

Association Between Glutathione Peroxidase-I (GPx-I) Polymorphisms and Schizophrenia in the Chinese Han Population

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Objective: The dopamine and oxidative stress hypotheses are leading theories of the pathoetiology of schizophrenia (SCZ). Glutathione Peroxidase 1 (GPx-1), a major antioxidant enzyme, and the most abundantly expressed member of the GPx family, plays an important role in metabolic dopamine changes, which are closely related to neurological and psychiatric disorders. The impact of GPx-1 polymorphisms has rarely been explored in the field of SCZ. Here, we explored the possible relationship between GPx-1 gene polymorphisms and SCZ in Chinese Han subjects by using the polymerase chain reaction-restriction fragment length polymorphism method.

Methods: DNA from 786 patients (360 patients with schizophrenia and 426 healthy controls) was genotyped for the single-nucleotide polymorphisms rs1800668 C/T and rs1050450 C/T in GPx-1 using polymerase chain reaction-restriction fragment length polymorphism analysis. Analysis of the association between GPx-1 and SCZ was performed using SPSS 22.0, while Haploview 4.2 software and SHEsis software were used to perform linkage disequilibrium analysis and haplotype analysis.

Results: The results indicated that the GPx-1 polymorphisms rs1050450 and rs1800668 were associated with SCZ. We found that the C-allele of rs1800668 C/T may be a protection factor against SCZ in general, but in particular, for males. Furthermore, the CT and TC (GPx-1 rs1800668 C/T and rs1050450 C/T) haplotypes may be susceptible to SCZ in the population. Finally, no significant differences in allelic or genotypic frequencies of rs1050450 were detected between cases and controls from whole or stratification analyses by gender.

Conclusion: GPx-1 polymorphisms are related to SCZ in Chinese Han subjects. Our results suggested that GPx-1 may be a potential gene that influences SCZ.

Keywords: case-control study, Chinese Han population, GPx1, polymorphism, schizophrenia

Introduction

Schizophrenia (SCZ) is a disabling and severe mental illness, which usually manifests in early adulthood and is clinically characterized by sensory, mental, emotional and behavioral disorders. Studies have shown that the lifetime prevalence of SCZ is about 1%, although the incidence of SCZ is increasing year by year.¹⁻³ The etiology and pathophysiology of SCZ, however, are not clear, and it is acknowledged that they are almost certainly multifactorial and comprehensive. A multitude of evidence has shown that genetic factors,⁴ disturbances in various neurotransmitters (eg, dopamine [DA], glutamine, serotonin),⁵ neuroanatomical structure changes,⁶ and psychosocial factors⁷ all increase the risk of SCZ.

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The DA hypothesis,⁸ which proposes excessive dopaminergic activity in the mesolimbic pathway results in the increased likelihood of SCZ, has been illustrated by the onset of psychosis induced by excessive amphetamine (which causes the release of DA).⁹ As a result, pharmacologists have been developing DA receptor blockade use for use as antipsychotic drugs.¹⁰ Several studies have used meta-analysis, a powerful tool to summarize contradicting results from different studies, to show that genetic variants of the dopamine D2 receptor gene and dopamine D4 receptor gene play major roles in etiology of SCZ.^{11–13}

Glutathione peroxidase (GPx) is a key reactive oxygen species (ROS) scavenger¹⁴ that combines with catalase (CAT) and superoxide dismutase (SOD) to form an antioxidant defense system.¹⁵ GPx utilizes a reducing agent to eliminate hydrogen peroxide and lipid peroxides, preventing peroxidative damage to the cell membrane and other organelles by regulating glutathione (GSH).^{16,17} GPx is responsible for recycling GSH¹⁸ as well as regulating GSH regeneration.¹⁹ GSH is an electron donor in the redox process of GPx.²⁰ GPx-1 is the most widely distributed enzyme of the five GPx homologues, and is especially abundant in vascular endothelial cells.²¹ The GPx-1 locus is located on chromosome 3p21.3²² and contains two exons and one intron.²³

