

Effects of *GSTA1* and *GPX3* Polymorphisms on the Risk of Schizophrenia in Chinese Han Population

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Purpose: Several lines of evidence support the fact that the presence of oxidative stress plays an important role in the pathophysiological mechanisms of schizophrenia (SCZ). The glutathione peroxidases (GPXs) and glutathione S-transferases (GSTs) are the major anti-oxidant enzymes. Polymorphic variants of *GPX* and *GST* can affect the antioxidant activities of their encoded enzymes. This study explored the possible associations of the *GSTA1* and *GPX3* gene polymorphisms and schizophrenia in Chinese Han population.

Methods: DNA from 648 healthy controls and 617 schizophrenic patients was genotyped for single-nucleotide polymorphisms (SNPs) rs3957357 in *GSTA1* and rs736775 in *GPX3* using a PCR-LDR genotyping assay. The χ^2 test compared differences in genetic distributions between the two groups in a case-control study. The generalized multifactor dimensionality reduction (GMDR) was used to explore the interaction between the *GSTA1* gene and the *GPX3* gene on the risk of SCZ.

Results: Significant differences in allelic and genotypic frequencies of *GSTA1* rs3957357 were present between SCZ and control groups (*GSTA1* rs3957357 $\chi^2=6.172$, $P=0.046$ by genotype, $\chi^2=5.847$, $P=0.016$, odds ratio=1.329, 95% confidence interval=1.055–1.674 by allele). No significant differences in allelic or genotypic frequencies of *GPX3* rs736775 were detected between cases and controls (*GPX3* rs736775: $\chi^2=2.058$, $P=0.357$ by genotype, $\chi^2=1.853$, $P=0.173$, odds ratio=1.131, 95% confidence interval=0.953–1.342 by allele). Moreover, the GMDR model showed that the interaction between *GSTA1* rs3957357 and *GPX3* rs736775 was associated significantly with SCZ risk, $P=0.0107$.

Conclusion: Our results suggest that *GSTA1* rs3957357 SNP has an effect on the risk of SCZ and the interaction between *GSTA1* rs3957357 and *GPX3* rs736775 may affect the development of SCZ in Chinese Han population. However, these results should be validated by replication in different populations with large sample sizes.

Keywords: oxidative stress, schizophrenia, glutathione peroxidase, glutathione S-transferase, gene polymorphism

Introduction

Schizophrenia (SCZ) is a complex and severe mental disorder and is the most common among psychotic illness, with a prevalence of around 1% in the worldwide population.^{1–3} Although the detailed mechanisms underlying the pathophysiology of SCZ is unknown for certain, multiple pieces of evidence illustrated that a complex interaction between genetic background and environmental factors was likely to be involved in the development of SCZ.^{4,5}

Dopamine (DA) is the principal neurotransmitter in the brain and plays a significant role in the functions of neurons. However, the oxidative metabolites of dopamine are hydrogen peroxide (H₂O₂) and DA quinones, which are the principal

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source of reactive oxygen species (ROS) in the brain.⁶ Oxidative stress arises when the balance between antioxidant activity and the formation of ROS is disrupted, and ROS can cause neuronal inflammation as a consequence of oxidative stress. Interestingly, several studies suggested that neuronal inflammation induced by oxidative stress plays an important role in SCZ pathophysiological mechanisms.^{7–9}

Recently, glutathione (GSH) levels were reported to be decreased in the cerebrospinal fluid and in the prefrontal cortex of SCZ patients.^{10–12} Furthermore, some studies showed changes in antioxidant enzyme activity in the plasma and postmortem brain of schizophrenia patients.^{7,13} Taking all these factors into consideration, we had to focus our attention on the role of oxidative stress in the pathophysiology of SCZ through investigating two important antioxidant enzymes: glutathione peroxidases (GPXs) and glutathione S-transferases (GSTs).

