmacology & Biological Psychiatry	Human peripheral blood cells	Nscz = 528, NNC = 528	All exons, introns, regulatory regions	The rs140700 G/A polymorphism is significantly associated with SCZ susceptibility and strongly linked to negative and depressive/anxiety symptoms
Bilic *et al.*[38]	2014	Gene	Human peripheral blood cells	Nscz = 173	SERT-PR, SERT-in2	TRS is associated with the SERT-PR polymorphism of *SLC6A4*
Alfimova *et al.*[36]	2015	Neuroscience and Behavioral Physiology	Human peripheral blood cells	Nscz = 299, NNC = 232	5-HTTLPR	The 5-HTTLPR polymorphism is significantly associated with emotion recognition in SCZ patients
Jing *et al.*[25]	2016	Journal of Shanghai Jiao Tong University	Human peripheral blood cells	Nscz = 624, NNC = 683	5-HTTLPR	Association of *SLC6A4* promoter polymorphisms with SCZ susceptibility and atypical antipsychotic efficacy in the Chinese Han population

A variable-length repeat polymorphism in the promoter region of the *SLC6A4* gene on chromosome 17 that encodes the serotonin transporter protein; Intron 2 STin2 VNTR: variable number of tandem repeats in intron 2 of the *SLC6A4* gene; Antipsychotic-induced extrapyramidal symptoms: motor dysfunction (e.g., acute dystonia, Parkinsonism, tardive dyskinesia, akathisia) caused by antipsychotic treatment. SCZ: Schizophrenia; NC: healthy control; 5-HTTLPR: 5-hydroxytryptamine transporter gene-linked polymorphic region.

Investigations in Japanese[31], Korean[32], and other populations[33] have failed to replicate these findings, highlighting significant ethnic heterogeneity.

Table 2. Studies on *SLC6A4* gene methylation in SCZ

Author	Year	Journal	Biological material	Sample size	*SLC6A4* region	Main findings
Philibert *et al.*[44]	2007	American Journal of Medical Genetics Part B: Neuropsychiatric Genetics	Human lymphoblastoid cell lines	Nscz = 49	CpG island near exon 1A (799 bp)	Significant correlation between mean methylation and mRNA levels in CpG islands
Wang *et al.*[41]	2010	Schizophrenia Research	Human peripheral blood cells	Nscz = 46, NNC = 44	Region encoding 5-HTT mRNA	In male SCZ patients, 5-HTT mRNA expression was significantly increased in peripheral blood leukocytes
Wockner *et al.*[40]	2014	Translational Psychiatry	Human postmortem prefrontal cortex tissue	Nscz = 24, NNC = 24	genome-wide	In SCZ patients, 4641 probes corresponding to 2929 unique genes were differentially methylated
Beach *et al.*[48]	2014	Biological Psychology	Human peripheral blood cells	Nscz = 388	CpG islands in exon 1 and 5'UTR	Under high SES risk, women carrying the S allele showed higher methylation levels
Ikegame *et al.*[45]	2020	Schizophrenia Bulletin	Human peripheral blood cells	Nscz = 440, NNC = 488	CpG islands in promoter region	Male SCZ patients exhibited significantly higher methylation levels at the CpG3 locus than controls
Shen *et al.*[49]	2021	EBioMedicine	Human peripheral blood cells	Nscz = 106	genome-wide	DNA methylation patterns tended to cluster within families
Ikegame *et al.*[45]	2022	Neuroscience Letters	Human peripheral blood cells	Nscz = 70, NNC = 68	CpG islands downstream of exon 1	DNA methylation levels were significantly higher in SCZ patients, with levels notably higher in females than males
Koning *et al.*[50]	2024	Psychoneuroendocrinology	Human saliva samples	Nscz = 384	CpG islands in promoter region	Early life adversity was significantly associated with promoter methylation of *SLC6A4*

SCZ: Schizophrenia; NC: healthy control.

Several studies have also linked *SLC6A4* polymorphisms to an increased risk of suicide in SCZ patients[31,34,35]. Additionally, certain polymorphisms (e.g., rs140700, rs2054847, and rs140700) have been associated with negative symptoms, cognitive deficits (such as fear recognition), and aggressive behavior[26,28,29,36].

SLC6A4 polymorphisms may also influence response to antipsychotic medications. For example, the S allele may be associated with a poorer response to clozapine[37], while other genotypes may predict treatment-resistant schizophrenia or the extent of improvement in negative symptoms[38,39].

Overall, *SLC6A4* polymorphisms appear to contribute to SCZ susceptibility, clinical presentation, and drug response, although their effects vary across populations, highlighting the gene's multidimensional role in schizophrenia pathophysiology [Table 1, Figure 1].

Methylation of the SLC6A4 gene and schizophrenia

Recent studies indicate that epigenetic modifications, particularly DNA methylation, play a crucial role in mediating the interactions between genetic and environmental factors. The methylation status of the *SLC6A4* gene may be involved in the pathophysiology of SCZ by regulating its expression and influencing the 5-HT signaling pathway.

