

Possible associations between antioxidant enzyme polymorphisms and metabolic abnormalities in patients with schizophrenia

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Background: This study investigated the possible association between common and potentially functional polymorphisms of antioxidant enzymes and metabolic abnormalities in patients with schizophrenia.

Methods: The possible associations of the *glutathione S-transferase (GST) M1* null and *GSTT1* null genotypes, and the *superoxide dismutase 2 (SOD2)* Val16Ala polymorphism with the risks of being overweight and having metabolic syndrome were examined using a logistic regression analysis in 154 schizophrenic Japanese patients and 203 controls.

Results: Among smokers with schizophrenia, the risks of being overweight and having decreased high-density lipoprotein cholesterol were significantly higher in those with the *GSTM1* null genotype than in those with the present genotype (odds ratio 3.20 and 3.15, $P=0.03$ and $P=0.04$, respectively), while among nonsmokers with schizophrenia, the risk of an abnormal waist circumference was lower in those with the *GSTM1* null genotype (odds ratio 0.34, $P=0.04$). The risk of a decreased high-density lipoprotein cholesterol level was significantly higher in patients with the combined *GSTM1* null and *GSTT1* present genotypes than in those with the present genotypes of both genes (odds ratio 3.60, $P<0.01$). The *SOD2* Val16Ala polymorphism was not associated with risk of metabolic abnormalities in either group.

Conclusion: The present study suggests that the *GSTM1* null genotype, in combination with smoking status or *GSTT1* genotype, might be associated with the metabolic abnormalities in patients with schizophrenia.

Keywords: schizophrenia, metabolic syndrome, oxidative stress, glutathione *S*-transferase, superoxide dismutase 2, polymorphism

Introduction

People with schizophrenia tend to have a shorter life expectancy than the general population, not only due to their high suicide rate, but also due to cardiovascular events.^{1,2} People with schizophrenia are more likely to have metabolic abnormalities, including obesity, glucose intolerance, hypertension, dyslipidemia, and metabolic syndrome than the general population.^{2,3} These cardiometabolic risk factors are attributable to atypical antipsychotic-related weight gain and an unhealthy lifestyle, including dietary abnormalities, sedentary behavior, and a high prevalence of smoking.^{1,2,4-7}

Among the risk factors for metabolic syndrome in patients with schizophrenia, antipsychotic treatment and a longer duration of disease course are associated with a higher risk of developing metabolic syndrome;⁸⁻¹² however, drug-naïve individuals with first-episode psychosis are also reported to have metabolic abnormalities.¹³ Therefore, innate factors, such as genetic predisposition, may play a role in determining the risk

of metabolic dysregulation in patients with schizophrenia, and many researchers have made an attempt to identify these genetic risk factors.¹⁴ Consequently, there is growing evidence that genetic factors are, at least in part, responsible for the metabolic abnormalities in patients with schizophrenia.¹⁴ To identify these genetic factors, previous studies have been focused on target genes implicated in the antipsychotic action of drugs and weight regulation,¹⁴ but identification of numerous novel susceptibility genes is now ongoing, and can provide a better understanding of these conditions.

The major components of metabolic syndrome are generally agreed to include central obesity, hypertension, dyslipidemia, and glucose intolerance or insulin resistance. Commonly used definitions for metabolic syndrome include the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) metabolic syndrome definition¹⁵ and the adapted NCEP ATP III (ATP III-A) definition.¹⁶ Because the small physique of Asians makes it difficult to use the same waist circumference criteria for those of European descent,¹⁷ modified criteria for waist circumference have been proposed for Asians in the ATP III-A definition.¹⁸ To be diagnosed with metabolic syndrome according to the ATP III-A definition for Asians, individuals should meet or receive treatment for at least three of the following five criteria: an abnormal waist circumference (males ≥ 90 cm, females ≥ 80 cm), elevated blood pressure ($\geq 130/85$ mmHg), a decreased high-density lipoprotein level (HDL; males <40 mg/dL, females <50 mg/dL), an elevated triglyceride level (≥ 150 mg/dL), and an elevated fasting glucose level (≥ 100 mg/dL).¹⁸

