Neuropsychiatric Disease and Treatment

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Influence of Polymorphisms in Gene SATB2 on Antipsychotics Response in Chinese Han Population

Xinzhe Du[1,2,*], Yukun Wang[1,*], Qian Zhang[3,*], Yao Gao[1,2], Xiao Wang[1,2], Wentao Zhao[1,2], Xiaodong Hu[1], Yu Zhang[4,5], Yong Xu[1,2], Bo Chen[6], Jihui Zhang[6], Sha Liu[1], Xinrong Li[1]

[1]Department of Psychiatry, the First Hospital of Shanxi Medical University, Taiyuan, People's Republic of China; [2]Shanxi Key Laboratory of Artificial Intelligence Assisted Diagnosis and Treatment for Mental Disorder, First Hospital of Shanxi Medical University, Taiyuan, People's Republic of China; [3]Department of Medical Psychology, Shanxi Province Mental Health Center/Taiyuan Psychiatric Hospital, Taiyuan, Shanxi Province, People's Republic of China; [4]Key Laboratory of Cellular Physiology (Shanxi Medical University), Ministry of Education, Taiyuan, People's Republic of China; [5]Department of Physiology, School of Basic Medical Sciences, Shanxi Medical University, Taiyuan, People's Republic of China; [6]Department of Psychiatry, Sinopharm North Hospital, Baotou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xinrong Li; Sha Liu, Department of Psychiatry, The First Hospital of Shanxi Medical University, 85 Jiefang Road, Yingze District, Taiyuan City, Shanxi Province, People's Republic of China, Email lixinrong1225@163.com; liusha@sxmu.edu.cn

Background: Responses to antipsychotic drugs vary significantly among patients with schizophrenia. This study explored the correlation between rs1900327, rs7557687, rs733156, and rs6745135 in gene SATB2 and antipsychotics response in the Chinese Han population.

Methods: This study included 228 patients with schizophrenia. The polymorphisms of SATB2 gene (rs1900327, rs7557687, rs733156, and rs6745135) in patients were measured using the KASP technique. During the study, patients received a single antipsychotic medication for a duration of eight weeks. The clinical efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS) scores. A patient with a decrease of at least 50% in the total PANSS score was categorized as a good responder, whereas those who did not meet this threshold were classified as poor responders.

Results: Polymorphisms of rs1900327, rs7557687 and rs733156 were associated with the decrease in PANSS on week 8; however, this was no longer significant after Bonferroni correction ($p > 0.05$). Four SNP polymorphisms of SATB2 were associated with reduced general psychopathology scores at week 8. At week 4, only rs733156 was associated with negative symptom changes at the 4th week. Good responders and poor responders showed no significant difference in the distribution of alleles and genotypes of the four loci ($p > 0.05$). The haplotype frequencies of rs6745135, rs1900327, rs7557687, and rs733156 were not significantly different between the two groups ($p > 0.05$). No SNP was significantly associated with antipsychotic treatment response under any of the five genetic models (codominant, dominant, recessive, overdominant, or Log -additive; $p > 0.05$).

Conclusion: The SATB2 gene polymorphisms were related to the effectiveness of antipsychotics in treating general psychopathological symptoms.

Keywords: schizophrenia, SATB2, gene polymorphism, antipsychotics

Introduction

Schizophrenia is a multifaceted psychiatric disorder with a strong genetic component that significantly contributes to its pathophysiology.[1] Affecting approximately 1% of the global population,[2] schizophrenia imposes a substantial financial burden on both individuals and society.[3] Schizophrenia contributes 13.4 million YLDs (years of life lived with disability) to burden of disease globally, equivalent to 1.7% of total YLDs globally in 2016.[4] Pharmacological treatment with antipsychotic medication is the primary approach to managing the disorder.[5] However, the individual responses to these medications differ significantly,[6] and at least 20% of patients with schizophrenia experience limited benefit from antipsychotic monotherapy.[7]

Received: 5 January 2025
Accepted: 17 July 2025
Published: 25 July 2025

In clinical practice, optimal dosing regimens are often determined by repeated medication reconciliation. Evidence suggests that genetic factors play a crucial role in the variability of patient responses to antipsychotic medications.[8] Pharmacogenetic studies provide a valuable approach by predicting drug side effects and responses to inform personalized treatment strategies.[9] Previous studies have linked antipsychotic medications response to genes related to synaptic function, neurotransmitter receptors, and schizophrenia risk.[10]

Current research has identified over 287 genomic loci associated with schizophrenia, encompassing multiple pathways such as neuronal development, synaptic function, and metabolic regulation. However, the specific mechanisms linking genes to the disease remain to be further explored.[11] The special AT-rich sequence-binding protein 2 (SATB2) gene is located in a gene-poor region of chromosome 2q32-q33. Its transcript spans 11 exons and 191 kb, encoding a large protein composed of 733 amino acids.[12] The SATB2 protein is an essential gene expression regulator that controls higher-order chromatin organization.[13,14] Mutations and alterations in this gene have been associated with behavioral problems, intellectual disability, developmental delays, and speech impairment in human patients.[15,16] SATB2 has also been identified as a risk locus for schizophrenia.[17,18] Notably, the rs6704641 variant, located in the intronic region of SATB2, is one of the 108 schizophrenia-associated loci previously reported by genome-wide association studies (GWAS).[18] Another study[19] discovered a significant association between this locus and schizophrenia in the Uygur Chinese population. Additionally, the study revealed two SATB2 haplotypes that were also significantly linked to the disorder.

