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Glutathione S-transferase gene polymorphisms (GSTT1 and GSTM1) and risk of schizophrenia

A case–control study in Chinese Han population

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Abstract

Schizophrenia (SCZ) is a chronic disability disorder related to oxidative stress. Glutathione S-transferase (GST) is a group enzyme that protects cells and tissues from oxidative stress damage. Among GSTs, GSTT1 and GSTM1 have well defined genetic polymorphisms. The purpose of our research was to explore the correlation between GSTT1 and GSTM1 polymorphism and SCZ risk in Chinese Han population.

A total of 650 subjects (386 SCZ patients and 264 healthy individuals) were included in this case–control designed study. The GSTT1 and GSTM1 polymorphisms were analyzed by multiplex polymerase chain reaction (PCR). We explored the relationship between these 2 polymorphisms and the risk of SCZ.

We found that the GSTT1 null genotype had a protective effect on the development of SCZ [odds ratio (OR) = 0.601, 95% confidence interval (95% CI) = 0.412–0.986, $P = .031$]. We also found that the combination of null genotypes of the GSTT1 and GSTM1 genes was made at a lower risk of SCZ (OR = 0.452, 95% CI = 0.238–0.845, $P = .028$). However, we found no correction between Positive and Negative Syndrome Scale score (PANSS) and GSTM1, GSST1 genotypes in SCZ patients.

Our finding revealed that GSTT1 null polymorphisms may be related to the reduced risk of SCZ in Chinese Han population, and this risk was further reduced with the combination of GSTT1 null polymorphisms and GSTM1 null polymorphisms.

Abbreviations: BD = bipolar disorder, DEPC = diethyl pyrocarbonate, DSM = diagnostic and Statistical Manual of mental disorders, EDTA = ethylenediamine tetraacetic acid, GSTs = Glutathione S-transferase, MDD = major depression disorder, PANSS = Positive and Negative Syndrome Scale, PCR = polymerase chain reaction, SCZ = Schizophrenia.

Keywords: gene polymorphisms, glutathione S-transferases, oxidative stress, schizophrenia

1. Introduction

Schizophrenia (SCZ) is a chronic disability disorder with a lifetime prevalence estimate of 4 per 1000 individuals in developing countries.[1] SCZ is a complex polygenetic disorder with over 80% heritability.[2] To date, the underlying genetic and molecular mechanisms for SCZ are still not fully understood.

Increasing evidences support that the pathophysiology of SCZ involves oxidative stress.[3,4] Oxidative stress is general related to many disease, including vascular disease,[5] cancer,[6] neurodegenerative diseases,[7] and psychosis.[8] Oxidative stress refers to an increase in reactive oxygen species or a decrease in antioxidant capacity in cells.[4] Granulocyte colony-stimulating factor (G-CSF) is a growth factor that stimulates the proliferation, differentiation, and survival of myeloid hematopoietic cells.[9] More and more evidences show that G-CSF is easy to combine with its receptor through blood–brain barrier, and play a role in mobilizing hematopoietic stem cells and bone marrow mesenchymal stem cells, anti-apoptotic, anti-inflammatory, promoting neuron differentiation and angiogenesis.[10,11] Abnormal oxidative stress parameters in patients with SCZ have been found in blood,[12] platelets,[13] cerebrospinal fluid,[14] and red blood cells.[15]

Glutathione S-transferases (GSTs) are classified as α, μ, ω, π, ☒, and ζ, and they are encoded by *GSTA*, *GSTM*, *GSTO*, *GSTP*, *GSTT*, and *GSTZ* genes, respectively.[16] GSTs are phase II biotransferase, involved in detoxification of various toxicants.[17] GSTT1 (OMIM: 600436) and GSTM1 (OMIM: 138350) have

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Xin Zhang and Jinmei Yang contributed equally to this work.

The study was approved by the Ethics committee of Shandong Mental Health Center. Informed consent was obtained.