Recently, there has been increasing interest in the role of free radicals and oxidative stress in the pathogenesis of obesity and metabolic syndrome in the general population.^{19–21} Oxidative damage and inflammation are present at the onset of obesity.²⁰ The harmful effects of free radicals, primarily reactive oxygen species, and/or reactive nitrogen species, have been implicated in the physiopathology of obesity, hypertension, endothelial dysfunction, and metabolic syndrome, suggesting that oxidative stress is a mechanism underlying the dysfunctional metabolism observed in obese subjects.^{19–21} For example, smoking and obesity are associated with low HDL cholesterol levels,²² and oxidative stress modifies specific amino acids in apolipoprotein A-I, a major component of HDL, resulting in a decrease in large HDL particles, such as HDL2.²³

The glutathione *S*-transferase (GST) supergene family consists of phase 2 detoxifying enzymes and plays a crucial role in antioxidant defense mechanisms by detoxifying electrophilic xenobiotics and inactivating a variety of endogenous

byproducts of oxidative stress.^{24–26} The most extensively studied *GST* polymorphisms occur in two isozymes found in the cytosol, ie, mu (*GSTM1*) and theta (*GSTT1*).^{24,26} The human *GSTM1* gene contains eight exons located at 1p13.3, and the most common polymorphism in *GSTM1* is a deletion of the whole gene (“null” genotype) that results in a lack of functional activity of the enzyme.^{24,26} The human *GSTT1* gene contains four exons located at 22q11.2, and a homozygous deletion in *GSTT1* (“null” genotype) has also been reported.^{24,26} These two common deletion polymorphisms of *GSTM1* and *GSTT1* are reported to be associated with an increased susceptibility to certain oxidative stress-related diseases.^{24,26–30} Meanwhile, superoxide dismutase 2 (*SOD2*, also known as manganese superoxide dismutase) converts superoxide to hydrogen peroxide and molecular oxygen in the mitochondrial matrix, representing the first line of cellular defense against oxidative stress.³¹ The *SOD2* gene contains five exons and spans almost 20 kb located at 6p25. The T to C nucleotide polymorphism (rs4880, Val16Ala) has been identified in exon 2 of the human *SOD2* gene, and the Ala variant is more efficiently imported into the mitochondria than the Val variant.³² Several studies have revealed that this *SOD2* polymorphism is associated with cardiovascular and metabolic diseases in the general population.^{28,29,33}

An increase in systemic oxidative stress in patients with schizophrenia has been reported, which may be due to the pathophysiology of schizophrenia, the sequelae of the therapeutic drugs used to treat schizophrenia, and/or the high prevalence of smoking among such individuals.^{34–36} Therefore, it is possible that the influence of the *GST* and *SOD2* polymorphisms on development of metabolic abnormalities is more pronounced in patients with schizophrenia, especially under high oxidative stress conditions (eg, smokers). However, only one group has investigated the association between *GST* polymorphisms and olanzapine-induced weight gain,³⁷ and there are presently no data regarding the effects of *GST* polymorphisms in association with other patient characteristics on the development of metabolic abnormalities in patients with schizophrenia. Meanwhile, no study has been published regarding the relationship between *SOD2* polymorphisms and metabolic abnormalities in patients with schizophrenia.

The present study investigated the possible associations between the most common and potentially functional polymorphisms in three antioxidant enzyme genes, ie, *GSTM1*, *GSTT1*, and *SOD2*, and the risks of being overweight and having metabolic syndrome in Japanese patients with schizophrenia in comparison with the general population, while also

paying careful attention to associations with other patient characteristics.

Materials and methods

Subjects

A cross-sectional, case-control analysis was conducted in 154 Japanese patients with schizophrenia and 203 Japanese controls. The patients with schizophrenia were recruited from the participants of a previous study.³⁸ All patients were diagnosed with schizophrenia based on Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-IV-TR) criteria, and had been treated with antipsychotic medication for at least 3 months at Hirosaki University Hospital in Japan prior to enrollment in the study. The diagnoses of the patients were recorded from their medical charts. Exclusion criteria included psychosis due to general medical conditions, substance-related psychosis, and mood disorders with psychotic features. Age-matched and sex-matched controls were recruited from participants in a 2-day health screening program conducted at the Japanese Red Cross Kumamoto Hospital Health Care Center. This study was approved by the institutional review boards of the Faculty of Life Sciences, Kumamoto University, the Hirosaki University School of Medicine, and the Japanese Red Cross Kumamoto Hospital Health Care Center. Informed consent, including a statement regarding the privacy policy, was obtained in writing from each volunteer before entry into the study.