Numerous studies have investigated the role of SATB2 in neurodevelopmental processes, offering insights into its potential involvement in the pathophysiology of schizophrenia. In the cerebral cortex, SATB2 regulates the normal development of projection neurons in the corpus callosum by inhibiting CITP2 expression.[20,21] Prior research has also implicated SATB2 in cognitive and pathophysiological processes associated with schizophrenia, particularly through brain-derived neurotrophic factor signaling pathways and the post-transcriptional regulation of miRNA-mediated gene expression.[22] The crucial role of SATB2 in neurodevelopment is increasingly recognized as a contributing factor to the etiology of schizophrenia.[23]

Population-based studies have indicated that SATB2 might be involved in the neurodevelopmental processes underlying the etiology of schizophrenia. However, its potential influence on the efficacy of antipsychotic medications has not yet been investigated. We selected the single nucleotide polymorphism (SNPs) within the SATB2 gene to evaluate their role in treatment outcome in individuals from the Han Chinese population.

Materials and Methods

Subjects

This study is based on the "Schizophrenia Molecular Typing and Individualized Diagnosis and Treatment Research" project led by "Shanxi Schizophrenia Collaboration Group.[24] At total of 228 patients diagnosed with schizophrenia and receiving treatment were recruited between December 2018 and December 2021 from six institutions: the First Hospital of Shanxi Medical University, Shanxi Province Social Welfare Kangning Psychiatric Hospital, Yangquan Mental Health Hospital, Changzhi Mental Health Center, Gaoping Disabled Persons' Federation Mental Rehabilitation Hospital and the Second Hospital of Yangquan Coal Industry Group Co. Ltd.

The inclusion criteria were: 1) age 18–90 years; 2) patients needed a schizophrenia diagnosis from at least two psychiatrists who had undergone rigorous training and had a wealth of clinical experience, as per the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV).; 3) during the study, each participant received just one medication—olanzapine, risperidone, aripiprazole, or quetiapine.; 4) The subject (or legal guardian) had provided informed consent and agreed to take part in the study. The exclusion criteria were: 1) using other antipsychotic and antiepileptic medications within a month was prohibited.; 2) making use of stabilizers and antidepressants simultaneously; 3) for a month, refrain from using modified electric convulsive therapy (MECT); 4) patients suffering from genetic illness; 5) patients who have a severe health condition, suicidal thoughts, or attempted suicide; 6) the patient is expecting or nursing.

The studies involving human participants were reviewed and approved by the Ethics Committee of BIO-X Institutes, Shanghai Jiaotong University in accordance with the Declaration of Helsinki (M16035). The patients offered their written informed consent to take part in this research.

SNPs Selection

Selection criteria for single nucleotide polymorphisms (SNPs): (1) derived from the SATB2 gene; (2) linked to the occurrence of schizophrenia in earlier research; and (3) a SNP locus with a minimum allele frequency (minor allele frequency, MAF) > 0.1 in the Chinese Han population. The International HapMap Project, SZDB database (http://www.szdb.org), and Database of Single Nucleotide Polymorphisms (dbSNP) all have filters for SNPs. Four SNPs were screened out, namely rs1900327, rs7557687, rs733156 and rs6745135. These were located at 181941bp, 181859bp, 175345bp and 190241bp of STAB2 DNA sequence respectively, which are all located in intron 9 of the STAB2 gene.

DNA Extraction and SNPs Genotyping

First, 5 mL of the subjects' blood was drawn into EDTA anticoagulant blood collection tubes and kept at −80°C in the refrigerator. The DNA was extracted from the blood and quantified using the RelaxGene Blood DNA System (Tiangen, DP319-01). The Kompetitive Allele-Specific PCR genotyping system (KASP) was used to conduct SNP analysis.

Drug Intervention and Clinical Rating Scale

Over an 8-week period, subjects received treatment with one of five antipsychotic medication: risperidone (n = 67), olanzapine (n = 98), aripiprazole (n = 41), quetiapine (n = 4), or amisulpride (n = 18). The dosing regimens were as follows: risperidone, 1–6 mg/day (initial–maximum); olanzapine, 5–20 mg/day; aripiprazole, 10–30 mg/day; quetiapine, 100–800 mg/day; and amisulpride, 100–1200 mg/day.

All participants reached an effective therapeutic dose of their assigned medication within the first two weeks, after which dosages were adjusted according to individual tolerance. Treatment continued for a total of eight weeks.

The Positive and Negative Syndrome Scale (PANSS) is a medical scale used to assess the severity of symptoms in patients with schizophrenia. The PANSS consists of a positive symptom scale (7 items), a negative symptom scale (7 items), a general psychopathology symptom scale (16 items), and supplementary items (3 items). Positive symptoms include hallucinations, delusions, and disorganized thinking. Negative symptoms include emotional flatness, social withdrawal, impoverished speech, and lack of will. Clinical symptoms and severity were evaluated at baseline and again at the end of weeks 2, 4, and 8 using the Positive and Negative Syndrome Scale (PANSS). Evaluations were conducted independently by two senior psychiatrists who were blinded to the subjects' genotype. The primary measure for treatment efficacy was the percentage change in PANSS scores. The PANSS endpoint score was defined as the score at week 8. Patients were classified as good responders if their PANSS score decreased by 50% or more from baseline; otherwise, they were classified as poor responders.