Several studies have demonstrated a significant association between *SLC6A4* methylation and both the incidence and severity of SCZ. For instance, a genome-wide methylation analysis of prefrontal cortex tissue from SCZ patients conducted by Wockner identified 2,929 genes, including *SLC6A4*, with abnormal

Table 3. Studies on *SLC6A4* gene polymorphisms and MDD

Author	Year	Journal	Biological material	Sample size	*SLC6A4* region	Main findings
Caspi *et al.*[59]	2003	Science	Human peripheral blood cells	NMDD = 847	5-HTTLPR	Polymorphisms in the 5-HTTLPR region significantly influence individual sensitivity to life stress
Tsang *et al.*[61]	2017	Neuroscience & Biobehavioral Reviews	Human peripheral blood cells	NLLD = 406, NNC = 688	5-HTTLPR	The 5-HTTLPR polymorphism is significantly associated with an increased risk of late-life depression
Mendonça *et al.*[62]	2019	Journal of Affective Disorders	Human oral epithelial cells	NMDD = 30, NNC = 30	5-HTTLPR	No statistically significant difference between S allele carriers and depression diagnosis
Ren *et al.*[65]	2020	Journal of Affective Disorders	Human peripheral blood cells	NMDD = 6,644	5-HTTLPR	The 5-HTTLPR polymorphism is significantly associated with antidepressant response and tolerance, especially in White patients
Jang *et al.*[68]	2021	Pharmacopsychiatry	Human peripheral blood cells	NMDD = 464	5-HTTLPR	The SS genotype of 5-HTTLPR is significantly associated with better antidepressant response and remission rates
Ugartemendia *et al.*[66]	2021	Clinical Nutrition	Human peripheral blood cells, urine	NMDD = 218	5-HTTLPR	5-HTTLPR polymorphisms significantly influence the beneficial effects of tryptophan supplementation on age-related depression and social cognition
Hasan *et al.*[69]	2021	Heliyon	Database analysis	NMDD = 360	SNPs	Five high-risk mutant SNPs (R104C, Y121C, W82R, R79W, W151R) were identified through computational simulations
Alshogran *et al.*[63]	2021	PLOS ONE	Human peripheral blood cells	NMDD = 265	5-HTTLPR VNTR	Polymorphisms in 5-HTTLPR and rs25531 were not significantly associated with anxiety or depressive symptoms
Garvert *et al.*[72]	2022	Progress in Neuro-Psychopharmacology and Biological Psychiatry	Human peripheral blood cells	NMDD = 44,586, NNC = 229,407	5-HTTLPR	Interaction between rs8105676 and 5-HTTLPR polymorphisms had a significant effect on lifetime depression

A variable-length repeat polymorphism in the promoter region of the *SLC6A4* gene on chromosome 17 that encodes the serotonin transporter protein. LLD: Late-life depression; MDD: major depressive disorder; NC: healthy control; 5-HTTLPR: 5-hydroxytryptamine transporter gene-linked polymorphic region.

methylation patterns[40]. In a study of an East Chinese population, the expression of 5-HTT mRNA in peripheral blood leukocytes was significantly increased in male SCZ patients[41]. Although some studies reported no significant differences[42], subsequent research by Abdolmaleky and Philibert revealed that DNA methylation levels in the promoter region of *SLC6A4* were significantly increased in postmortem brain tissue, saliva samples of SCZ patients, and human lymphoblastic cell lines, correlating with decreased gene expression[43,44]. These findings suggest that promoter hypermethylation may impair 5-HTT function by inhibiting transcriptional activity, thereby exacerbating SCZ pathology. Methylation of *SLC6A4* not only appears linked to disease pathogenesis but may also influence core symptoms. In male SCZ patients, the CpG3 locus in the promoter region exhibited significantly higher methylation than in controls[45]. Our team pre-analyzed 17 CpG islands downstream of exon 1 of *SLC6A4* and found that methylation levels upstream of exon 1 were significantly higher in female patients than in males, indicating a potential sex-specific role of methylation in regulating gene expression and contributing to SCZ development[46].

Environmental factors, particularly early-life adversity, have been proposed to increase the risk of SCZ by altering *SLC6A4* methylation[47-50].