There is considerable evidence that GPx has a strong association with some diseases, many with links to the DA system.^{24–28} In fact, DA is a major source of ROS in the central nervous system, as it can produce ROS and DA-quinone during its autooxidation.²⁹ GPx is expressed in neurons and glial cells and is involved in the endogenous response to central nervous system oxidative stress as a key enzyme in the antioxidant system¹⁸ in the brain. Mice deficient in GPx-1 were particularly susceptible to 6-hydroxydopamine injury, which is a hydroxylated derivative of dopamine.³⁰ Meanwhile, both in vitro and in vivo, GPx-1 can protect against and attenuate 6-hydroxydopamine toxicity in dopaminergic neurons.³¹ GPx is also closely related to neurological and psychiatric disorders. Studies have found that in Alzheimer's disease (AD), degeneration of the central cholinergic system and free radical metabolism are gradually aggravated, and that SOD and GPx activities in the hippocampus, which are closely related to the DA system, are significantly decreased over time.³² It has also been reported in animal experiments that the activities of GPx and reductase in AD-related APP/PS-1 mice treated with antioxidants before induced oxidation were higher than those in

controls. Antioxidant treatment was able to significantly reduce oxidative stress and improve the cognitive impairment AD model mice.³³ Studies have shown that in Parkinson's disease (PD) patients, GSH loss occurs in the cell bodies and dendritic processes of dopaminergic nigral neurons,³⁴ and total PD GSH is selectively exhausted in the early stages of PD.^{35,36}

Many studies have shown that GPx plays an important role in the pathophysiology of SCZ. One study found that GPx activity in patients with SCZ was lower than in healthy controls.³⁷ Vincent et al reported that low GSH and ascorbic acid levels in the brain are associated with dopaminergic system disorders, which are implicated in the development and progression of cognitive impairment in SCZ.³⁸ Buckman et al found that brain atrophy measured after head computerized tomography scans in patients with chronic SCZ was negatively correlated with GSH-px activity in platelets, which was more significant in patients with SCZ with negative symptoms as the core clinical manifestation.³⁹

Currently, a tremendous amount of domestic and foreign scientific research have proven that GPx-1 polymorphisms are associated with different diseases, such as coronary artery disease,²² cancer,^{40–45} diabetes and its vascular complications,⁴⁶ rheumatoid arthritis,⁴⁷ Huntington's disease,⁴⁸ PD,^{26,49} autism,⁵⁰ and postpartum hemorrhage.⁵¹ However, research into the involvement of GPx-1 in SCZ is lacking.

This study detected GPx-1 polymorphisms by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method, and explored whether there was a correlation between GPx-1 polymorphisms and SCZ in the Chinese Han population.

Materials and Methods

Patients and Controls

SCZ was confirmed in 360 subjects (male = 196, female = 164) with a mean age of 36.81 ± 10.75 years according to Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) (American Psychiatric Association, 2004) criteria and confirmed independently by two senior psychiatrists based on a structured interview and medical records. All subjects were recruited from six hospitals in Liaoning Province, China. We also recruited 426 healthy Chinese Han subjects (male = 203, female = 223) with a mean age of 36.16 ± 8.89 years, who were without any mental disorders or neurological or physical diseases as controls.

All subjects underwent a complete interview to exclude psychiatric disorders.

Principles of Ethical Review

This study was based on the Declaration of Helsinki. All volunteers were informed of the experimental method, objective, experimental benefits, risks, and their rights prior to signing informed consent. This study was approved by the Ethics Committee of China Medical University (Shenyang, Liaoning, China).