Clinical assessments

The height and weight of the subjects were measured, and the body mass index (BMI) was calculated. Overweight was diagnosed as a BMI ≥ 25 kg/m². Presence of the metabolic syndrome was assessed based on the definitions proposed by the NCEP ATP III for Asians.¹⁸ The waist circumference was measured at the umbilical level in a standing position, to the nearest 0.1 cm, by a technician in the morning. Trained technicians measured blood pressure using a standard mercury sphygmomanometer on the right arm of seated participants after a 5-minute rest. HDL cholesterol and triglyceride levels were measured using standard enzymatic methods with kits (MetaboLead HDL-C and Determiner L TG II, respectively) from Kyowa Medex Co, Ltd (Tokyo, Japan) with an automated analyzer (Labospect 008; Hitachi Ltd, Tokyo, Japan). Fasting blood glucose levels were also measured using a glucose oxidase-immobilized enzyme membrane-hydrogen peroxide electrode method with glucose analyzers (GA-1170 and GA-1171; Arkray, Inc, Kyoto, Japan). Information on

the subjects' demographics (age, sex, smoking status) and medical history were obtained from their medical records and by face-to-face interviews with medical staff members using a structured questionnaire.

Genotyping

Genomic DNA was extracted from whole blood using a DNA purification kit (Qiagen, Flexi Gene DNA kit; Hilden, Germany). Null genotypes of *GSTM1* and *GSTT1* were determined using polymerase chain reaction (PCR) amplification based on the presence or absence of a PCR amplification product according to the method of Watanabe et al,³⁹ with minor modifications. Briefly, null genotyping of *GSTT1* and *GSTM1* was determined using agarose electrophoresis. The *GSTM1* and *GSTT1* genes were amplified via PCR in the same reaction mixture described herein containing specific primer sets for *GSTM1* and *GSTT1*. The primer sequences for *GSTM1* were 5'-GAACTCCCTGAAAAGCTAAAGC-3' (forward primer) and 5'-GTTGGGCTCAAATATACGGTGG-3' (reverse primer), while those for *GSTT1* were 5'-TTCCTTACTGGTCCTCACATCTC-3' (forward primer) and 5'-TCACCGGATCATGGCCAGCA-3' (reverse primer), and those for β -globin as an internal control were 5'-CAACTTCATCCACGTTCCACC-3' (forward primer) and 5'-GAA-GAGCCAAGGACAGGTAC-3' (reverse primer). The PCR analysis was performed using 30 cycles of 30 seconds at 94°C (degeneration), 30 seconds at 60°C (annealing), and 30 seconds at 72°C (elongation). The amplified DNA fragments were electrophoresed in 3% agarose gel, stained with ethidium bromide, and visualized under ultraviolet illumination. When the PCR products exhibited 0.23-kb or 0.46-kb bands, they were designated as wild-type *GSTM1* or *GSTT1* genes, respectively, and when no amplified bands were observed, they were designated as the null genotype (Figure 1). *SOD2* c.47T>C (Val16Ala, rs4880) was genotyped by real-time PCR with 5'-nuclease allele discrimination assays (Step One Plus Real-Time PCR system version 2.1; Applied Biosystems, Tokyo, Japan). Genotyping for rs4880 was done using commercially available assays (assay ID: C_8709053_10). The reagents were purchased from Applied Biosystems, and genotyping was performed according to the manufacturer's protocol. To ensure genotyping quality, we included DNA samples as internal controls, hidden samples of a known genotype, and negative controls (water). Regarding *GSTM1* and *GSTT1*, the genotypes were classified as follows: subjects with homozygous deleted alleles (ie, the "null" genotype) and others (ie, the "present" genotype). Regarding *SOD2* c.47T>C (Val16Ala), the genotypes were

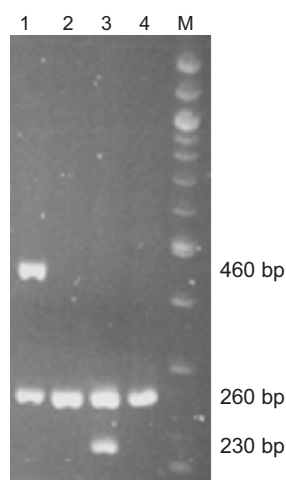


Figure 1 Genotyping of *GSTM1* and *GSTT1* using polymerase chain reaction. M, 100 bp DNA marker. Lane 1: *GSTT1* present (460 bp) genotype and β -globin (260 bp). Lane 2: *GSTT1* null genotype and β -globin (260 bp). Lane 3: *GSTM1* present genotype (230 bp) and β -globin as an internal control (260 bp). Lane 4: *GSTM1* null genotype and β -globin (260 bp). Present: subjects with homozygous or heterozygous wild-type allele(s). Null: subjects with homozygous deleted alleles.

classified into three groups: homozygous for the *SOD2* T allele (ie, the Val/Val genotype), heterozygous for the T and C alleles (ie, the Val/Ala genotype), and homozygous for the C allele (ie, the Ala/Ala genotype).