Emerging evidence also suggests that *SLC6A4* methylation may influence the response to antipsychotic treatment. One study found that hypermethylation of the *SLC6A4* promoter was significantly higher in SCZ

Table 4. Studies on *SLC6A4* gene methylation and MDD

Author	Year	Journal	Biological material	Sample size	*SLC6A4* region	Main findings
Kim *et al.*[85]	2013	Journal of Psychiatric Research	Human peripheral blood cells	NPSD = 133, NNC = 475	CpG island in promoter region	Hypermethylation of the promoter region of the *SLC6A4* gene is independently associated with the development of post-stroke depression
Kang *et al.*[74]	2013	Progress in Neuro-Psychopharmacology and Biological Psychiatry	Human peripheral blood leukocytes	NMDD = 108	Promoter CpG-enriched region	Methylation status of the promoter region of the *SLC6A4* gene is significantly associated with certain clinical features of depression
Wankerl *et al.*[79]	2014	Translational Psychiatry	Human peripheral blood cells	NMDD = 133	Promoter region	Both the S allele of 5-HTTLPR and early early-life stress (prenatal stress and childhood trauma) are associated with reduced SERT gene expression
Okada *et al.*[84]	2014	Journal of Psychiatric Research	Human peripheral blood cells	NMDD = 50, NNC = 50	CpG island in promoter region	DNA methylation of the SLC6A4 promoter CpG island is associated with symptom severity, early adversity, and treatment response
Frodl *et al.*[76]	2015	Journal of Psychiatry and Neuroscience	Human peripheral blood cells	NMDD = 25, NNC = 35	Promoter region (CpG5-15)	Methylation status of the *SLC6A4* gene is significantly associated with functional brain changes during emotional processing
Schneider *et al.*[82]	2018	Neuropsychopharmacology	Human peripheral blood cells	NMDD = 122, NNC = 176	AluJb elements in promoter region	The methylation rate of the AluJb element in the *SLC6A4* promoter is significantly lower in patients with depression
Peng *et al.*[80]	2018	Psychosomatic Medicine	Human peripheral blood cells	NEG = 126, NUG = 112	CpG island in promoter region	DNA methylation levels of the *SLC6A4* gene are significantly associated with depressive symptoms in two independent studies
Consoloni *et al.*[86]	2018	European Neuropsychopharmacology	Human peripheral blood mononuclear cells	NMDD = 103, NNC = 100	*SLC6A4* mRNA expression	Changes in *SLC6A4* mRNA expression from baseline to week 8 predict suicide attempts
Palma-Gudiel *et al.*[83]	2019	Progress in Neuro-Psychopharmacology and Biological Psychiatry	Human peripheral blood cells, postmortem brain tissue	NMDD = 43, NNC = 105	CpG island in promoter region	Methylation levels of the *SLC6A4* promoter are significantly associated with somatization symptoms
Mendonça *et al.*[62]	2019	Journal of Affective Disorders	Human oral epithelial cells	NMDD = 30, NNC = 30	CpG island in promoter region	DNA methylation of the AluJb repetitive element in the *SLC6A4* promoter is significantly reduced in depression
Webb *et al.*[102]	2020	International Journal of Molecular Sciences	Human peripheral blood mononuclear cells, saliva, brain tissue	NMDD = 313, NNC = 115	Promoter region	Methylation levels of the *SLC6A4* promoter are significantly associated with antidepressant treatment response
Zhu *et al.*[77]	2023	Journal of Affective Disorders	Human peripheral blood cells, saliva	NMDD = 3,965	Promoter region	Hypermethylation of the *SLC6A4* gene was not significantly associated with depression risk in the overall analysis
Comtois-Cabana *et al.*[81]	2023	PLOS ONE	Human Saliva	NMDD = 156	Specific CpG sites	DNA methylation of the *SLC6A4* gene may mediate the relationship between childhood maltreatment and depressive symptoms in early adulthood
Bruzzone *et al.*[78]	2024	Clinical Epigenetics	Human peripheral blood cells	NMDD = 90, NNC = 254	Specific CpG sites in promoter region	No significant association between *SLC6A4* methylation and symptoms of depression, anxiety, or early-life stress
Bruzzone *et al.*[75]	2025	Progress in Neuro-Psychopharmacology and Biological Psychiatry	Human peripheral blood cells	NMDD = 90	CpG island in promoter region	No significant association between *SLC6A4* methylation at baseline and clinical response or symptom change after 8 weeks of treatment (ΔHAMD6)

PSD: Post-stroke depression; EG: individuals with childhood trauma; UG: individuals without childhood trauma; MDD: major depressive disorder; NC: healthy control.

Table 5. Studies on *SLC6A4* gene polymorphisms, methylation and other psychiatric disorders

