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Study of the relationship between Glyoxalase 1 polymorphism and cognitive function in patients with schizophrenia

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Abstract: Background: Emerging evidence suggests that Glyoxalase 1 (Glo-1) may be associated with cognitive function in schizophrenia. Objective: This study aimed to examine the association between Glo-1 polymorphism and cognitive function in Han Chinese patients with schizophrenia. Methods: We recruited 1,055 Han Chinese patients with schizophrenia and collected peripheral blood samples to genotype the Glo-1 rs9470916 locus using the SNaPshot technique. Results: Letter fluency scores differed significantly across rs9470916 genotypes in patients with schizophrenia (F=3.358, p=0.04). No significant differences were observed in age, education level, age at onset, family history, or psychiatric symptom scores across Glo-1 rs9470916 genotypes. Conclusion: Glo-1 single-nucleotide polymorphisms may affect cognitive function in Han Chinese patients with schizophrenia, suggesting that Glo-1 may play a role in susceptibility to schizophrenia.

Keywords: Schizophrenia, Glo-1, Cognitive Function, Han Chinese Population

1. Introduction

Schizophrenia is a complex neuropsychiatric disorder characterized by deficits in sensation, perception, emotion regulation, and cognitive function, with onset occurring most commonly in young adulthood (Hosák et al., 2012; Tandon et al., 2013). Genetic factors play a substantial role in the pathogenesis of schizophrenia. To date, multiple susceptibility genes and single-nucleotide polymorphisms (SNPs) associated with schizophrenia have been identified by genome-wide association studies (GWAS). Inherited genetic susceptibility, combined with environmental stressors, may lead to dysregulation of biological regulatory processes or the accumulation of neurotoxic substances, ultimately resulting in the complex symptom phenotype of schizophrenia (Kirby et al., 2010). However, the relevant genetic regulatory networks and their relationships with symptom phenotypes remain incompletely defined (Dennison et al., 2020; Owen et al., 2023). Cognitive impairment is a sensitive indicator, and patients may exhibit cognitive deficits before disease onset. Accordingly, the assessment of cognitive function may be valuable for evaluating schizophrenia severity and improving early identification of the disorder.

Recent studies suggest that carbonyl stress may increase the risk of schizophrenia. Carbonyl stress can lead to the abnormal accumulation of dicarbonyl compounds, such as methylglyoxal (MG) (Kalapos, 1999; Miyata et al., 1999), thereby promoting the formation of advanced glycation end products (AGEs) and inducing substantial cytotoxicity in neurons. Glyoxalase 1 (Glo-1), a rate-limiting enzyme of the glyoxalase system, converts toxic MG to nontoxic lactate and facilitates the cellular detoxification of reactive carbonyl species (Sousa Silva et al., 2013). Accumulating evidence indicates that Glo-1 may be associated with the pathogenesis of schizophrenia (Bangel et al., 2015; Tosic et al., 2006; Yin et al., 2021). The Glo-1 gene is located on chromosome 6p21.2, a region considered highly relevant to schizophrenia susceptibility (Purcell et al., 2009; Ripke et al., 2014; Shi et al., 2009; Stefansson et al., 2009). Evidence suggests that Glo-1 may be associated with cognitive impairment. Increased serum levels of MG and Glo-1 have been reported in patients with mild cognitive impairment. Glo-1 expression is upregulated during the early stage of Alzheimer disease (AD) but gradually downregulated during the middle and late stages of AD; regardless of age, Glo-1 levels are associated with cognitive scores. These findings suggest that reduced Glo-1 expression may contribute to cognitive decline (Haddad et al., 2021). In schizophrenia, cognitive impairment is a core clinical feature and a sensitive indicator for early identification of the disorder. Aberrant Glo-1 gene expression may be associated with the cognitive impairment phenotype in schizophrenia. In our previous work, we identified several Glo-1 polymorphic loci potentially related to schizophrenia in Han Chinese patients, including rs9470916, rs1130534, rs4746, and rs1781735. Among these, rs1781735 was associated with susceptibility to schizophrenia and was linked to altered brain function in patients with schizophrenia.(Yin et al., 2021). These loci may influence Glo-1 protein expression and enzymatic activity, thereby contributing to changes in cognitive function. In linkage disequilibrium (LD) analyses, rs1781735 showed strong LD with rs9470916 ($D' = 0.967$). Accordingly, the present study further examined the association between the Glo-1 polymorphism rs9470916 and cognitive function in Han Chinese patients with schizophrenia. This may contribute to understanding schizophrenia pathogenesis and provide clues to protective molecular mechanisms.