Polymorphism Genotyping

In this case-control study, rs1800668 and rs1050450 were selected based on a vast multitude of literature. For genomic DNA isolation, 2 mL of EDTA-treated blood from each volunteer was taken for DNA isolation using a DNA extraction kit (Wizard Genomic DNA purification kit, Thermo Fisher Scientific, Waltham, MA, USA). Detection of two single nucleotide polymorphisms, including rs1800668 and rs1050450, were performed by a PCR-based amplification strategy. RFLP analysis was carried out using the restriction enzymes HpyCH4III and BlnI (New England Biolabs, Ipswich, MA, USA). PCR primers were assembled by a local representative of Takara Biotechnology (Dalian, China). The forward primer 5'-CAGCCTCCTATGCCAAACC-3' and reverse primer 5'-GCTCGTTCATCTGGGTGTAGTC-3' were used to amplify rs1800668; the forward primer 5'-CTCCCTTGTGGTTAG-3' and reverse primer 5'-CCTCCCTCGTAGTTT-3' were used to amplify rs1050450. PCR reaction conditions included 5 min denaturation (94 °C), 30 s denaturation (94 °C, 30 cycles), 30 s annealing (62.4 °C for rs1800668 and 55 °C for rs1050450), 30 cycles of elongation for 1 min (72 °C), and a 10 min elongation (72 °C). The sizes of PCR products were 561 bp (rs1800668) and 529 bp (rs1050450). A 2% agarose gel was used to resolve PCR products and digested products. The lengths of restriction digest products were 330/231 bp for rs1800668 C/T, and 419/110 bp for rs1050450 C/T polymorphisms. The 561 bp PCR product for rs1800668 was cleaved into two fragments of 330 bp and 231 bp for the CC homozygote and three fragments of 561 bp, 330 and 231 bp were generated for the CT heterozygote, while an uncleaved PCR product of 561 bp was generated for the TT homozygote. For rs1050450, two fragments of 419 bp and 110 bp were generated for the CC homozygote and three fragments of 529 bp, 419 and 110 bp were generated

for the CT heterozygote, while an uncleaved PCR product of 529 bp was generated for the TT homozygote.

Statistical Analysis

The research data involved in this experiment are expressed using frequency, percentage, and mean \pm standard deviation (SD). The chi-square test or Fisher's exact test were used to analyze the frequency of allele and genotype in patients and controls. All tests, including the odds ratio (OR) and 95% confidence interval (CI) were performed using SPSS v23.0 for windows (SPSS Inc., Chicago, IL, USA). Haploview 4.2 software (<https://www.broadinstitute.org/haploview/haploview>) and SHEsis software (<http://analysis.bio-x.cn>) were used to perform linkage disequilibrium and haplotype analysis. *P*-values <0.05 were defined as statistically significant.

Results

Genotype Analysis

Rs1800668 and rs1050450 were genotyped by PCR-RFLP in this study. Agarose gels demonstrating homozygotes and heterozygotes for both SNPs are shown in [Supplementary Figure S1](#) and [Supplementary Figure S2](#).

Hardy–Weinberg Equilibrium

[Table 1](#) describes the results for Hardy–Weinberg equilibrium estimations along with genotype and allele frequencies. These data indicated that the two selected single nucleotide polymorphisms (SNPs; rs1800668 and rs1050450) were in accordance with the genetic balance of Hardy–Weinberg equilibrium; thus, the selected samples were representative of the population.

Association Between GPx-1 Polymorphisms and SCZ

[Table 2](#) describes the genotype and allele distributions of the GPx-1 polymorphism (rs1800668) in the SCZ group and controls. There were significant associations in rs1800668 polymorphism genotype between the SCZ group and controls ($X^2 = 6.120$, $P = 0.013$). There were significant differences in the frequency of the allele ($X^2 = 4.065$, $P = 0.044$). We found that the C-allele of rs1800668 C/T may be a protective factor for SCZ (OR = 0.716, CI: 0.517–0.992). The frequency of GPx-1 rs1800668 in dominant and recessive models was then analyzed. The results showed that there was a significant difference in GPx1 rs1800668 in dominant models between the SCZ group and controls