Author	Year	Journal	Biological material	Sample size	*SLC6A4* region	Main findings
Ikeda *et al.*[31]	2006	Journal of Neural Transmission	Human peripheral blood cells	NBP = 109, NNC = 288	All exons, promoter, introns	Neither common nor rare *SLC6A4* variants showed significant association with BP in the Japanese population
Sugawara *et al.*[19]	2011	Translational Psychiatry	Human lymphoblastoid cell lines, peripheral blood cells, postmortem brain tissue	NBD = 53, NNC = 54	Promoter region	Hypermethylation of the *SLC6A4* promoter is significantly associated with bipolar disorder
Hesse *et al.*[105]	2014	European Journal of Nuclear Medicine and Molecular Imaging	Human peripheral blood cells, brain tissue	NMS = 23, NNC = 22	Promoter, STin2-VNTR	SERT-LPR and STin2-VNTR polymorphisms in *SLC6A4* do not differ significantly between MS patients and controls
Dukal *et al.*[98]	2015	Borderline Personality Disorder and Emotion Dysregulation	Human neonatal cord blood cells	NELS = 45, NNC = 45	Promoter CpG islands (CpG1-4)	Female newborns exhibited significantly higher *SLC6A4* methylation than males
Park *et al.*[94]	2015	Psychological Medicine	Human peripheral blood cells	NADHD = 102	Promoter region	Hypermethylation of the *SLC6A4* promoter is significantly associated with ADHD symptom presentation in children
Schiele *et al.*[95]	2019	European Neuropsychopharmacology	Human peripheral blood cells	NPD = 119, NNC = 119	Promoter region	Hypermethylation of the *SLC6A4* promoter is significantly associated with comorbid depression (MDD) in PD patients
Calabrò *et al.*[97]	2020	Molecular Biology Reports	Human peripheral blood cells	NP = 786 NNC = 539	SNPs in promoter, introns, coding regions (rs2066713, rs4251417, rs6354, rs7224199)	Polymorphisms in *SLC6A4* are significantly associated with alcohol dependence and Alzheimer's disease
Cheng *et al.*[96]	2021	Acta Neurologica Belgica	Human peripheral blood cells	NPD = 466, NC = 504	5-HTTLPR	5-HTTLPR genotypes (especially the S allele) are significantly associated with depression risk in Parkinson's disease (PD) patients

PD (Miriam A. Schiele, 2019), panic disorder; P (Marco Calabrò, 2020), mixed psychiatric group (ALC, ALZ, SCZ, *etc.*); PD (Pengfei Cheng, 2021), Parkinson's disease; NC: Healthy control, BP/BD: Bipolar disorder; MS: multiple sclerosis; ELS: early-life stress; ADHD: attention-deficit/hyperactivity disorder.

patients who had not received antipsychotic treatment compared with controls, and this hypermethylation was closely correlated with reduced 5-HTT expression[43]. Overall, the methylation status of *SLC6A4* appears to affect both disease onset and severity, highlighting its potential as a focus for future research [Table 2, Figure 2].

SLC6A4 and imaging changes in schizophrenia

Recent advances in molecular genetics and neuroimaging have increasingly highlighted the potential role of *SLC6A4* in SCZ.

Alterations in *SLC6A4* expression during brain development may significantly contribute to the pathogenesis of SCZ. Evidence from animal models suggests that developmental changes in *SLC6A4* expression are associated with structural abnormalities in brain regions implicated in SCZ[51].

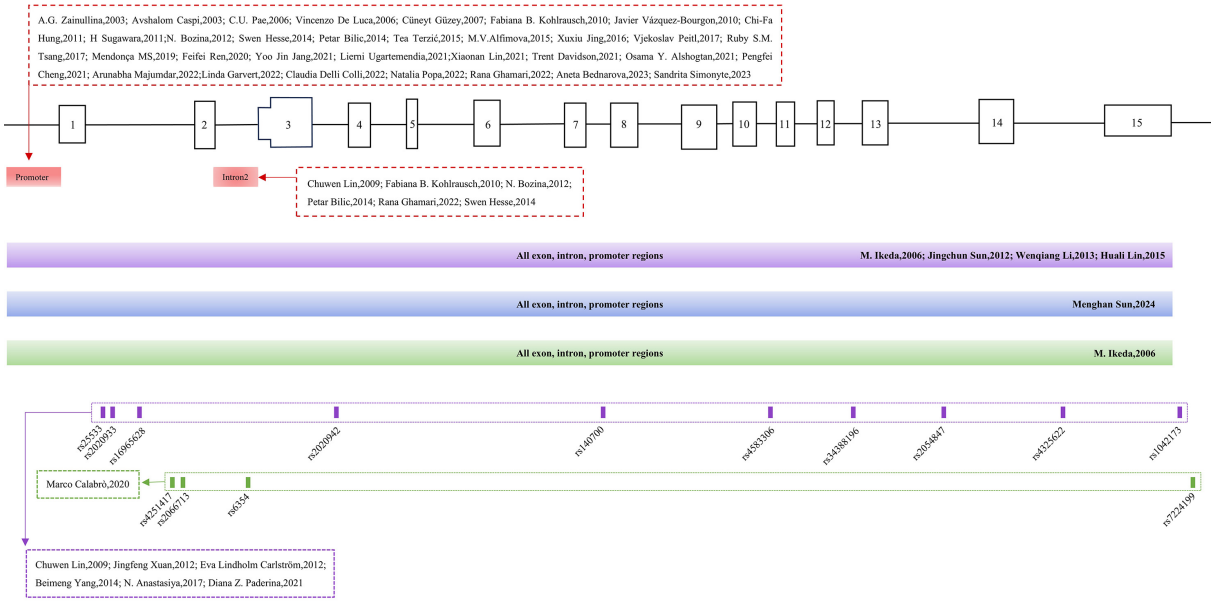

Figure 1. Polymorphic sites in the *SLC6A4* gene in studies of SCZ, MDD and other psychiatric disorders. The red sections indicate study sites in SCZ, MDD, and other disorders; purple indicates SCZ-specific sites; blue indicates MDD-specific sites; green indicates sites related to other psychiatric disorders.