2. Materials and Methods

This study collected clinical data and peripheral blood samples from 1,055 Han Chinese patients with schizophrenia (725 men and 330 women) who were treated at the Department of Psychiatry and Psychology, the Affiliated Hospital of Guangdong Medical University, between October 2012 and February 2023. During enrollment, two attending psychiatrists independently confirmed the diagnosis. Inclusion criteria were (1) meeting the diagnostic criteria for schizophrenia in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and (2) being 18 to 55 years of age. Exclusion criteria were: (1) Secondary psychiatric disorders (e.g., organic brain disorders, mental disorders caused by somatic diseases, intellectual disability, or mental disorders induced by psychoactive substances); (2) Other psychiatric disorders (e.g., major depressive disorder, bipolar disorder, manic episode, or anxiety disorder); (3) Concurrent severe somatic diseases; or (4) Pregnancy or lactation.

Psychotic symptoms and severity were assessed using the Positive and Negative Syndrome Scale (PANSS). Cognitive function in schizophrenia was evaluated using the Brief Assessment of Cognition in Schizophrenia (BACS), which includes verbal memory, working memory, motor speed, verbal fluency, attention and processing speed, and reasoning and problem solving. Scale ratings were completed by 2 trained psychiatrists,

and interrater reliability was assessed. Final scores were calculated as the mean of the 2 raters' scores. Cases with large discrepancies between raters or poor cooperation during testing were excluded.

On the morning after enrollment, 0.5 mL of peripheral venous blood was collected from each patient into anticoagulant tubes and stored at -20 °C. Genomic DNA was extracted using a commercial kit (Tiangen Biotech Co, Ltd, Beijing, China) and stored at -80 °C. A 1-μL DNA aliquot was subjected to 1% agarose gel electrophoresis to assess sample quality and estimate DNA concentration, after which samples were diluted to a working concentration of 5-10 ng/μL according to the test results. Primers for polymerase chain reaction (PCR) amplification were designed using Primer3 software (http://frodo.wi.mit.edu/primer3/).

For the rs9470916 polymorphic locus, the upstream primer sequence was 5'-ACTCCAGCCCAAGAGCCAAGAG-3', and the downstream primer sequence was 5'-AAGGGGAGGAGGAAGGAAATGA-3'. A 20-μL reaction system was established, containing 5.0 μL of 1× GC Buffer I, 4.0 μL of 3.0 mM Mg^{2+}, 4.0 μL of 0.3 mM dNTPs, 4.0 μL of 1 U hot-start Taq DNA polymerase (Tiangen Biotech Co, Ltd, Beijing, China), 1 μL of sample DNA, and 2 μL of multiplex PCR primers. The PCR conditions were as follows: initial denaturation at 95 °C for 2 minutes; 11 cycles of 94 °C for 20 seconds, 65 °C for 40 seconds with a decrease of 0.5 °C per cycle, and 72 °C for 1.5 minutes; followed by 24 cycles of 94 °C for 20 seconds, 59 °C for 30 seconds, and 72 °C for 1.5 minutes; and a final extension at 72 °C for 2 minutes. A 15-μL aliquot of PCR product was then used for the extension reaction with the SNaPshot Multiplex Kit. The extension primer sequence was 5'-TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTCCTAGCCCAGTGTCTGGGTAC-3'. Finally, 0.5 μL of the purified extension product was analyzed by sequencing on an ABI 3130XL genetic analyzer.

Statistical analyses were performed using MATLAB 2021. Hardy-Weinberg equilibrium was assessed using the $\chi 2$ goodness-of-fit test. The genotype distribution of rs9470916 was compared using the $\chi 2$ test. Clinical characteristics across Glo-1 genotypes were compared using one-way analysis of variance. Continuous variables were expressed as mean (SD), and $p<0.05$ was considered statistically significant.