PANNS percentage change = (PANSS baseline score - PANSS endpoint score)/(PANSS baseline score - 30)×100

Statistical Analyses

The SPSS package (version 26.0) was used to conduct statistical analyses. Age and PANSS baseline scores were compared between groups using an independent samples *t*-test. The gender, allele frequency, and genotype frequency differences between the subjects' various qualitative data were examined using the chi-squared test. Spearman correlation analysis was used to determine the relationship between the efficacy of antipsychotic medications and various SNP genotypes. The Bonferroni correction was used for multiple testing. The risk under five inheritance models—codominant, dominant, recessive, overdominant, and additive models—was assessed using SNPStats (https://www.snpstats.net). Linkage disequilibrium (LD) and haplotype analysis were done using Haploview v4.0. The D' value is used to quantify the level of LD at the various NPY gene loci.

Result

Patient-Related Demographic Information and Clinical Parameters

Of the 228 participants included in this study, 192 were classified as good responders and 36 as poor responders. Table 1 provides a summary of descriptive statistics, including sex, age, and baseline PANSS scores. There was no significant

Table 1 Descriptive Statistics for Patient-Related Variables with Regard to Response

Response	Sex	p^a	Age	p^b	Baseline PANSS Score	p^b
Good responders	Male (49%) Female (51%)	0.112	38.92±11.64	0.577	85.11±6.73	0.051
Poor responders	Male (64%) Female (36%)		37.73±11.68		87.23±55.75	

Notes: [a]Chi-square test; [b]Two-tail *t*-test.

difference in gender ($\chi 2 = 2.521$, $p = 0.112$), age (t=0.559, $p = 0.577$) and PANSS baseline score ($t = -1.96$, $p = 0.051$) between the two groups. The Hardy–Weinberg equilibrium test showed no significant deviation in the cohort.

Effects of SATB2 Gene Polymorphisms on Antipsychotic Treatment Response

The PANSS total reduction rate was calculated at week 2, 4, and 8 during the study. We found that polymorphisms of rs1900327, rs7557687, and rs733156 were associated with a reduction rate at the 8th week. However, this was no longer significant after Bonferroni correction (p-value × 4 > 0.05; Table 2).

The Relationship Between SATB2 Gene Polymorphism and PANSS Score

The PANSS scale includes a positive symptom scale, negative symptom scale and general psychopathological symptom scale. We calculated the positive score change, negative score change and general psychopathology score change at different stages. We found that all four SNP polymorphisms were associated with changes in general psychopathology scores at week 8. The significance remained after correction (p-value × 4 < 0.05). Except rs6745135, the other SNP site polymorphisms were also associated with changes in positive symptoms at week 8. However, after the Bonferroni correction, these correlations were no longer significant (p-value × 4 > 0.05).

With regard to the change in the negative symptom score, we found that all four SNP loci were associated with changes at week 4. At week 8, rs733156 was also associated with a negative symptom change. However, after correction, only rs733156 remained associated with changes in negative symptom scores at the 4th week (Table 3).

Genotypic and Allelic Distributions of SATB2 Genes in Two Groups

We subsequently compared allele and genotype frequencies at four loci between the two groups. No statistically significant differences were observed in either allele or genotype frequencies at any of the loci (all $p > 0.05$; Tables 4 and 5).

Relationship Between Haplotypes and Antipsychotic Treatment Response

LD was observed among rs6745135, rs1900327, rs7557687, and rs733156 within the SATB2 gene. Haplotype frequencies were compared between good and poor responder. A high LD block spanning 14 kb was identified, encompassing all four SNPs (Figure 1). Additionally, the total frequency differences between the two responder groups were compared

Table 2 Association of SATB2 Gene Polymorphisms with PANSS Total Deduction Rate

SNP	Deduction Rate for 8th Week	Deduction Rate for 4th Week	Deduction Rate for 2nd Week
rs1900327	**0.016**	0.529	0.895
rs7557687	**0.035**	0.724	0.921
rs733156	**0.018**	0.553	0.867
rs6745135	0.052	0.654	0.878

Notes: The values in the table represent the *p*-value of the Spearman correlation between the total reduction rate of PANSS and SNP polymorphism. Bold texts indicate significant for the association (The *p-value* is not corrected).

Table 3 Association of SATB2 Gene Polymorphisms with PANSS Score

SNP	Positive Score Change			Negative Score Change			Psychopathology Score Change		
	8th week	4th week	2nd week	8th week	4th week	2nd week	8th week	4th week	2nd week
rs1900327	**0.028**	0.173	0.432	0.066	**0.019**	0.356	**0.007**	0.178	0.458
rs7557687	**0.038**	0.293	0.411	0.119	**0.027**	0.28	**0.01**	0.208	0.513
rs733156	**0.033**	0.203	0.442	**0.046**	**0.012**	0.335	**0.007**	0.161	0.385
rs6745135	0.06	0.292	0.377	0.171	**0.04**	0.253	**0.01**	0.149	0.554

Notes: The values in the table represent the *p*-value of the Spearman correlation between the reduction rate of PANSS and SNP polymorphism at different stages. Bold texts indicate significant for the association (The *p-value* is not corrected).