Beyond structural effects, *SLC6A4* also influences brain function by regulating 5-HT signaling. Neuroimaging studies have revealed that *SLC6A4* availability is closely related to the functioning of brain regions such as the thalamus and prefrontal cortex, as well as to negative symptoms and insight deficits in patients with SCZ[52-54].

SLC6A4 gene and depression

Depression (or major depressive disorder; MDD) is one of the most common mental disorders worldwide, affecting approximately 3.8% of the global population in 2023[55]. The World Health Organization predicts that depression will be one of the two leading causes of global health burden and disability, and the largest contributor to the global disease burden by 2030[56,57]. Its pathogenesis involves multiple biological factors, including genetics, epigenetics, and interactions with environmental factors[58].

In recent years, numerous studies have investigated the correlation between the *SLC6A4* gene and MDD, examining its role in the pathogenesis, clinical manifestations, and treatment response. The following section provides a review of the current understanding of the relationship between the *SLC6A4* gene and MDD.

Polymorphisms of the SLC6A4 gene and depression

A growing body of evidence suggests that the 5-HTTLPR polymorphism plays a major role in depression. This polymorphism affects the risk of developing depression in several ways, including altering individual susceptibility to life stress, influencing antidepressant response, and interacting with other genes. Studies indicate that carriers of the S allele are more likely to develop depression under stressful conditions[59], and in high-stress environments, individuals with certain genetic polymorphisms show more severe depressive symptoms[60]. These findings suggest that 5-HTTLPR not only modulates stress sensitivity but also influences depressive symptom severity in high-stress contexts. Furthermore, the risk of late-life depression appears to depend not solely on the 5-HTTLPR genotype but on its interaction with stressful life events.