Statistical analysis

The data are presented as the mean \pm standard deviation or number (%) of subjects. All continuous variables were analyzed using the Student's *t*-test. Categorical variables were compared by Fisher's exact test. The strength of the association between each genotype and the risk of being overweight, and that of having metabolic syndrome and abnormalities for each component of the metabolic syndrome was measured as odds ratios (ORs) with 95% confidence intervals (CIs) in patients with schizophrenia and the age-matched and sex-matched controls. The ORs were calculated via a logistic regression analysis that included all of the genotypes, patient categorical factors (ie, sex, smoking status, treatment with or without atypical antipsychotics, or inpatient/outpatient status), interactions between genotypes, and those between the genotype and each patient's factors as fixed effects, and age as a random effect. The use of atypical antipsychotics with a particular propensity to induce weight gain, ie, clozapine, olanzapine, risperidone, quetiapine, or perospirone, was included as a fixed effect. A value of $P < 0.05$ was considered to be statistically significant. These statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software package for Windows (version 17.0; IBM Japan Ltd, Tokyo, Japan). The statistical power of the

associations between the genotypes and the risk of metabolic abnormalities was also calculated at a significance (α) level of 0.05 (two-tailed) and the adequate effect size (eg, an OR of 2.0 or 3.0) based on the sample size of this study and the observed frequencies of the genotypes and metabolic abnormalities using the SPSS Sample Power software program (version 3.0; IBM Japan Ltd).

Results

Study population

The demographic and clinical characteristics of the study population are shown in Table 1. The mean (\pm standard deviation) age was 50.2 ± 15.3 years and 52.4 ± 9.0 years ($P = 0.124$), and the number (%) of females was 74 (48.1%) and 86 (42.4%) in the patients with schizophrenia and controls, respectively ($P = 0.334$). Patients with schizophrenia had significantly greater body weight and a higher BMI than controls ($P = 0.011$ and $P < 0.0001$, respectively). A total of 72 (46.8%) and 49 (24.1%) patients with schizophrenia and controls, respectively, were overweight ($P < 0.0001$). The prevalence of metabolic syndrome was 34 (22.1%) and 15 (7.4%) in patients with schizophrenia and controls, respectively ($P < 0.0001$). Waist circumference, systolic/diastolic blood pressure, and triglyceride levels were all significantly

Table 1 Demographic and clinical characteristics of study subjects

	Schizophrenia patients (n=154)	Controls (n=203)	P
Age (years)	50.2 \pm 15.3	52.4 \pm 9.0	0.124
Male	80 (51.9%)	117 (57.6%)	0.334
Height (cm)	161.7 \pm 8.4	162.9 \pm 8.9	0.205
Weight (kg)	65.1 \pm 13.6	61.7 \pm 10.9	0.011
BMI (kg/m ²)	24.8 \pm 4.1	23.2 \pm 3.2	<0.0001
Overweight	72 (46.8%)	49 (24.1%)	<0.0001
Metabolic syndrome	34 (22.1%)	15 (7.4%)	<0.0001
Waist circumference (cm)	86.2 \pm 11.9	82.8 \pm 8.1	0.003
Systolic blood pressure (mmHg)	125.9 \pm 16.5	117.2 \pm 16.2	<0.0001
Diastolic blood pressure (mmHg)	76.8 \pm 12.0	72.9 \pm 11.0	0.001
High-density lipoprotein (mg/dL)	52.1 \pm 14.6	65.6 \pm 17.2	<0.0001
Triglycerides (mg/dL)	149.0 \pm 138.7	121.0 \pm 88.1	0.029
Fasting glucose (mg/dL)	103.0 \pm 32.4	96.3 \pm 20.1	0.070
Smoker	78 (50.6%)	43 (21.2%)	<0.0001
Outpatient	93 (60.4%)	—	—
Treatment with AAP(s)	112 (72.7%)	—	—

Note: Data expressed as the mean \pm standard deviation or number (%).