Table 4 Comparison of SNPs Genotype Distribution in Two Groups

SNP	Genotype	Good Responder (%)	Poor Responder (%)	$\chi 2$	*P-value*	*Adjusted-p*
rs1900327	AA	141 (76.2)	22 (61.1)	3.621	0.164	0.656
	AT	40 (21.6)	13 (36.1)			
	TT	4 (2.2)	1 (2.8)			
rs7557687	AA	141 (75.8)	22 (61.1)	3.394	0.183	0.732
	AG	41 (22.0)	13 (36.1)			
	GG	4 (2.2)	1 (2.8)			
rs733156	CC	139 (48.4)	22 (61.1)	3.473	0.176	0.704
	TC	40 (51.6)	13 (36.1)			
	TT	4 (2.2)	1 (2.8)			
rs6745135	CC	135 (73.8)	28 (77.8)	0.384	0.825	3.3
	CT	44 (24.0)	7 (19.4)			
	TT	4 (2.2)	1 (2.8)			

Note: The adjusted *p-value* was corrected by Bonferroni.

Table 5 Comparison of SNPs Allele Distribution in Two Groups

SNP	Allele	Good Responder (%)	Poor Responder (%)	$\chi 2$	*p-value*	*Adjusted-p*
rs1900327	A	322 (87.0)	57 (79.2)	3.047	0.018	0.072
	T	48 (13.0)	15 (20.8)			
rs7557687	A	323 (86.8)	57 (79.2)	2.870	0.09	0.360
	G	49 (13.2)	15 (20.8)			
rs733156	C	318 (86.9)	57 (79.2)	2.911	0.088	0.352
	T	48 (13.1)	15 (20.8)			
rs6745135	C	314 (85.8)	63 (87.5)	0.146	0.702	2.808
	T	52 (14.2)	9 (12.5)			

Note: The adjusted *p-value* was corrected by Bonferroni.

across all potential haplotypes. Block 1 contained two haplotypes—TTGT and CAAC—neither of which showed a significant association with antipsychotic treatment response (Table 6).

Five Genetic Models Analysis

We further investigated the association between four SNPs and antipsychotic drug response under five genetic models, adjusting for sex and age. Across all five models, we found no significant differences in genotype distributions between the good and poor responder groups for any of the four SNPs ($p > 0.05$; Tables S1–S4).

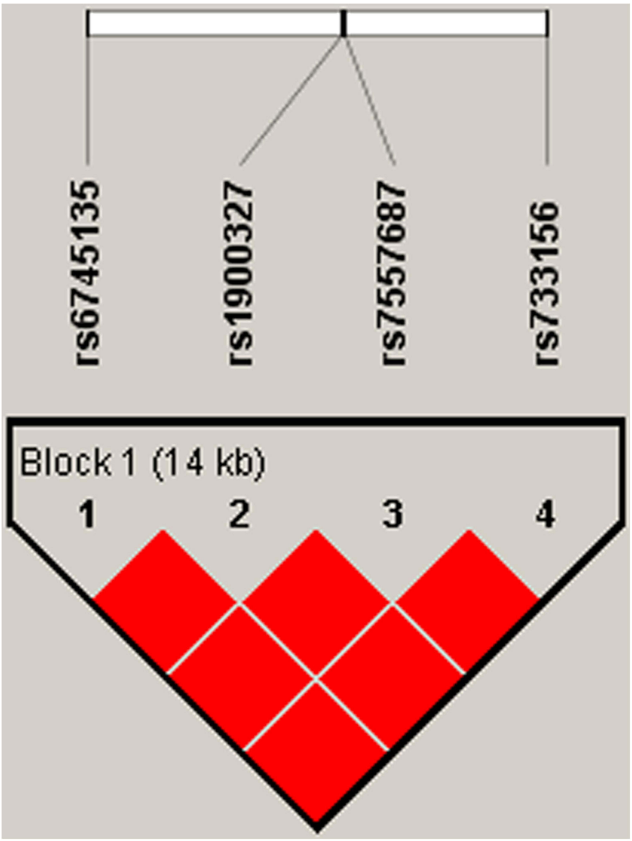

Figure 1 Linkage disequilibrium block structure across SATB2 gene.The figure show the output of Haploview (version 4.0) LD Plot where each square (with D, values 1) represents a pair-wise LD relationship between the two SNPs. Red squares indicate statistically significant LD between the pair of SNPs as measured by the D, statistic.

Discussion

SATB2 is significantly involved in the etiology of schizophrenia. To explore the interaction between SATB2 and schizophrenia, we used the tool Pathway studio (http://www.pathwaystudio.com). Figure 2 shows a strong functional association between SATB2 and schizophrenia through multiple small molecules and proteins. Research on the impact of SATB2 variants on the effectiveness of antipsychotic drug treatment outcomes is limited. In the current study, we explored the potential of four SNPs (rs1900327, rs7557687, rs733156, rs6745135) as genetic markers for predicting the effectiveness of antipsychotic treatment. Our study found that all four SNP polymorphisms were associated with changes in general psychopathology scores after eight weeks of treatment. The significance remained after correcting for multiple testing (p-value $\times$ 4 $<$ 0.05). These findings suggest that polymorphisms in the SATB2 gene may be linked to improvements in general psychopathological symptoms in response to antipsychotic treatment.