There are no potential conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Table 1

Characteristic data of SCZ patients and controls.

Characteristics	SCZ patients (n = 386)	Controls (n = 264)	t/χ^2	P
Age, y*	41.02 ± 5.01	40.65 ± 3.28	1.140	.255
Duration of the illness, y*	14.25 ± 6.01	–		
Age at the onset of the illness, y*	25.51 ± 6.47	–		
Olanzapine equivalents, mg/d*	25.39 ± 14.33	–		
PANSS-positive symptom score*	26.25 ± 4.01			
PANSS-negative symptom score*	29.36 ± 5.01			
PANSS general psychopathology symptom score*	53.00 ± 6.42			
PANSS total score*	108.36 ± 12.64			
Body mass index, kg/m^2	21.26 ± 5.12	21.39 ± 6.33		
Gender, n (%)				
Male	302 (78.24)	197 (74.62)	1.150	.284
Female	84 (21.76)	67 (25.38)		
Marital status, n (%)				
Single	72 (18.65)	59 (22.35)		
Married	229 (59.33)	166 (62.88)	5.705	.058
Divorced	85 (22.02)	39 (14.77)		

PANSS = Positive and Negative Syndrome Scale, SCZ = schizophrenia.
* The data represent mean ± SD.

definite genetic polymorphisms.[18–21] There are studies showing that the frequencies of GSTT1 and GSTM1 genes variants are different among ethnic groups.[22,23] The genotype distributions of GSTT1 genes as well as GSTM1 genes variants in Chinese populations are similar to those of Korean populations,[24,25] but were different from the Europeans, American, and Africans.[26,27]

GSTT1 null genotype and GSTM1 null genotype could lead to complete absence of the enzyme,[28] further increasing the risks of various diseases, such as diabetes,[29] male infertility,[30] hypertension,[31] and some types of cancer.[22–34] To date, many researches have indicated the correlation between SCZ and gene polymorphisms of GSTT1, GSTM1.[35–38] However, the results were inconsistent. We found that there were few studies where the relationship between GSTT1, GSTM1 gene polymorphisms, and SCZ among Chinese people was investigated. Therefore, a case–control designed study, including 386 SCZ patients and 264 healthy individuals, was conducted to explore the relationship between susceptibility to SCZ among Chinese Han population and GSTT1 and GSTM1 polymorphism.

2. Materials and methods

2.1. Subjects

A total of 386 patients with SCZ (SCZ group) and 264 healthy individuals (control group) were included in our study. All subjects were between 18 and 80 years old. The demographic characteristics of the subjects are summarized in Table 1. Three hundred eighty-six SCZ patients were recruited from Shandong Mental Health Center. Diagnosis were assessed by at least 2 psychiatrists according to the Diagnostic and Statistical Manual of mental disorders (DSM)-5 criteria.[39] Moreover, Positive and Negative Syndrome Scale (PANSS) was used to assess the severity of SCZ.[40] These 386 SCZ patients had no other mental disorder, including bipolar disorder (BD), major depression disorder (MDD), substance abuse, or mental retardation. The study was approved by the Ethics committee of Shandong Mental Health Center. Informed consent were obtained from all subjects.

The control individuals were recruited in the same geographic area. They had no history of mental disorder including SCZ, MD, BD, substance abuse. Moreover, those who had a first-degree relative with SCZ were excluded. Their current psychological status and medical history were evaluated through unstructured interview.