GPX family belongs to selenium-dependent peroxidases and plays an important role in protecting cells from oxidative damage by reducing free hydrogen peroxide to water. The GPX3, a member of GPX family, was found to be highly expressed in the prefrontal cortex suggests that *GPX3* may be involved in antioxidant activity in the brain.¹⁴ Human *GPX3* is located on chromosome 5q33.1 and has a common single-nucleotide polymorphism (SNP), *GPX3* rs736775. Several studies have suggested the effect of this variant on GPX3 activity and many disorders.^{15–18}

GSTs consist of Phase II detoxication enzyme and can catalyze the conjugation of the reduced form of glutathione (GSH) to xenobiotic substrates for the purpose of detoxification.¹⁹ The GST alpha, a member of GSTs family, is located in chromosome 6 and shows an important detoxifying activity that protects the cell from ROS. GST alpha 1 (*GSTA1*) represents one of the most abundant alpha-class GST isoenzymes. In addition, *GSTA1* can also inactivate quinones.²⁰ SNP rs3957357 in *GSTA1* is just located in the promoter region of *GSTA1* genes, and several studies suggested the pathogenic effects of this variant in many disorders.^{21,22}

Although polymorphic variants of oxidative stress-related candidate genes including *GSTP1*, *GSTT1*, *GSTM1*, *GPX1* and *GSTA1* have been shown to be risk factors for SCZ,^{23–25} genetic polymorphism vary by race considerably and we, therefore, estimated the possible associations of the *GSTA1* rs3957357 and *GPX3* rs736775 gene polymorphisms and schizophrenia in the Chinese Han population for the

purpose of identifying potential prognostic or predictive tools for the individuals at risk of SCZ.

Methods

Subjects

The study was approved by the Ethical Committees of Jining Medical University (2018-YX-005, 2018.02–2023.12) in accordance with the Code of Ethics of the Declaration of Helsinki. The participants were recruited from the Rizhao Mental Health Center and Affiliated Hospital of Jining Medical University and they were original northern Han Chinese individuals. The sample consisted of 617 patients with SCZ (301 men and 316 women, mean age 48.2 ± 4.8 years) and 648 healthy controls (312 men and 336 women, mean age: 47.9 ± 4.6 years) living in the same geographic area. The patients with SCZ were interviewed by two board-certified psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) criteria. The normal controls were confirmed to be free from any mental illness by two board-certified psychiatrists. All participants gave written informed consent to participate in the study.

Genetic Studies

Total genomic DNA was extracted from whole blood using TIANamp Genomic DNA Kit (TIANGEN, China), according to the manufacturer's instructions. Genotyping for SNPs *GSTA1* rs3957357 and *GPX3* rs736775 was performed using the polymerase chain reaction-ligase detection reaction (PCR-LDR) method. The sequences of primers are listed in Table 1. PCR was performed in a volume of 15 μ L reaction system, containing 7.5 μ L 2 \times PCR Master Mix, 2 μ L Primer mix, and 2 μ L genomic DNA and DNase-free water. Multiplex PCR amplifications were performed under the following conditions: an initial denaturation at 94°C for 3mins, followed by 35 cycles at 94°C for 30s, 55°C for 30s, 7°C for 30s, and a terminal extension 72°C for 3mins. After multiplex PCR amplification, the LDR was performed

Table 1 The Information of Primer of *GPX3* rs736775 and *GSTA1* rs3957357 Polymorphism

Primer Name	Sequence (5'-3')	PCR Length
rs736775	F:TAAACCCAAGTCCCCTGAGT R:CTCTTGAGTAATGGTGACGTATCA	96bp
rs3957357	F:ACAACTGAATCCAGGTCCTAATG R:GCCATGAAATGTGTGGGAGT	114bp

in a volume of 10 μ L reaction system, including 3 μ L PCR product, 1 μ L 10 \times Taq DNA ligase buffer, 0.125 μ L Taq DNA ligase (40 U/ μ L), 2 μ L Probe mix, and ddH₂O, followed by 30 cycles at 94°C for 30s, 56°C for 3mins. The sequences of probes are listed in Table 2. Hence, the final reaction system containing 1 μ L LDR product and 9 μ L highly deionized formamide were performed under denaturation at 95°C for 3mins, and the genotypes were analyzed by ABI 3730XL sequencer and Genemapper software.

Statistical Analysis

The χ^2 test was used to test the Hardy–Weinberg equilibrium (HWE) of the genotype distribution and to compare the differences in genotypic and allelic frequencies of *GSTA1* rs3957357 and *GPX3* rs736775 between cases and controls. The degree of relative risk was estimated by odds ratios (ORs) and 95% confidence intervals (CIs). Statistical analysis in this study was carried out using the Statistical Package (version 21.0 for Windows; SPSS Inc., Chicago, Illinois, USA). Generalized multifactor dimensionality reduction (GMDR Software 0.9, <http://www.ssg.uab.edu/gmdr/>) analysis was used to explore the interaction between the *GSTA1* gene and the *GPX3* gene on the risk of SCZ.²⁶ The values of testing accuracy, sign test (*P*)

and the cross-validation (CV) consistency score were provided by GMDR analysis. *P*<0.05 was considered to denote statistical significance.