The general psychopathology subscale of the PANSS includes items assessing depression, anxiety, tension, orientation, attention, judgment, impulse control, and related domains. It provides an overall assessment of the patient's

Table 6 Frequency Distribution and Association Analysis of Haplotypes of SATB2 Gene with Antipsychotics Response

Haplotype				Haplotype Frequency	Good Responder (%)	Poor Responder (%)	$\chi 2$	*pa*	*Adjusted-pb*
Rs6745135	Rs1900327	Rs7557687	Rs733156						
C	A	A	C	0.855	0.691	0.569	2.794	0.0946	0.2230
T	T	G	T	0.143	0.255	0.306	3.028	0.0819	0.1900

Notes: [a]Uncorrected *p-value*. [b] *Adjusted-p*, number of permutations: 1000.

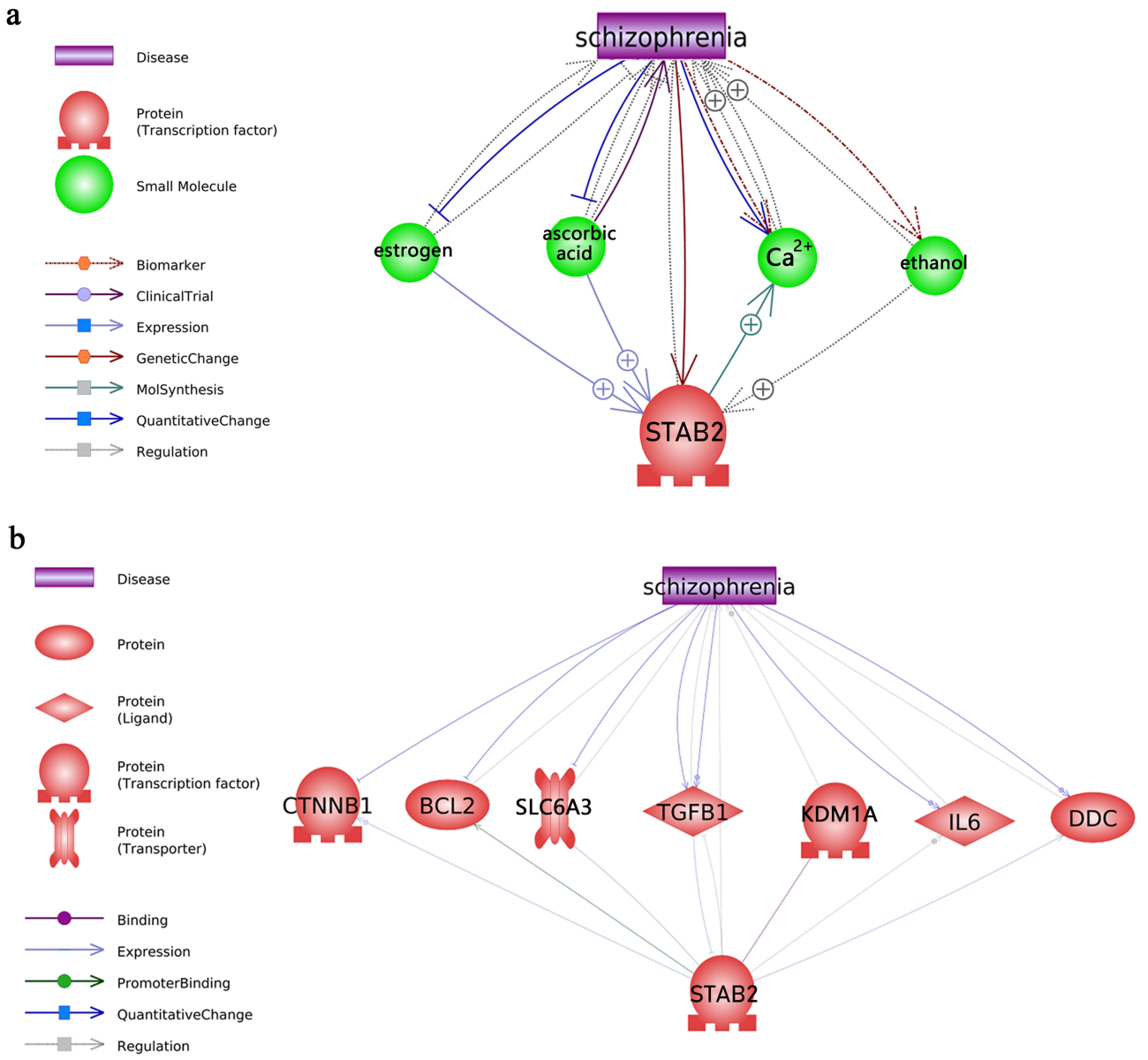

Figure 2 Functional network connecting SATB2 and schizophrenia. The networks were built using "network building" module of Pathway Studio. (**a**) Small molecule associated with the SATB2 gene and schizophrenia. (**b**) The protein between the SATB2 gene and schizophrenia.

condition, including cognitive, emotional, and social functioning, as well as daily living abilities. Therefore, our results may reflect a potential role of the SATB2 gene in the cognitive symptoms associated with schizophrenia.

A core feature of schizophrenia is cognitive dysfunction manifested by impaired memory, attention and IQ.[25] SATB2 plays a crucial role as a transcription factor regulating neocortical organization and circuitry.[26] Rare mutations in SATB2 cause a syndrome that includes developmental delay, mild to severe intellectual disability, speech and behavioral problems and abnormal craniofacial features.[27] In addition, mouse studies have demonstrated a significant role for SATB2 in learning and memory processes. Notably, SATB2 mutant mice were similar to those observed in patients with SATB2 mutations.