Table 1 Genotype Frequencies of GPx-1 Rs1800668 and Rs1050450

SNP	Genotype	Observed N (%)	Expected N	χ^2	P value
rs1800668	TT	4(0.94%)	2.184	1.753	0.186
	CT	53(12.44%)	56.633		
	CC	369(86.62%)	367.184		
rs1050450	TT	4(0.94%)	2.479	1.093	0.296
	CT	57(13.38%)	60.041		
	CC	365(85.68%)	363.479		

Table 2 Genotype and Allele Distributions of Rs1800668 in the SCZ Group and Controls

SNP	Case, n (%)	Controls, n (%)	χ^2	P	OR	CI
rs1800668	CC	290(80.6)	369(86.6)	6.120	0.013*	1.633
	CT	68(18.9)	53(12.4)			
	TT	2 (0.6)	4(0.9)			
Allele	C	648(90.5)	791(92.8)	4.065	0.044*	0.716
	T	72(9.5)	61(7.2)			
Dominant Model	CC	290(80.6)	369(86.6)	5.296	0.021*	0.930
	CT+TT	70(19.4)	57(13.4)			
Recessive Model	TT	2 (0.6)	4 (0.9)	0.379	0.693	0.589
	CT+CC	358(99.4)	422(99.1)			

Note: *P < 0.05 (indicates statistical significance).

($\chi^2 = 5.296$, $P = 0.021$), but no significant difference was obtained using the recessive model frequency ($\chi^2 = 0.379$, $P = 0.693$). Therefore, no significance was observed between the rs1050450 genotype and SCZ (see [Supplementary Table S1](#)). When analyzed separately by sex, we found a significant difference in rs1800668 among the frequency of different genotypic groups, alleles, and dominant models in males. Meanwhile, no difference was obtained in the recessive model. There was no difference between the females in the SCZ group and controls for rs1800668 ([Table 3](#)). Therefore, no sex effect was observed between the rs1050450 genotype and SCZ (see also the [Supplementary Table S2](#)).

Linkage Disequilibrium Analysis

Linkage disequilibrium, described by D' and r^2 , refers to the occurrence of alleles belonging to two or more gene seats on a chromosome at the same time, which is higher than the random occurrence frequency, that is, the phenomenon of non-random distribution of haplotype genes.

Here, $D' = 0.600$ and $r^2 = 0.349$; the linkage disequilibrium between rs1800668 and rs1050450 is shown in [Figure 1](#).

Haplotype Analysis

Haplotype analysis of rs1800668 and rs1050450 in the SCZ group and controls showed that the frequencies of CC, CT, TC, and TT were significantly different; as shown in [Table 4](#).

Discussion

Various GPx-1 SNPs are evident in the general population, including Prol98Leu (rs1050450) in Exon 2, -602A/G, 2T/C in the promoter region, and Ala5/Ala6/Ala7 repeat polymorphisms in Exon 1.⁴⁶ Additionally, there are 592G/A,⁵² and -46C/T (rs1800668)⁵³ polymorphisms, among others. In this study, rs1050450 and rs1800668 were selected to evaluate associations between selected SNPs and SCZ in Chinese Han subjects as well as to establish the effect of sex. The principal findings of this study were

Table 3 Genotype and Allele Distributions of GPx-1 (Rs1800668) in the SCZ Group and Controls Separated by Gender