2.2. Genotyping of GSTT1 and GSTM1 polymorphisms

For genotyping, 5 mL cubital venous blood was drawn into an ethylenediamine tetraacetic acid (EDTA) tube. Gnomic DNA was isolated from whole blood by DNA extraction kit (Jianlun Biotechnology Co., Ltd, Guangzhou, China; No. JL45852). DNA purity was determined by Epoch microplate spectrophotometer (Bio Tek). In this study, we used multiplex PCR assay to assess the null or presence of GSTT1 and GSTM1 gene null polymorphism. The β-globin gene was used as an internal reference. The amplification reaction was conducted at the final volume of 20 μL, containing 7 μL diethyl pyrocarbonate (DEPC) water, 1 μL DNA, 1 μL primer (10 μmol/L), and 10 μL Taq polymerase master mix (Hengfei Biotechnology Co., Ltd, Shanghai, China; No. PCR-TAQ-MX-1). PCR was done using Veriti Dx Thermal Cycler (ABI). The amplification condition in our study was as follows: introductory denaturation for 300 seconds at 94°C, amplification for 30 cycles, denaturation for 60 seconds at 92°C, annealing at 60°C for 0.5 minutes, and final extension at 72°C for 300 seconds. Electrophoretic amplification of PCR products was performed on 2% agarose gel (Huazhong Haiwei Gene Technology Co., Ltd, Beijing, China; No. S2016) and stained with ethidium bromide (Zhijie Fangyuan Technology Co., Ltd, Beijing, China; No. Amresco 0492). In this study, we took the gel imagings under UV transilluminator (Cleaver, UK). The primer sequences and the sizes of PCR products are summarized in Table 2 and Fig. 1, respectively.

2.3. Statistical analysis

SPSS 19.0 was used for statistical analyses. Comparison between SCZ group and controls group were performed using Student *t*

Table 2

Primer sequencing for GSTT1, GSTM1, and β-globin and amplicon size.

Gene	Forward primer	Reverse primer	bp
GSTT1	5′ - TTCCTTACTGGTCCTCACATCTC - 3′	5′ - TCACCGGATC ATGGCCAGCA - 3′	480
GSTM1	5′ - GAACTCCCTGAAAAGCTAAAGC - 3′	5′ - GTTGGGCTCAAATATACGGTGG - 3′	215
β-globin	5′ - ACACAACTGTGTTCACTAGC - 3′	5′ - CAACTTCATCCACGTTCACC - 3′	113

test and χ^2 test. In order to evaluate the combined effects of GSTT1 and GSTM1, we used logistic regression analysis. All tests in this study were 2-tailed. $P < .05$ was statistically significant.

3. Results

A total of 650 subjects were included in present research. Three hundred eighty-six were patients with SCZ who aged 41.02 ± 5.01 years, and 264 were healthy individuals aged 41.02 ± 5.01 years. There was no statistical difference in demographic data between SCZ patients and healthy individuals ($P > .05$).

In our study, Hardy–Weinberg test was not performed to GSTT1 and GSTM1 genotypes, due to that multiplex PCR assay could not distinguish the heterozygous presence of the allele (null/presence) from the homozygous presence. Nevertheless, the distributions of GSTT1-null and GSTM1-null polymorphism in our study were not different from the previous studies in Chinese Han population.[41–43]

Genotype frequencies of SCZ patients and healthy individuals are summarized in Table 3. The frequencies of GSTM1 null genotype were 53.89% and 56.82% for SCZ patients and healthy individuals, respectively. The frequencies of GSTT1 null genotype were 45.60% and 50.38% for SCZ patients and healthy individuals, respectively. The GSTT1 null polymorphism showed a reduced risk of SCZ ($P = .031$). However, the GSTM1 null genotype tended to reduce the risk of SCZ, but there was no significant difference ($P = .197$). Furthermore, we found that 24.09% of SCZ patients and 29.55% of healthy individuals carried both null genotypes of *GSTT1* and *GSTM1* genes, which reduced the risk of SCZ ($P = .028$).