In the adult central nervous system, SATB2 plays a crucial role in regulating synaptic plasticity in the hippocampus, an essential process for memory functions. Jaitner et al discovered that deletion of SATB2 in the forebrain of mice led to long-term memory deficits and impaired the stabilization of synaptic long-term potentiation.[22] SATB2 has also been shown to regulate the expression of FosB by interacting with its promoter. FosB is classified as an immediate early gene (IEG) involved in synaptic

https://doi.org/10.2147/NDT.S511374

plasticity and long-term memory formation.[28] Laura et al[29] studied genes associated with epigenetic mechanism in schizophrenia, and found that eight candidate risk SNPs—including SATB2 (rs6704641)—were associated with cognitive functions such as IQ, working memory, episodic memory, and attention. Furthermore, a study revealed that common variants linked to human cognitive ability are more prevalent among the genes encoding SATB2 interactors in adults, but not in neonates.[14]

Associations between polymorphisms in multiple genes and responses to antipsychotic drugs have been reported in schizophrenia. Fragile X mental retardation syndrome-related 1 (FXR1) and glycogen synthase kinase-3β (GSK3β) are associated with SZ. Interaction of rs496250 in FXR1 and rs12630592 in GSK3β also on response to antipsychotics, SZ patients with GSK3β rs12630592 TT genotype and FXR1 rs496250 A genotype have higher improvement in negative symptom compared with other genotype SZ patients.[30] Metabotropic glutamate receptor 7 (GRM7) gene has been implicated as a potential risk locus for schizophrenia. SNPs in GRM7 significantly associated with treatment response in antipsychotic drugs such as aripiprazole, haloperidol, olanzapine, perphenazine, quetiapine, risperidone and ziprasidone and has the potential as biomarkers for therapeutic responses of antipsychotic drugs.[31] BDNF (Brain-Derived Neurotrophic Factor), a member of the neurotrophins family, plays an important physiological role in SZ. After risperidone and clozapine treatment, the level of BDNF in Peripheral blood of SCZ patients with good responder was higher compared with that in non-response patients. In additionally, The BDNF Val66Met variant (rs6265) affects antipsychotic response, with Val/Val individuals demonstrating a better therapeutic response to clozapine and olanzapine.[32] In this study, we further compared the genotype and allele distribution of four SNPs of SATB between two groups: good responders (PANSS decrease by 50% or more) and poor responders (PANSS decrease less than 50%). Unfortunately, no statistical difference was found between the groups. This lack of association may suggest that these sites are not directly involved in modulating the effectiveness of antipsychotic medications. Additionally, differences in the mechanisms of action of olanzapine, risperidone, aripiprazole, and quetiapine may also play a role. Therefore, we cannot entirely dismiss the possibility of genetic loci related to drug efficacy. We selected patients with single drug therapy as the study object, and no relationship was found between the efficacy of these antipsychotics and the polymorphism of SATB2 gene (Tables S5 and S6).

Previous studies have indicated haplotype-based methods are more effective than those based on single loci.[33] The present study conducted haplotype-based association analyses to examine the potential impact of SATB2 polymorphisms on antipsychotic treatment response. We found a block comprising four SNPs in the chromosome.; however, no significant association was found between SATB2 gene polymorphism and treatment outcomes. While our results did not support a link with drug response, previous research has reported associations between haplotypes and schizophrenia risk. For example, a recent study, identified significant associations involving the haplotypes rs6704641-rs7600663-rs13028839 and rs12052310-rs4673339-rs16831466-rs16831496, with the GCG and CAAC haplotypes acting as protective factors against schizophrenia (OR = 0.822, 95% CI = 0.697–0.969; OR = 0.756, 95% CI = 0.605–0.944).[19]

Unconditional logistic regression can be used to analyze genetic associations under five inheritance models (codominant, dominant, recessive, overdominant, and log-additive). In the present study, we found no significant differences in genotypes distributions between the two groups under any of these five models.

Currently, numerous studies are exploring the role of SATB2 in the genetic etiology of schizophrenia. One study integrating brain imaging and SNP data in patients with schizophrenia found that both gray matter volume and functional connectivity were impaired in the hippocampus, temporal gyrus and cerebellum—alterations that were associated with SATB2 gene variants.[34] Zhuo et al[35] further combined neuropsychometrics and found that SNPs of several genes, including SATB2, were associated with decreased GMV in the hippocampus, temporal lobe, amygdala and cerebellum. These changes may contribute to the development of cognitive impairment. The pathological effect of SATB2 on schizophrenia provides a basis for us to explore the antipsychotic reaction. This study is the first to explore the relationship between SATB2 and antipsychotic response, and is expected to potentially identify new markers of antipsychotic response.

Our study also had certain limitations. First, the study's genetic sample size was small, which results in low heritability. Second, some potential nongenetic factors, such as drug type, disease duration, and drug dose, were not taken into consideration in this investigation, which may have had some influence on the accuracy of the findings. Third, our study only involved the Chinese population; thus, other ethnic groups need to be tested. In general, more research into the relationship between the

SATB2 gene polymorphism and antipsychotic medications is still necessary. Future research could broaden the selection range of the SATB2 gene's SNP loci, include more races, and divide drug types to produce more solid findings. Whether SATB gene polymorphism affect the side effects of antipsychotic medications is also a future research direction. The findings of this research could help optimize treatment, reduce the occurrence of side effects, and provide a basis for individualized medication for schizophrenia patients.