SNP (rs1800668)	Male Cases, n (%)	Male Controls, n (%)	X ²	P	OR	CI	Female Cases, n (%)	Female Controls, n (%)	X ²	P	OR	CI
Genotypes												
CC	156(79.6)	181(89.2)					134(81.7)	188(84.3)				
CT	38(19.4)	22(10.8)	5.920	0.015*	2.004	1.137–3.533	30(18.3)	31(13.9)	1.199	0.274	1.358	0.784–1.150
TT	2 (1.0)	0(0.0)	–	0.216	1.013	0.995–1.031	0 (0.0)	4(1.8)	1.369	0.242	0.979	0.959–1.000
Allele												
C	350(89.3)	384(94.6)			0.944	0.906–0.984	298(90.9)	407(91.3)				
T	42(10.7)	22(5.4)	7.582	0.006*	1.977	1.203–3.250	30(9.1)	39(8.7)	0.038	0.846	1.051	0.638–1.730
Dominant Model												
CC	156(79.6)	181(89.2)			0.893	0.819–0.927	134(81.7)	188(84.3)				
CT+TT	40(20.4)	22(10.8)	6.960	0.008*	1.883	1.163–3.049	30(18.3)	35(15.7)	0.456	0.499	1.203	0.704–2.055
Recessive Model												
TT	2 (1.0)	0 (0.0)					0 (0.0)	4 (1.8)				
CT+CC	194(99.0)	203(100.0)	–	0.24	1.010	0.996–1.025	164(100.0)	219(98.2)	–	0.141	0.982	0.965–1.000

Note: *P < 0.05 (indicates statistical significance).

that the GPx-1 polymorphisms rs1050450 and rs1800668 were significantly associated with SCZ in the Chinese Han population, and that, in particular, the CT and TC (rs1800668 and rs1050450) haplotypes may be risk factors for SCZ. Furthermore, the C allele may be a protective factor for SCZ in general, and in particular for males patients with the GPx-1 rs1800668 polymorphism.

Although a pathological mechanism of SCZ and a therapeutic strategy still remain unknown, the theory that oxidative stress plays an important role in SCZ pathophysiological mechanisms by triggering neuronal inflammation has gained increased attention.⁵⁴ Oxidative stress is defined as the imbalance between ROS and antioxidant protection systems. When the brain's demand for oxygen increases and the body fails to provide this oxygen in a timely manner, cerebral oxidative stress will occur,⁵⁵ which subsequently causes damage to lipids, DNA, and proteins, all of which are related to the pathogenesis of SCZ.⁵⁶ In cells exposed to ROS, GPx-1 showed superior protection against SOD and CAT.⁵⁷ Studies have shown that GPx-1 polymorphisms, especially rs1800668, can affect the activity of the GPx-1 promoter, and that the C allele is related to increased GPx activity,^{40,58} which may play a role in improving antioxidant activity. Here, we found that the genotype and dominant model frequency of GPx-1 rs1800668 C/T showed statistically significant differences between the SCZ group and controls, which

indicated that rs1800668 likely play a major role in the pathogenesis of SCZ in the Chinese Han population and significant differences were found between the dominant model and the recessive model in the two groups. To the best our knowledge, this study is the first to thoroughly investigate associations between GPx-1 rs1800668 and SCZ. GPx-1 rs1800668 increases the antioxidant capacity of patients with SCZ and protects proteins, lipids, and DNA from oxidative stress, and also helps to maintain normal signal transmission between neurons and normal transmission of neurotransmitters; all of which may be due to C-allele-mediated increases in GPx-1 activity.⁵⁹ The GPx-1 polymorphism rs1800668 affects GPx-1 activity, and studies have shown that GPx-1 activity is strongly negatively correlated with brain atrophy and the ventricle/brain ratio in patients with SCZ, that is, the higher the GPx-1 activity the smaller the area of brain atrophy.⁶⁰ The results of this study, meanwhile, showed that there was a statistical difference in the GPx-1 rs1800668 C/T alleles between the SCZ group and controls. Specifically, the C-allele may reduce the odds of SCZ, a result consistent with the conclusion that the C-allele may increase GPx-1 activity, and thus, increase antioxidant capacity and reduce the incidence of SCZ. Regarding sex stratification, there was a significant difference in the allelic and genotypic frequencies, as well as the dominant model in SCZ among men for rs1800668, with



Figure 1 Linkage disequilibrium of rs1800668 and rs1050450.

the C-allele having a protective effect. There was no difference detected between SCZ patients and controls in our study for rs1800668 in females. Indeed, many studies

have found that men and women have different levels of oxidative stress, which are mainly the result of women having higher levels of oxidative stress in their lifetime,^{61–63} and also of genetic factors, which may impact the levels of oxidative stress. Taken together, the results indicate that the rs1800668 polymorphism is significantly related to SCZ, and this relation is likely due to fact that rs1800668 can reduce GPx-1 activity.