3. Results

There were no significant differences in age or sex among the three rs9470916 genotype groups ($p>0.05$). The allelic distribution at this locus was consistent with Hardy - Weinberg equilibrium ($p>0.05$).

Among patients with schizophrenia, no significant differences were observed across Glo-1 rs9470916 genotypes with respect to age, years of education, age at onset, or family history (all $p>0.05$). The mean (SD) PANSS total scores for the AA, CA, and CC genotypes were 79.41 (19.47), 77.30 (18.54), and 77.14 (19.75), respectively, with no significant between-group difference ($p=0.69$). No significant associations were observed for the PANSS positive, negative, or general psychopathology subscale scores (all $p>0.05$). Neurocognitive function was assessed in 345 patients with schizophrenia using the Brief Assessment of Cognition in Schizophrenia (BACS). As shown in Table 1, rs9470916 was associated with letter fluency scores ($F=3.358$, $p=0.04$). The mean (SD) letter fluency scores for the AA, CA,

and CC genotypes were 8.30 (5.85), 10.78 (6.30), and 9.34 (5.18), respectively, suggesting lower letter fluency in the AA genotype group. No significant differences were found in the remaining BACS domain scores (all $p>0.05$). We calculated statistical power using the minor allele frequency of rs9470916 (MAF=0.11). With the current sample size, a significance level of 0.05, and an assumed odds ratio of 1.5, statistical power was 1.00.

4. Discussion

Schizophrenia is a phenotypically complex neuropsychiatric disorder characterized by multidimensional clinical manifestations, including positive symptoms such as hallucinations, delusions, and disorganized speech or behavior; negative symptoms such as avolition and anhedonia; and, in many patients, varying degrees of cognitive impairment. Available evidence suggests that cognitive impairment, one of the core features of schizophrenia, may be closely related to Glo-1. Reduced Glo-1 activity may lead to the accumulation of neurotoxic metabolites such as MG, and MG and its end products may impair cognition by disrupting neurotransmitter homeostasis. By limiting MG accumulation, Glo-1 plays a critical role in protecting against carbonyl and oxidative stress, and dysregulation of this process may contribute to cognitive impairment in schizophrenia. In addition, Glo-1 activity has been associated with cognitive dysfunction in patients with diabetes and in mouse models of Alzheimer disease (More et al., 2013). More recently, decreased Glo-1 expression and enzymatic activity have been found to be significantly associated with reduced neural activity in the middle frontal gyrus (MFG), a cortical region central to cognitive function, in patients with schizophrenia (Distler et al., 2012; Yin et al., 2021).

On the basis of this evidence, the present study examined the association between Glo-1 polymorphisms and cognitive function in schizophrenia. Using rs9470916 genotypes, we conducted association analyses of clinical characteristics and cognitive performance among patients with schizophrenia. We found that rs9470916 was significantly associated with letter fluency, providing evidence that variation in Glo-1 may contribute to cognitive impairment in schizophrenia. In our previous work, Glo-1 variants were associated with an increased risk for Han Chinese patients with schizophrenia, and the promoter - region polymorphism rs1781735 has been shown to be significantly associated with schizophrenia. In LD analyses, rs1781735 and rs9470916 showed strong LD (D' = 0.967), suggesting that the observed signal at rs9470916 may reflect its linkage disequilibrium (LD) with rs1781735.

Cognitive impairment can emerge during the early stages of illness. Early assessment, detection, and intervention are important for improving prognosis. The association observed in this study between rs9470916 and letter fluency supports the potential development of early screening tools based on genetic biomarkers. Detection of Glo-1 polymorphisms, integrated with other clinical indicators and cognitive assessment instruments, may improve the identification of individuals at elevated risk and facilitate early intervention. Future research could examine associations between Glo-1 polymorphisms and specific symptom phenotypes of schizophrenia, as well as patterns of expression across illness stages, to inform intervention strategies. Glo-1 may also represent a potential therapeutic target. If pharmacologic or other approaches can modulate Glo-1 activity and enhance the clearance of toxic dicarbonyl metabolites, such strategies may contribute to symptom improvement in schizophrenia. Because population stratification may introduce bias, the association

between rs9470916 and cognitive function should be further validated in independent samples. In addition, our findings are based on a Chinese Han population from South China. Allele frequencies and linkage disequilibrium patterns of rs9470916 may differ across ethnic groups. Therefore, our results should be extended to other populations with caution.