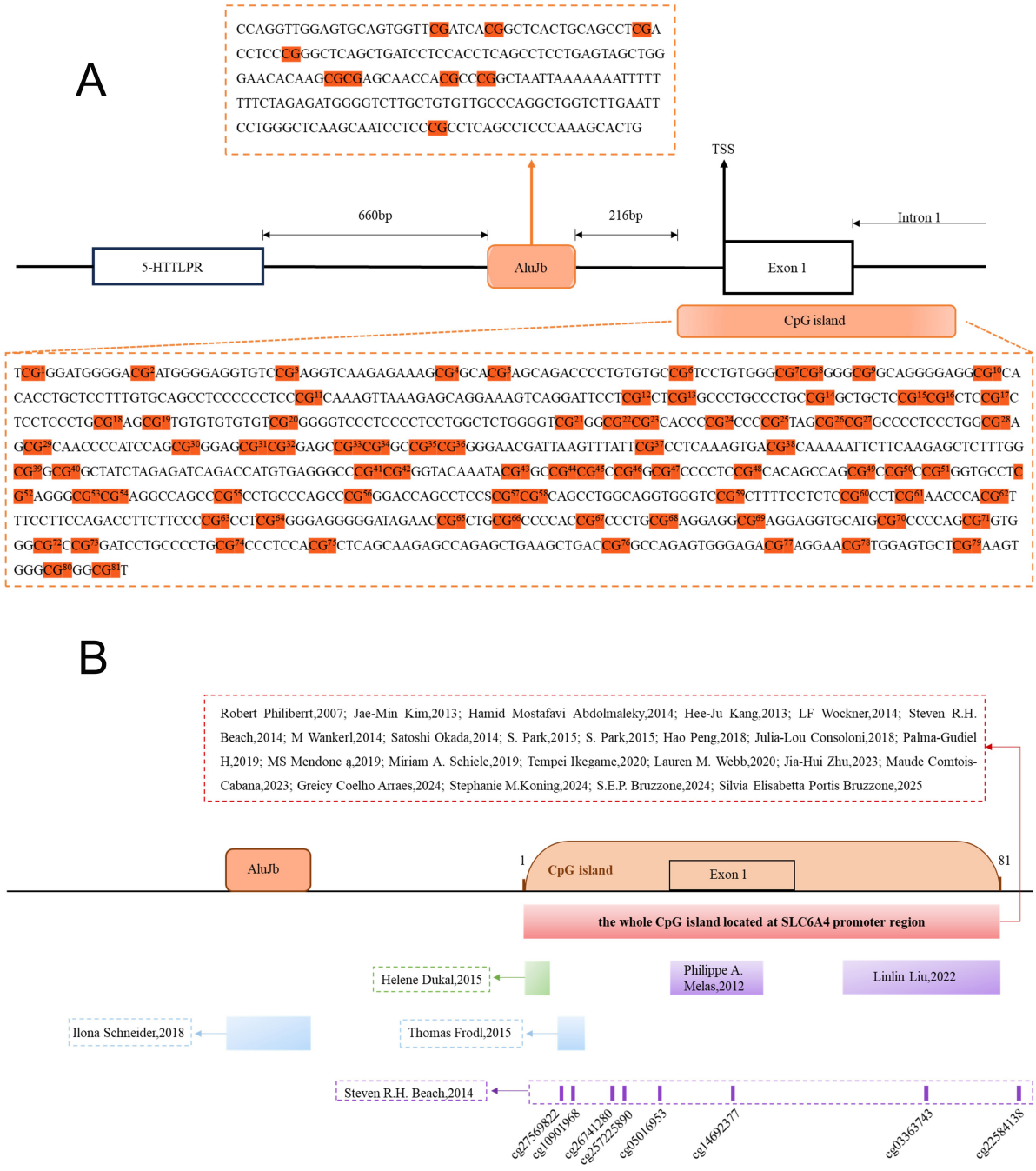

Figure 2. Methylated CpG sites in the *SLC6A4* gene from studies on SCZ, MDD, and other psychiatric disorders. (A) CpG sites examined in studies included in this review. (B) Red indicates study sites in SCZ, MDD, and other disorders; purple indicates SCZ-specific sites; blue indicates MDD-specific sites; green indicates sites related to other psychiatric disorders.

Higher frequency or intensity of stress is associated with a dose-dependent increase in depression risk among S allele carriers[61-64]. Thus, *SLC6A4* gene polymorphisms (particularly the S allele), may elevate depression risk by increasing stress susceptibility, highlighting the central role of gene-environment interactions in MDD pathogenesis.

The 5-HTTLPR polymorphism also affects antidepressant efficacy and tolerability, with the L allele generally associated with a better treatment response[65-68].

Beyond 5-HTTLPR, other single-nucleotide polymorphisms (SNPs) in *SLC6A4* have been implicated in depression. These SNPs may influence depression risk by altering the expression, function, or stability of 5-HT, thereby affecting receptor activity. Functional prediction studies and animal models support the central role of *SLC6A4* dysfunction in MDD[69,70].

Depression arises not solely from genetic or environmental factors in isolation but from their complex interplay. Recent studies have highlighted the importance of dynamic interactions between genetic polymorphisms and environmental stressors, such as peer bullying, in the onset of MDD[71-73]. In summary, interactions between *SLC6A4* polymorphisms and environmental factors are critical to depression pathogenesis.

Overall, the 5-HTTLPR polymorphism significantly influences depression risk and is closely linked to antidepressant response and tolerance. These findings highlight the need to explore depression mechanisms from multiple angles, considering additional *SLC6A4* variants and environmental influences [Table 3].

Methylation of the SLC6A4 gene and depression

Studies examining the relationship between SLC6A4 methylation and antidepressant efficacy have yielded inconsistent results[74,75]. These discrepancies indicate that future research should integrate additional epigenetic markers and clinical characteristics to improve the accuracy of predicting treatment response in depression. Thomas Frodl reported that SLC6A4 methylation may contribute to the onset of depression by affecting insular and pontine emotional processing[76]. However, not all studies support a link between SLC6A4 polymorphisms and susceptibility to MDD, with several meta-analyses and individual studies failing to find a significant correlation with MDD risk or symptoms[77,78].

Early-life environmental stressors, such as prenatal stress and childhood trauma, are closely related to the methylation levels of the *SLC6A4* gene. Numerous studies have confirmed significant correlations between childhood trauma and changes in *SLC6A4* methylation, suggesting a potential role in mediating the risk of depression in adulthood[79-81]. These findings imply that childhood trauma may increase the likelihood of adult depression by modifying *SLC6A4* methylation patterns. The methylation status of *SLC6A4* is also influenced by gene-environment interactions. For instance, the methylation rate of the AluJb element in the *SLC6A4* promoter is significantly reduced in patients with depression, and this reduction shows a notable interaction with the 5-HTTLPR/rs25531 polymorphism. This indicates that genetic variants and environmental stressors may jointly affect depression risk through changes in methylation[82]. Gender differences have also been observed: *SLC6A4* promoter methylation is related to somatization symptoms, with higher methylation levels found in females, suggesting that sex may be an important moderating factor[83].

MS Mendonca examined DNA methylation of the AluJb repeat element in the *SLC6A4* promoter and found that methylation levels were significantly reduced in patients with SCZ[62]. Additionally, methylation at specific CpG sites of *SLC6A4* has been linked to symptom severity and treatment response[84,85]. For example, hypermethylation in the promoter region may correlate with better antidepressant efficacy[85] and with the development of post-stroke depression[86], while alterations in *SLC6A4* mRNA expression can predict changes in suicide risk during treatment[87]. In summary, the methylation status of the *SLC6A4* gene holds potential as a biomarker for both the diagnosis and treatment of depression [Table 4].