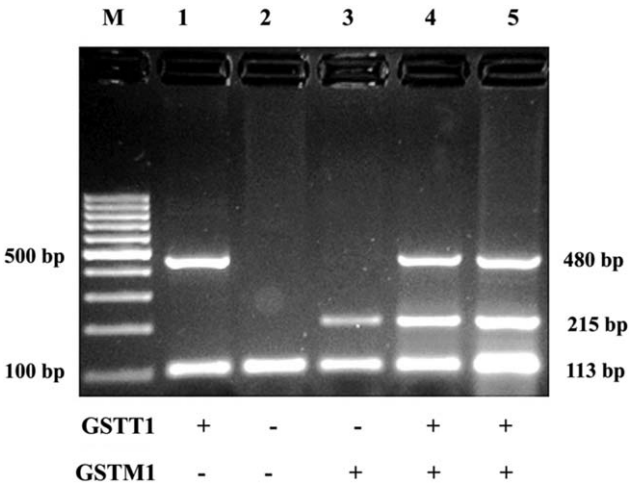

Figure 1. Genotyping of GSTT1, GSTM1, and β-globin polymorphisms. There are 4 types of genotype showed as null genotypes of GSTT1 (–) and GSTM1 (–) and functional GSTT1 (+) and GSTM1 (+).

We found no association between PANSS score and GSTM1, GSST1 genotypes in SCZ patients (Table 4).

4. Discussion

SCZ is a complex polygenetic disorder. Increasing evidences support that the pathophysiology of SCZ involves oxidative stress.[3,4] The relationship between GST gene polymorphism and SCZ susceptibility had been studied in many previous studies, but the results were inconclusive. GSTT1 (OMIM: 600436) and GSTM1 (OMIM: 138350) have definite genetic polymorphisms.[18–21] In our research, we evaluated the relationship between SCZ susceptibility and polymorphism of GSTT1 and GSTM1. Our research is first to explore the relationship between these 2 genetic polymorphisms and SCZ in Chinese Han population. We found that GSTT1 null polymorphism may be related to reduce the risk of SCZ in Chinese people. Furthermore, when GST1 null polymorphisms and GSTM1 null polymorphisms are combined, the risk of SCZ was decreased.

Our results indicated that GSTT1 active genotype was associated with SCZ. Previous study has shown that GSTT1 gene maps on region 2qq11.2, and this gene is associated with susceptibility to SCZ by genome scanning analysis.[44] Moreover, several reports showed that *GSTT1* gene increased the risk of certain types of cancer.[32–34,45] However, there is not a common rule, the disease protection effect of GSTT1 null genotype has also been found.[29,46] GSTT1 is associated with the metabolism of detoxification. In mammals, the empty genotype encoding GSTT1 protein leads to a lack of active protein,[47] reduces the detoxification ability of specific substrate induced by oxidative stress damage, and increases sensitivity to oxidative DNA damage.[48] Previous studies have also found that SCZ patients had a higher proportion of GSTT1 enzymes than healthy individuals.[44] The fact that GSTT1 active genotype is a risk factor for SCZ has been confirmed in many previous studies.[35,37,49] In this study, the null genotype proportion of GSTT1 were 45.60% and 50.38% for SCZ patients and healthy individuals, respectively. The results indicated that GSTT1 could be a candidate gene for predisposing to SCZ in Chinese Han population. The results of our study are supported by Raffa et al,[37] and they suggested that GSTT1 null genotype might decrease the risk of SCZ in Tunisian. However, Pejovic-Milovancevic et al[35] and Matsuzawa et al[50] have demonstrated that GSTT1 polymorphism is not associated with susceptibility to SCZ independently.

GSTM1 gene has also been emphasized in genetic epidemiologic studies in SCZ patients. GSTM1 null genotype is the result of a 1500 base pairs deletion. Previous study indicated that GSTM1 null genotype resulted in a complete lack of GSTM1 activity.[51] Thus, GSTM1 null genotype could lead to the decrease of oxidative stress. Present study showed that GSTM1 null genotype in SCZ patients and healthy individuals was 53.89% and 56.82%, respectively, although there was no

Table 3

Genotype distribution of GSTM1 and GSTT1 in SCZ patients and controls.