Conclusion

This study aimed to explore whether antipsychotic treatment outcomes in the Chinese Han population are influenced by the SATB2 gene in schizophrenia. According to our research, the SATB2 gene polymorphism is presumably related to the effectiveness of antipsychotics in the treatment of general psychopathological symptoms. This study revealed the relationship between SATB2 and antipsychotic response, and is expected to potentially identify new markers of antipsychotic response. Due to the limited total sample size (only over 200 cases), we were unable to further stratify by medication type to examine whether the four SNPs have differential effects on the efficacy of different drugs. Larger samples and diverse populations should be used in future studies to better inform personalized medicine.

Data Sharing Statement

The datasets used during the current study are available from Xinrong Li on reasonable request.

Ethics Approval and Consent to Participate

The studies involving human participants were reviewed and approved by Ethics Committee of BIO-X Institutes, Shanghai Jiaotong University(M16035). The patients provided their written informed consent to participate in this study.

Acknowledgments

The authors wish to acknowledge "Schizophrenia molecular typing and individualized diagnosis and treatment research" project leaded by "Shanxi Schizophrenia Collaboration Group", Xinyuan Biotechnology Ltd. Co (Shanghai, China), and Professor Hongbao Cao from George Mason University.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Natural Science Foundation of China (82271546 to Sha Liu and 82371511 to Yong Xu); the Fundamental Research Program of Shanxi Province (202203021212038 to Xinzhe Du and 202403021211162 to Zhiyong Ren); Shanxi Medical University School-level Doctoral Initiation Fund Project (XD 1904 to Xinzhe Du); Special Fund for Science and Technology Innovation Teams of Shanxi Province (202304051001049 to Sha Liu); Fund Program for the Scientific Activities of Selected Returned Overseas Professionals in Shanxi Province (20240041 to Sha Liu); Shanxi Province Higher Education "Billion Project" Science and Technology Guidance Project (BYJL062 to Sha Liu); Six batches Special Action of Shanxi Taiyuan Municipal Health Committee (Z2023002 to Zhiyong Ren). Science and technology innovation project of higher education in Shanxi Province (2020L0204 to Xinzhe Du).

Disclosure

The authors declare that there is no competing of interest in this work.