SLC6A4 gene and imaging changes in depression

Numerous studies have shown that the 5-HTTLPR polymorphism and DNA methylation levels of the *SLC6A4* gene are closely related to structural brain changes, white matter integrity abnormalities, and dysfunction in emotion-related brain regions in MDD patients.

The 5-HTTLPR polymorphism of the *SLC6A4* gene has a significant impact on hippocampal volume. Specifically, carrying different alleles (S or L) is associated with heterogeneous reductions in hippocampal volume, and these effects vary between genders[87,88].

Abnormal amygdala function, a core component of the brain's emotion-processing network, is strongly linked to MDD susceptibility. Epigenetic mechanisms play a crucial role; environmental stressors, such as low socioeconomic status, can increase the methylation of the *SLC6A4* gene, leading to heightened amygdala responsiveness to negative stimuli and an elevated risk of depression[89,90].

White matter integrity abnormalities constitute another important neuroimaging finding. Patients with depression often exhibit reduced integrity in the corpus callosum and other white matter tracts, which is associated with both the 5-HTTLPR genotype and elevated *SLC6A4* methylation levels[91,92]. Additionally, evidence suggests that *SLC6A4* may interact synergistically with other risk genes (such as BDNF and COMT) to exacerbate prefrontal cortical thinning and white matter damage[93].

SLC6A4 gene and other psychiatric disorders

Dysfunction of the *SLC6A4* gene has also been implicated in other psychiatric disorders. In bipolar disorder (BD), evidence for an association with *SLC6A4* gene polymorphisms is weak, but epigenetic studies suggest that hypermethylation of its promoter region may be linked to the disease[19,31]. In children with attention-deficit/hyperactivity disorder (ADHD), hypermethylation in the *SLC6A4* promoter region correlates with clinical symptoms[94]. Parkinson's disease (PD) patients frequently experience depression, potentially due to increased methylation of the *SLC6A4* promoter and the presence of the 5-HTTLPR S allele[95,96]. Furthermore, polymorphisms in this gene have been linked to the risk or progression of alcohol dependence and Alzheimer's disease[97].

Sex differences have also been reported in epigenetic modifications, with higher *SLC6A4* promoter methylation observed in female neonates, which partially explains the increased risk of depression in females later in life[98]. Animal studies further support a regulatory role of *SLC6A4* genetic variants in anxiety-like behaviors[99]. In summary, *SLC6A4* contributes to the pathophysiology of multiple neuropsychiatric diseases through epigenetic regulation and gene-environment interactions, although findings are heterogeneous across populations [Table 5].

DISCUSSION

As the key gene encoding 5-HTT, *SLC6A4* has been extensively studied for its association with polymorphisms, epigenetic modifications, and dysfunction in a variety of mental disorders. This review highlights the crucial role of *SLC6A4* in schizophrenia (SCZ), major depressive disorder (MDD), bipolar disorder (BD), attention-deficit/hyperactivity disorder (ADHD), and other psychiatric conditions. Its mechanisms involve genetic variation, epigenetic regulation, and neuroimaging changes, profoundly influencing clinical manifestations by modulating 5-HT reuptake efficiency and synaptic plasticity.

Polymorphisms in *SLC6A4*, such as 5-HTTLPR and the intron 2 VNTR region, exhibit heterogeneous associations across psychiatric disorders. For example, the 5-HTTLPR S allele is linked to negative SCZ

symptoms[29], suicidal behavior[35], and altered drug response[67], while the L allele is often associated with better antidepressant efficacy in MDD[65]. These polymorphisms influence not only transcriptional activity and mRNA stability but also directly affect 5-HTT kinetics at the protein level: the S allele reduces 5-HTT expression on the cell membrane and increases 5-HTT internalization, impairing 5-HT reuptake, prolonging synaptic 5-HT retention, and affecting neurotransmission efficiency and receptor desensitization[100]. Additionally, some SNPs (e.g., rs25531) may further modulate 5-HTT transport activity and stability through changes in mRNA secondary structure or post-translational modifications[69]. These molecular and cellular alterations ultimately lead to abnormal expression of synaptic plasticity-related proteins (e.g., BDNF, PSD-95), which are closely related to clinical symptoms such as cognitive deficits in SCZ and emotional processing disorders in MDD.

Epigenetic modifications, especially DNA methylation, play a key role in regulating *SLC6A4* expression. Promoter and exon hypermethylation recruit methyl-binding proteins (e.g., MeCP2) and histone deacetylases (HDACs) to form condensed chromatin structure, inhibiting transcription factor binding and downregulating *SLC6A4* expression. In SCZ, this mechanism is associated with reduced synaptic 5-HT reuptake, impaired signal transduction, and severity of negative symptoms[45]. In MDD, environmental stressors such as childhood trauma induce hypermethylation at specific CpG sites of *SLC6A4* via the glucocorticoid receptor-DNMT signaling axis. This not only decreases 5-HTT expression but also inhibits neurotrophic signaling (e.g., *BDNF* transcription) through epigenetic cross-talk, impairing neuroplasticity in the hippocampus and prefrontal cortex, and aggravating cognitive and emotional symptoms[81,101].