Results

The genotype distributions of the two tested alleles were in accordance with Hardy–Weinberg equilibrium (for rs736775, *P*=0.17; rs3957357, *P*=0.08). The allelic and genotypic frequencies of *GPX3* rs736775 and *GSTA1* rs3957357 in SCZ and control groups are shown in Table 3. Significant differences in allelic and genotypic frequencies of *GSTA1* rs3957357 were observed between schizophrenic and control groups. (*GSTA1* rs3957357: $\chi^2=6.172$, *P*=0.046 by genotype, $\chi^2=5.847$, *P*=0.016, odds ratio=1.329, 95% confidence interval=1.055–1.674 by allele.) No significant differences in allelic or genotypic frequencies of *GPX3* rs736775 were found between schizophrenic and control groups. (*GPX3* rs736775: $\chi^2=2.058$, *P*=0.357 by genotype, $\chi^2=1.853$, *P*=0.173, odds ratio=1.131, 95% confidence interval=0.953–1.342 by allele.) Furthermore, additive, dominant and recessive genetic models were used to analyze genotype frequencies of *GSTA1* rs3957357 and *GPX3* rs736775. Table 4 shows that rs3957357 was the risk factor for SCZ on the basis of

Table 2 The Information of Probe of *GPX3* rs736775 and *GSTA1* rs3957357 Polymorphism

Probe Name	Sequence (5'-3')	LDR Length
Rs736775_modify	P- TGCCCTACCCTCAGGGAGGCCTGAC-FAM	
rs736775_C	CCTAGGCTCCTCCACTGCCCCGGC	50
rs736775_T	CTGCCTAGGCTCCTCCACTGCCCCGGT	53
Rs3957357_modify	P- GTCAAGTTAGGGAAAAGCCCTGACTGAC -FAM	
rs3957357_A	CTGAATAGTTCTCTCCACTGAAAGAAGA	57
rs3957357_G	CTGACTGATAGTTCTCTCCACTGAAAGAAGG	60

Table 3 The Comparison of Genotypic and Allelic Frequencies Between SCZ and Control Groups

SNP	Allelic Test					Genotypic Test			
	Allele	SCZ/Control	P	χ^2	OR(95% CI)	Genotype	SCZ/Control	P	χ^2
rs3957357	G	1050/1145	0.016	5.847	1.329 (1.055–1.674)	GG	442/503	0.046	6.172
	A	184/151				AG	166/139		
rs736775	T	857/933	0.173	1.853	1.131 (0.953–1.342)	TT	292/331	0.357	2.058
	C	377/363				CT	273/271		
						CC	52/46		

Table 4 Analysis of the Two SNPs Based on Three Genetic Models

SNP	Genotype	SCZ/Control	Additive Model		Dominant Model		Recessive Model	
			P	OR(95% CI)	P	OR(95% CI)	P	OR(95% CI)
rs3957357	GG AG AA	442/503 166/139 9/6	0.31	0.59 (0.21–1.66)	0.01	0.73 (0.56–0.94)	0.38	0.63 (0.22–1.78)
rs736775	TT CT CC	292/331 273/271 52/46	0.25	0.78 (0.51–1.20)	0.18	0.86 (0.69–1.07)	0.38	0.83 (0.55–1.26)

dominant models ($P = 0.01$) and rs736775 was not the risk factor for SCZ on the basis of these models (all $P > 0.05$).

In addition, the interaction between GSTA1 (rs3957357) and GPX3 (rs736775) was analyzed using GMDR software, with testing accuracy of 0.5330, CV consistency of 10/10, and $P=0.0107$. The results showed that the potential gene–gene interaction between GSTA1 and GPX3 was associated with SCZ risk.

Discussion

It is well known that the oxygen consumption of the brain is the highest in our body and hence generation of ROS increase. Moreover, the oxidative metabolites of dopamine are hydrogen peroxide (H_2O_2) and DA quinones, which are the principal source of ROS in the brain.⁶ Therefore, the brain is considered particularly vulnerable to ROS. Normally, ROS can be eliminated by the antioxidant system. When the balance between the formation of ROS and intrinsic antioxidant capacity is upset, oxidative metabolite damage to neurons arises. Increasing evidence indicates that oxidative injury to neurons can play important roles in the pathophysiology of neuropsychiatric disorders including schizophrenia.^{7,8,9}