Abbreviations: AAP(s), atypical antipsychotic(s) except for aripiprazole; BMI, body mass index.

higher in patients with schizophrenia than in controls ($P=0.003$, $P<0.0001$, and $P=0.029$, respectively), whereas HDL cholesterol was lower in patients with schizophrenia ($P<0.0001$). Fasting glucose levels tended to be higher in patients with schizophrenia, although the difference did not reach statistical significance ($P=0.070$). The number of smokers was significantly greater in patients with schizophrenia than in controls ($P<0.0001$). A total of 112 (72.7%) patients with schizophrenia were receiving atypical antipsychotics. Among them, 64, 32, 20, nine, and four were being treated with risperidone, olanzapine, quetiapine, perospirone, and aripiprazole, respectively. None of the patients was being treated with clozapine. Seventy patients were being treated with typical antipsychotics, including haloperidol ($n=29$), levomepromazine ($n=25$), chlorpromazine ($n=19$), sulpiride ($n=6$), and bromperidol ($n=5$). The patients had all been treated with either a single agent or a combination of these atypical and/or typical antipsychotic agents for at least 3 months prior to the analysis.

Allele and genotype frequencies in patients with schizophrenia and controls

The numbers (%) of patients with the *GSTM1* null genotype were 77 (50.0%) and 99 (48.8%) in the group with schizophrenia and the control group, respectively; those of the *GSTT1* null genotype were 68 (44.2%) and 99 (48.8%), respectively. The frequency (%) of the *GSTM1/GSTT1* double null genotype was 40 (26.0%) and 45 (22.2%) in patients with schizophrenia and controls, respectively. The allele frequencies of the *SOD2* Val16Ala polymorphism were 14.3% and 13.3% in patients with schizophrenia and controls, respectively. The numbers (%) of *SOD2* Ala/Ala and Val/Ala genotypes were three (1.9%) and 38 (24.7%), respectively, in patients with schizophrenia, and were four (2.0%) and 46 (22.3%), respectively, in controls. The observed *SOD2* genotype frequencies were consistent with the Hardy-Weinberg equilibrium ($P>0.05$). The genotype frequencies of *GSTM1*, *GSTT1*, *GSTM1/GSTT1*, and *SOD2* in the patients with schizophrenia did not differ from those observed in the controls ($P=0.831$, $P=0.394$, $P=0.164$, and $P=0.714$, respectively) and were comparable with the frequencies observed in the general Japanese population.^{40,41} Since the frequency of the *SOD2* Ala/Ala genotype was too small in both groups, we combined the Ala/Ala and Ala/Val genotypes in the subsequent analyses. The mean age was significantly higher in subjects with the *GSTM1* null genotype than in those with the present genotype among the patients with schizophrenia (Supplementary Table 1);

whereas the patient age and number of females did not differ according to *GSTT1*, *SOD2*, and *GSTM1/GSTT1* genotypes (Supplementary Tables 2–5).

Association between genotypes and incidence of metabolic abnormalities in schizophrenic patients

None of the *GSTM1*, *GSTT1*, and *SOD2* genotypes alone was associated with risk of overweight, metabolic syndrome, or abnormalities in each component of the metabolic syndrome in patients with schizophrenia (Table 2). Since significant interactive effects of the *GSTM1* genotype and smoking status on the risks for being overweight and having an abnormal waist circumference ($P=0.034$ and $P=0.018$, respectively) were observed, we assessed the effects of *GSTM1* genotype on the risks of being overweight, having metabolic syndrome, and having abnormalities in each component of the metabolic syndrome separately in smokers and nonsmokers (Table 3). Among the smokers, the incidences of being overweight and having decreased HDL cholesterol levels were significantly higher in those with the *GSTM1* null genotype than in those with the present genotype. Conversely, the incidence of having an abnormal waist circumference was significantly lower in nonsmokers with the *GSTM1* null genotype.

Given that an interactive effect of the *GSTM1* and *GSTT1* genotypes on the risk of having decreased HDL cholesterol was also observed ($P=0.020$), the relationships between the risk of metabolic abnormalities and the combinations of *GSTM1* and *GSTT1* genotypes were also analyzed (Table 4). The risk of having a decreased HDL cholesterol level was significantly higher in patients with the *GSTM1* null/*GSTT1* present genotypes, but not in those with the *GSTM1* present/*GSTT1* null genotypes or *GSTM1* null/*GSTT1* null genotypes, compared with those with the *GSTM1* present/*GSTT1* present genotype. No other interactions between genotypes or between genotype and other patient-related factors (age, sex, smoking status, treatment with or without atypical antipsychotics, inpatient/outpatient status) were observed in the patients with schizophrenia.