In summary, to our knowledge, this study provides the first evidence of a specific association between Glo-1 polymorphisms and cognitive function in schizophrenia. In the Han Chinese population, Glo-1 polymorphisms were associated with cognitive performance in schizophrenia, suggesting that Glo-1 may play a role in schizophrenia susceptibility, particularly in relation to cognitive impairment.

Table 1. Comparison of Clinical Characteristics and Cognitive Function by Glo-1 Polymorphism rs9470916 Genotype

Variable	No. (AA/CA/CC)	AA	CA	CC	Statistical Test	*p* Value
rs9470916						
Age, mean (SD), y	66/420/569	33.11 (12.36)	34.46 (12.85)	34.31 (12.98)	F = 0.32	0.73
Age at onset, mean (SD), y	64/424/573	23.81 (8.75)	25.08 (9.71)	24.99 (9.46)	F = 0.51	0.60
Family history, No. (%)						
Yes	139	8 (5.7)	49 (35.2)	82 (58.9)	$\chi^2 = 1.70$	0.43
No	930	58 (6.2)	378 (40.6)	494 (53.1)		
PANSS, mean (SD)						
Total score	60/412/552	79.41 (19.47)	77.30 (18.54)	77.14 (19.75)	F = 0.38	0.69
Positive scale score	60/412/552	22.83 (7.71)	21.76 (7.15)	21.37 (7.73)	F = 1.16	0.31
Negative scale score	60/412/552	18.01 (9.53)	17.74 (8.51)	18.16 (8.91)	F = 0.27	0.76
General psychopathology score	60/412/552	36.65 (10.03)	36.50 (9.26)	36.07 (9.84)	F = 0.29	0.75
BACS, mean (SD)						
Digit sequencing	20/137/188	14.05 (9.77)	16.83 (9.08)	16.13 (8.83)	F = 0.90	0.41
Semantic fluency	20/137/188	29.50 (10.00)	29.86 (12.83)	29.07 (12.17)	F = 0.16	0.85

Variable	No. (AA/CA/CC)	AA	CA	CC	Statistical Test	*p* Value
Letter fluency	20/137/188	8.30 (5.85)	10.78 (6.30)	9.34 (5.18)	F = 3.36	0.04*
Verbal memory	20/137/188	20.40 (13.68)	24.21 (14.65)	23.07 (13.80)	F = 0.73	0.48
Token motor	20/137/188	45.30 (13.60)	52.16 (17.68)	49.85 (17.57)	F = 1.64	0.19
Tower of London	20/137/188	6.70 (7.44)	7.79 (6.27)	7.71 (6.38)	F = 0.26	0.77
Symbol coding	20/137/188	19.60 (12.22)	23.25 (13.66)	20.37 (12.98)	F = 2.09	0.12

Abbreviations: PANSS, Positive and Negative Syndrome Scale; BACS, Brief Assessment of Cognition in Schizophrenia. *$P < 0.05$.

Competing Interests

The authors declare no conflict of interest.

Data Availability

Data will be made available on request.

Ethical Approval

The studies involving humans were approved by Ethics Committee of Affiliated Hospital of Guangdong Medical University. The studies were conducted in accordance with the local legislation and institutional requirements.

Informed Consent

The participants provided their written informed consent to participate in this study.

Author Contributions

Dong Lv and Susu Xiong conceived and designed the experiments and revised the manuscript. Qinyue Peng, Yani Tang, and Yekai Ma conducted genetic analyses. Kangdu Chen collected the clinical data. Jingwen Yin and Susu Xiong analyzed and interpreted the data and drafted the manuscript. All authors were involved in the revision of the manuscript.

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