The antioxidant system comprises of enzymatic and nonenzymatic antioxidants, and enzymes involved in the antioxidant systems comprise of glutathione peroxidase (GPx), glutathione S transferase (GST), and so on. Polymorphic variants of GPX and GST may affect their antioxidant activities, contributing to the imbalance of ROS production and antioxidant capacity in SCZ patients.^{23,24,27}

GPXs are encoded by the GPX gene family and consist of eight groups, GPX1–8. The GPX3, a member of the GPX family, was found to be highly expressed in the prefrontal cortex suggests that GPX may be involved in antioxidant activity in the brain. The human GPX3 gene is located on chromosome 5q33.1 and multiple GPX3 SNPs

have been reported, with rs736775 being one of the most common. For instance, Noci et al demonstrated that GPX3 rs736775 was associated with overall survival in colorectal cancer patients.¹⁶ Zhang et al also suggested that GPX3 rs736775 was a prognostic marker in patients with gastric cancer.¹⁷ Another study showed that the increased risk for cardiovascular toxicity among patients was associated with GPX3 rs736775.²⁸ Taking these results into consideration, GPX3 rs736775 might contribute to the altered antioxidant capacity in SCZ patients. In this study, we compared allelic and genotypic frequencies of rs736775 between 617 SCZ patients and 648 controls. However, we observed a TT genotype frequency of 47.32%, a CT genotype frequency of 44.25%, and a CC genotype frequency of 8.43% for patients with SCZ, compared with 51.08%, 41.82%, and 7.10%, respectively, in controls. No significant differences in allelic or genotypic frequencies of GPX3 rs736775 were observed between SCZ patients and controls in our study. This finding suggests that the GPX3 rs736775 polymorphism may not be the genetic risk factor for SCZ patients.

GSTs are encoded by the GST family of genes located on different chromosomes and the cytosolic GST can be classified into four major groups: Alpha, Mu, Pi, and Theta. The GST Alpha (GSTA) family is located in chromosome 6 and shows an important detoxifying activity that protects the cell from ROS. The GSTA1 rs3957357 is one of the five polymorphisms just located in the promoter region of GSTA1 genes, and its mutant genotype can result in decreased enzyme activity. In recent years, GSTA1 rs3957357 has been reported to be associated with many disorders including bladder cancer, leukemia and gestational hypertension, as well as SCZ. For instance, Rossi et al reported that GSTA1 rs3957357 may associate with event-free survival in patients with diffuse large B-cell lymphoma.²¹ Iorio et al suggested that the GSTA1 rs3957357 was significantly associated with

gestational hypertension risk.²⁹ However, we are intrigued by the effects of *GSTA1* polymorphisms on the risk of SCZ. Gravina et al found a higher frequency of the combined genotypes including *GSTA1* polymorphisms in Italy patients with SCZ.²³ Spalletta et al suggested that *GSTA1* polymorphisms were associated with the altered microstructure of the thalami in Italy patients with SCZ.²⁴ Because of several factors, such as population and sample, it is necessary to test the gene polymorphisms on the risk of some disorders, we sought to analyze the Chinese Han population in the present study. We found GG, AG and AA genotype frequencies of 71.64%, 26.90%, and 1.46% in patients with SCZ, compared with 77.62%, 21.45%, and 0.93%, respectively, in controls. Consequently, significant differences in allelic and genotypic frequencies of *GSTA1* rs3957357 were detected between SCZ patients and controls. Furthermore, rs3957357 was the risk factor for SCZ on the basis of dominant models. *GSTA1* rs3957357 appears to be a potential predictive tool for the Chinese population at risk of SCZ.

In addition, several published studies have shown that gene–gene (G–G) interactions can play important roles in the pathophysiological mechanisms of many complex diseases.^{30–32} In present study, the interaction between the *GSTA1* gene and the *GPX3* gene was analyzed using GMDR software,²⁶ with CV consistency of 10/10 and a *p* value of 0.0107. The results showed that the potential gene–gene interaction between *GSTA1* and *GPX3* was the genetic risk factor for SCZ patients.

Conclusion

In conclusion, this is the first report to investigate the effects of *GPX3* and *GSTA1* SNPs in SCZ in a Chinese population. Our results suggest that *GSTA1* rs3957357 SNP and the interaction between *GSTA1* (rs3957357) and *GPX3* (rs736775) have effects on the risk of SCZ and they are potential predictive tools for Chinese population at risk of SCZ. However, most subjects were Han nationality in the Shandong region in our study and the sample size is relatively small, and larger-scale studies are necessary to validate these findings.

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Disclosure

The authors report no conflicts of interest in this work.

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