Neuroimaging studies provide system-level evidence supporting these mechanisms. *SLC6A4* polymorphisms and methylation status are closely related to structural abnormalities (e.g., hippocampal atrophy, reduced amygdala volume), functional alterations (e.g., reduced SERT availability in the prefrontal cortex), synaptic plasticity markers, and clinical behavioral phenotypes. For example, in SCZ patients, S allele carriers exhibit thinner prefrontal cortices and reduced SERT binding in the thalamo-cortical pathway, correlating with negative symptoms and executive dysfunction[52]. In MDD patients, individuals with hypermethylation show enhanced amygdala responses to negative stimuli and abnormal default mode network connectivity, which are directly associated with core symptoms such as anhedonia and cognitive delays. Notably, decreased white matter integrity (e.g., reduced fractional anisotropy in the corpus callosum) interacts with *SLC6A4* hypermethylation and the 5-HTTLPR S allele, reflecting disrupted myelination and synaptic microstructure, thereby affecting network synchronization and information processing efficiency[92]. Collectively, these findings indicate that *SLC6A4* variants influence neural circuit development and function by regulating 5-HT reuptake and synaptic plasticity, ultimately contributing to specific clinical symptoms.

Despite significant progress, several limitations and points of contention remain. First, most studies focused on specific ethnic or regional populations (e.g., East Asian or European), limiting generalizability. For example, the association between 5-HTTLPR and SCZ was significant in Tatars[24] and Chinese Han populations[25] but not replicated in Japanese[31] or Korean cohorts[32]. These discrepancies may arise from genetic background differences (e.g., haplotype structure), environmental exposures (e.g., cultural stressors), or statistical limitations (e.g., small sample size). Second, gender differences are often overlooked, and most studies do not perform stratified analyses, despite females showing distinct methylation patterns and disease risks. Third, methylation studies largely rely on peripheral blood or saliva, with limited evidence from brain tissue. For example, *SLC6A4* promoter hypermethylation was observed in postmortem SCZ brains[43], whereas peripheral studies were inconsistent, suggesting differences between central and peripheral epigenetic regulation. Fourth, while associations between early adversity (e.g., childhood trauma[79]) and

SLC6A4 methylation are repeatedly reported, precise quantification of environmental factors (e.g., type, duration) and dynamics of interaction (timing-specific windows) remain underexplored. For example, the interaction between peer bullying and 5-HTTLPR was significant only in adolescents[73], whereas stress in adulthood may involve different mechanisms. Whether epigenetic modifications are reversible (e.g., through environmental interventions) remains unclear. Although *SLC6A4* polymorphisms and methylation status are suggested as potential predictors of drug response or disease prognosis, existing results are often contradictory. For instance, associations between *SLC6A4* methylation and antidepressant efficacy vary across cohorts: Kang reported hypermethylation linked to symptom severity[74], whereas Webb found it associated with better response[102]. Such discrepancies may stem from study design differences (baseline symptom heterogeneity, follow-up duration) or uncontrolled confounders (co-medication, comorbidities). Future studies should integrate multi-omics approaches (e.g., epigenome-transcriptome analysis), large cross-ethnic cohorts, and longitudinal designs to elucidate the precise regulatory networks of *SLC6A4* in psychiatric disorders and to explore its potential as a biomarker or therapeutic target.

CONCLUSION

As a core regulator of the 5-HT system, *SLC6A4* is susceptible to genetic and epigenetic alterations, which can disrupt 5-HTT expression, impair serotonergic signaling, and contribute to the development of psychiatric disorders. This highlights its key role in the pathophysiology of mental illnesses and underscores its potential as a target for research. However, current studies face challenges including significant heterogeneity, technical limitations, and gaps in understanding disease mechanisms. Addressing these issues through research on population diversity, brain-specific regulation, and dynamic gene-environment interactions is crucial for advancing knowledge and identifying innovative therapeutic strategies.

DECLARATIONS

Authors' contributions

Conceptualization, validation, writing-review and editing, supervision, project administration, funding acquisition: Nie S, Liu L
Conceptualization, supervision: Hu L
Software, writing-original draft preparation, writing-review and editing, visualization: Yuan H
Writing-original draft preparation, visualization, funding acquisition: Qing L
Software: Zou T
Methodology: Cheng T, Zhou C, Guo X, Li Y

Availability of data and materials

Not applicable.

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Conflicts of interest

Nie S and Liu L are Junior Editorial Board members of *Journal of Translational Genetics and Genomics*. Nie S and Liu L were not involved in any steps of editorial processing, notably including reviewer selection,

manuscript handling, or decision making, while the other authors have declared that they have no conflicts of interest.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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