Genotype	SCZ patients (n, %)	Controls (n, %)	OR	95% CI	*P*
GSTT1					
Present (+)	210 (54.40)	131 (49.62)	1 (reference)	0.412–0.986	.031
Null (−)	176 (45.60)	133 (50.38)	0.601		
GSTM1					
Present (+)	178 (46.11)	114 (43.18)	1 (reference)	0.513–1.167	.197
Null (−)	208 (53.89)	150 (56.82)	0.781		
GSTT1/GSTM1					
(+/+)	95 (24.61)	59 (22.35)	1 (reference)	–	–
(−/−)	93 (24.09)	78 (29.55)	0.452	0.238–0.845	.028
(+/−)	115 (29.79)	72 (27.27)	0.742	0.421–1.322	.310
(−/+)	83 (21.50)	55 (20.83)	0.653	0.384–1.296	.158

95% CI = 95% confidence interval, GST = glutathione S-transferases, OR = odds ratio, SCZ = schizophrenia.

Table 4

PANSS score (mean ± SD) according to GSTM1 and GSST1 genotypes in SCZ patients.

PANSS scale	Present (+)	Null (+)	*t*	*P*
GSTT1	n = 210	n = 176		
PANSS-positive symptom score	26.10 ± 5.36	26.35 ± 4.05	0.521	.603
PANSS-negative symptom score	30.26 ± 5.52	28.99 ± 7.87	1.789	.075
PANSS general psychopathology symptom score	54.36 ± 8.36	53.63 ± 13.23	0.634	.527
PANSS total score	108.36 ± 15.36	109.21 ± 16.35	0.523	.601
GSTM1	n = 178	n = 208		
PANSS-positive symptom score	27.69 ± 5.29	26.31 ± 8.96	1.872	.062
PANSS-negative symptom score	30.59 ± 8.02	29.67 ± 7.98	1.126	.261
PANSS general psychopathology symptom score	54.39 ± 8.35	53.04 ± 7.27	1.679	.094
PANSS total score	108.39 ± 17.95	109.37 ± 20.22	0.010	.992

GST = glutathione S-transferases, PANSS = Positive and Negative Syndrome Scale.

statistical difference between the 2 groups. However, Harada et al[52] found that GSTM1 null genotype was more present in disorganized-subtype schizophrenia individuals than normal individuals.

Previous study of combined effects of GSTM1 genotypes and GSTT1 genotypes was still inconsistent. This present study showed that combined GSTM1-null/GSTT1-null genotypes may reduce the susceptibility to SCZ in Chinese Han population. However, most previous studies found that the combination of GSTT1 and GSTM1 polymorphisms (null or presence) was not related to SCZ.[36–38,50] These discrepancies may be due to the sample size of study and ethnicity.

We also studied the relationship between SCZ severity and GSTM1 polymorphisms as well as GSTT1 polymorphisms. However, Student *t* test showed that there was no association between PANSS score and GSTM1 genotypes as well as GSST1 genotypes in SCZ patients. Raffa et al[37] found that there was no significant correlation between GSTM1 polymorphisms, GSTT1 polymorphisms, and SCZ subtypes (Undifferentiated, Paranoid, Disorganized). These results indicated that GSTM1 polymorphisms and GSTT1 polymorphisms may only be associated with the susceptibility to SCZ, but not with severity and type.

The advantage of our study lies in its comparatively large sample size as well as genetic homogeneity of the subjects. The limitation of our research is that GST enzyme activity has not been measured. Therefore, there is no direct evidence that GSTT1 and GSTM1 polymorphisms alter enzyme activity. Besides, we did not examine whether treatment response and prognosis are associated with gene polymorphism.

SCZ is a complex polygenetic disorder. Here, we demonstrated that GSTT1 null polymorphisms may be related to decrease the risk of SCZ in Chinese Han population, and that the risk was further reducing with the combination of both GSTT1 null polymorphisms and GSTM1 null polymorphisms. The relationship between these 2 gene polymorphisms and drug response and disease prognosis needs to be further explored in the future.

Author contributions

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