References

1. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia-an overview. *JAMA Psychiatry*. 2020;77(2):201–210. doi:10.1001/jamapsychiatry.2019.3360
2. Sarkar S, Hillner K, Velligan DI. Conceptualization and treatment of negative symptoms in schizophrenia. *World J Psychiatry*. 2015;5(4):352–361. doi:10.5498/wjp.v5.i4.352
3. Crespo-Facorro B, Such P, Nylander A-G, et al. The burden of disease in early schizophrenia: a systematic literature review. *Curr Med Res Opin*. 2020;37(1):109–121. doi:10.1080/03007995.2020.1841618
4. Charlson FJ, Ferrari AJ, Santomauro DF, et al. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. *Schizophr Bull*. 2018;44(6):1195–1203. doi:10.1093/schbul/sby058
5. McCutcheon RA, Krystal JH, Howes OD. Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. *World Psychiatry*. 2020;19(1):15–33. doi:10.1002/wps.20693
6. Jeun KJ, Kamal KM, Adhikari K, et al. A systematic review of the real-world effectiveness and economic and humanistic outcomes of selected oral antipsychotics among patients with schizophrenia in the United States: updating the evidence and gaps. *J Manag Care Spec Pharm*. 2024;30(2):183–199. doi:10.18553/jmcp.2024.30.2.183
7. Lähteenvuo M, Tiihonen J. Antipsychotic polypharmacy for the management of schizophrenia: evidence and recommendations. *Drugs*. 2021;81(11):1273–1284. doi:10.1007/s40265-021-01556-4
8. Arranz MJ, de Leon J. Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. *Mol Psychiatry*. 2007;12(8):707–747. doi:10.1038/sj.mp.4002009
9. Lisoway AJ, Chen CC, Zai CC, Tiwari AK, Kennedy JL. Toward personalized medicine in schizophrenia: genetics and epigenetics of antipsychotic treatment. *Schizophr Res*. 2021;232:112–124. doi:10.1016/j.schres.2021.05.010
10. Yu H, Yan H, Wang L, et al. Five novel loci associated with antipsychotic treatment response in patients with schizophrenia: a genome-wide association study. *Lancet Psychiatry*. 2018;5(4):327–338. doi:10.1016/S2215-0366(18)30049-X
11. Schizophrenia working group of the psychiatric genomics consortium; Trubetskoy V, Pardiñas AF, Qi T, et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature*. 2022;604(7906):502–508. doi:10.1038/s41586-022-04434-5
12. FitzPatrick DR, Carr IM, McLaren L, et al. Identification of SATB2 as the cleft palate gene on 2q32-q33. *Hum Mol Genet*. 2003;12(19):2491–2501. doi:10.1093/hmg/ddg248
13. Galande S, Purbey PK, Notani D, Kumar PP. The third dimension of gene regulation: organization of dynamic chromatin loopscape by SATB1. *Curr Opin Genet Dev*. 2007;17(5):408–414. doi:10.1016/j.gde.2007.08.003
14. Cera I, Whitton L, Donohoe G, et al. Genes encoding SATB2-interacting proteins in adult cerebral cortex contribute to human cognitive ability. *PLoS Genet*. 2019;15(2):e1007890. doi:10.1371/journal.pgen.1007890
15. Zarate YA, Kalsner L, Basinger A, et al. Genotype and phenotype in 12 additional individuals with SATB2 -associated syndrome. *Clin Genet*. 2017;92(4):423–429. doi:10.1111/cge.12982
16. Zarate YA, Smith-Hicks CL, Greene C, et al. Natural history and genotype-phenotype correlations in 72 individuals with SATB2 -associated syndrome. *Am J Med Genet Part A*. 2018;176(4):925–935. doi:10.1002/ajmg.a.38630
17. Li Z, Chen J, Yu H, et al. Genome-wide association analysis identifies 30 new susceptibility loci for schizophrenia. *Nat Genet*. 2017;49(11):1576–1583. doi:10.1038/ng.3973
18. Ripke S, Neale BM, Corvin A, et al. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511:421–427.
19. Zhou J, Chen J, Xu W, et al. Common variants in SATB2 are associated with schizophrenia in Uygur Chinese population. *Psychiatr Genet*. 2019;29(4):120–126. doi:10.1097/YPG.0000000000000229
20. Alcamo EA, Chirivella L, Dautzenberg M, et al. Satb2 regulates callosal projection neuron identity in the developing cerebral cortex. *Neuron*. 2008;57(3):364–377. doi:10.1016/j.neuron.2007.12.012
21. Britanova O, de Juan Romero C, Cheung A, et al. Satb2 is a postmitotic determinant for upper-layer neuron specification in the neocortex. *Neuron*. 2008;57(3):378–392. doi:10.1016/j.neuron.2007.12.028
22. Jaitner C, Reddy C, Abentung A, et al. Satb2 determines miRNA expression and long-term memory in the adult central nervous system. *Elife*. 2016;5:e17361. doi:10.7554/eLife.17361
23. Whitton L, Apostolova G, Rieder D, et al. Genes regulated by SATB2 during neurodevelopment contribute to schizophrenia and educational attainment. *PLoS Genet*. 2018;14(7):e1007515. doi:10.1371/journal.pgen.1007515
24. Zhang Q, Wan Y, Du X, et al. Association between neuropeptide Y gene polymorphism and antipsychotics effect. *Front Psychiatry*. 2022;13:1014952. doi:10.3389/fpsyt.2022.1014952
25. Menon V, Palaniyappan L, Supekar K. Integrative brain network and salience models of psychopathology and cognitive dysfunction in schizophrenia. *Biol Psychiatry*. 2023;94(2):108–120. doi:10.1016/j.biopsych.2022.09.029
26. Huang X, Chen Q, Luo W, et al. SATB2: a versatile transcriptional regulator of craniofacial and skeleton development, neurogenesis and tumorigenesis, and its applications in regenerative medicine. *Genes Dis*. 2020;9(1):95–107. doi:10.1016/j.gendis.2020.10.003
27. Docker D, Schubach M, Menzel M, et al. Further delineation of the SATB2 phenotype. *Eur J Hum Genet*. 2014;22(8):1034–1039. doi:10.1038/ejhg.2013.280
28. Li Y, You QL, Zhang SR, et al. Satb2 ablation impairs hippocampus-based long-term spatial memory and short-term working memory and immediate early genes (IEGs)-mediated hippocampal synaptic plasticity. *Mol Neurobiol*. 2017. doi:10.1007/s12035-017-0531-5
29. Whitton L, Cosgrove D, Clarkson C, et al. Cognitive analysis of schizophrenia risk genes that function as epigenetic regulators of gene expression. *Am J Med Genet B Neuropsychiatr Genet*. 2016;171(8):1170–1179. doi:10.1002/ajmg.b.32503
30. Rampino A, Torretta S, Gelao B, et al. Evidence of an interaction between FXR1 and GSK3β polymorphisms on levels of negative symptoms of schizophrenia and their response to antipsychotics. *Eur Psychiatry*. 2021;64(1):e39. doi:10.1192/j.eurpsy.2021.26
31. Liang W, Yu H, Su Y, et al. Variants of GRM7 as risk factor and response to antipsychotic therapy in schizophrenia. *Transl Psychiatry*. 2020;10(1):83. doi:10.1038/s41398-020-0763-4
32. Liberona A, Jones N, Zúñiga K, et al. Brain-derived neurotrophic factor (BDNF) as a predictor of treatment response in schizophrenia and bipolar disorder: a systematic review. *Int J Mol Sci*. 2024;25(20):11204. doi:10.3390/ijms252011204

33. Shifman S, Bronstein M, Sternfeld M, et al. A highly significant association between a COMT haplotype and schizophrenia. *Am J Hum Genet*. 2002;71(6):1296–1302. doi:10.1086/344514
34. Luo N, Tian L, Calhoun VD, et al. Brain function, structure and genomic data are linked but show different sensitivity to duration of illness and disease stage in schizophrenia. *Neuroimage Clin*. 2019;23:101887. doi:10.1016/j.nicl.2019.101887
35. Zhuo C, Tian H, Chen J, et al. Associations of cognitive impairment in patients with schizophrenia with genetic features and with schizophrenia-related structural and functional brain changes. *Front Genet*. 2022;13:880027. doi:10.3389/fgene.2022.880027