Among the existing reports of GPx-1 SNPs, rs1050450 has been the most extensively studied. This variation occurs at nucleotide 593 (rs1050450), creating a C ≥ T allele in Exon 2 that leads to a proline to leucine⁵² substitution at codon 198, which results decreased GPx-1 activity.⁶⁴ We found, in agreement with a previous study, that no statistical difference was obtained in allelic or genotypic frequencies of rs1050450 between the SCZ group and controls.⁶⁵ However, larger-scale studies from different regions are necessary to confirm these findings.

Although our results indicated that there was no association between GPx-1 gene polymorphisms and SCZ in women, we are not able to completely rule out any association between the two. We only detected the GPx-1 rs1800668 C/T and rs1050450 C/T polymorphisms. There are likely more polymorphisms on other loci that have yet to be discovered, several of which may shed new light on the associations between SCZ and sex. We also cannot rule out an important role of oxidative stress in the pathophysiology of SCZ in women, because antioxidants other than GPx-1, including SOD and CAT, act collectively in the response against oxidative stress, and each has an important role at different stages of free radical metabolism.^{66,67}

Based on linkage disequilibrium and haplotype analyses, we observed a linkage disequilibrium in rs1800668 C/T and rs1050450 C/T between the SCZ group and controls. The CT and TC haplotype were found to increase the risk of SCZ, whereas the CC and TT haplotypes were found to have a protective effect against disease development. Since the haplotype of the locus involved in this experiment has not been explored in other studies, the results found here are not comparable. Generally, the

Table 4 Haplotype Distribution of Rs1800668 and Rs1050450 Between the SCZ Group and Controls

Haplotype	Total Frequency	Case Group Ratio	Control Group Ratio	χ^2	P	OR	CI
CC	0.881	602.10(83.6)	782.98(91.9)	25.500	0.00**	0.450	0.328–0.167
CT	0.034	45.90(6.4)	8.02(0.9)	34.786	0.00**	7.167	3.362–15.279
TC	0.032	47.90(6.7)	2.02(0.2)	52.244	0.00**	30.012	7.313–123.175
TT	0.053	24.10(3.3)	58.98(6.9)	9.966	0.00**	0.0466	0.287–0.765

Note: **S = Highly significant ($P < 0.01$).

effect of a single SNP is not as effective as that of multiple sites, and the results of this experiment suggest that we should further carry out relevant site research in the future, and in particular, explore as many sites as possible for a gene to generate more accurate experimental results.

It should be noted that there were a few limitations to this study. First, the sample size was relatively small. We will expand the size in future studies to further explore relationships between GPx-1 and SCZ. Second, we could not determine GPx-1, SOD or CAT enzyme activities, or indeed any oxidative stress markers, such as GSH. Further research may draw reliable conclusions by detecting these enzyme activities in SCZ patients with different genotypes. Therefore, other factors, including cross-sectional data and different recruitment centers, should be considered when conducting future studies.

Conclusions

GPx-1 polymorphisms are related to SCZ in the Chinese Han population. This is the first study to observe that the GPx-1 polymorphisms rs1050450 and rs1800668 were related to SCZ in the Chinese Han population. The results showed the CT and TC (rs1800668 and rs1050450) haplotypes may be risk factors for SCZ. Our results also suggest, that the C allele in the polymorphism rs1800668 may be a protective factor against SCZ in general, and in particular in males.

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Disclosure

The authors report no conflicts of interest in this work.

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