When the magnitude of the effect size (ie, the OR value) was fixed at 2.0 and 3.0 in the 154 patients with schizophrenia, the statistical power of the associations between genotype and risk of metabolic abnormalities was 32%–56% and 56%–90%, respectively, based on the observed frequencies of the genotypes and metabolic abnormalities. Because we speculated that the influence of *GST* and *SOD2* polymorphisms on metabolic abnormalities would be more pronounced in patients under high oxidative stress conditions than in the remaining subjects, we also calculated

Table 2 Associations between genotypes and risk of metabolic abnormalities in patients with schizophrenia and age/sex-matched controls

Parameter	Genotype	Schizophrenia (n=154)			Controls (n=203)		
		Frequency (%) ^a	P ^b	OR (95% CI) ^c	P ^c	Frequency (%) ^a	OR (95% CI) ^c
Overweight	GSTM1						
	Present	34 (44.2%)	0.628	1		26 (25.0%)	1
	Null	38 (49.4%)		9.427 (0.763–116.452)	0.080	23 (23.2%)	0.887 (0.461–1.706)
	GSTT1						
MetS	Present	40 (46.5%)	1.000	1		24 (23.1%)	1
	Null	32 (47.1%)		0.209 (0.016–2.727)	0.232	25 (25.3%)	1.135 (0.588–2.189)
	SOD2 Val16Ala						
	Ala/Ala or Ala/Val	17 (41.5%)	0.469	1		15 (30.0%)	1
Abnormal waist circumference	Val/Val	55 (48.7%)		2.215 (0.137–35.922)	0.576	34 (22.2%)	0.677 (0.329–1.396)
	GSTM1						
	Present	16 (20.8%)	0.846	1		9 (8.7%)	1
	Null	18 (23.4%)		1.539 (0.071–33.414)	0.784	6 (6.1%)	0.720 (0.237–2.186)
Elevated blood pressure	GSTT1						
	Present	17 (19.8%)	0.442	1		5 (4.8%)	1
	Null	17 (25.0%)		2.496 (0.112–55.817)	0.564	10 (10.1%)	1.795 (0.572–5.630)
	SOD2 Val16Ala						
	Ala/Ala or Ala/Val	10 (24.4%)	0.666	1		4 (8.0%)	1
	Val/Val	24 (21.2%)		2.372 (0.069–81.138)	0.632	11 (7.2%)	0.909 (0.264–3.126)
	GSTM1						
	Present	44 (57.1%)	0.746	1		29 (27.9%)	1
	Null	41 (53.2%)		7.889 (0.717–86.793)	0.091	33 (33.3%)	1.445 (0.761–2.742)
	GSTT1						
	Present	46 (53.5%)	0.744	1		29 (27.9%)	1
	Null	39 (57.4%)		0.814 (0.083–7.965)	0.860	33 (33.3%)	1.181 (0.621–2.247)
	SOD2 Val16Ala						
	Ala/Ala or Ala/Val	20 (48.8%)	0.363	1		16 (32.0%)	1
	Val/Val	65 (57.5%)		2.216 (0.224–21.960)	0.497	46 (30.1%)	0.900 (0.431–1.880)
	GSTM1						
	Present	29 (37.7%)	0.414	1		31 (29.8%)	1
	Null	35 (45.5%)		8.366 (0.758–92.350)	0.083	31 (31.3%)	1.073 (0.583–1.975)
	GSTT1						
	Present	33 (38.4%)	0.412	1		36 (34.6%)	1
	Null	31 (45.6%)		1.962 (0.183–21.046)	0.578	26 (26.3%)	0.627 (0.338–1.165)
	SOD2 Val16Ala						
	Ala/Ala or Ala/Val	22 (53.7%)	0.095	1		15 (30.0%)	1
	Val/Val	42 (37.2%)		0.569 (0.044–7.420)	0.667	47 (30.7%)	1.033 (0.508–2.102)

Decreased HDL cholesterol	GSTM1	Present	22 (28.6%)	0.233	I			4 (3.8%)	0.530	I		
		Null	30 (39.0%)		11.428 (0.874–149.423)	0.063		6 (6.1%)		1.685 (0.446–6.367)		0.441
	GSTT1	Present	32 (37.2%)	0.391	I			5 (4.8%)	1.000	I		
		Null	20 (29.4%)		1.392 (0.119–16.261)	0.792		5 (5.1%)		1.115 (0.299–4.158)		0.872
Elevated triglycerides	SOD2 Val16Ala	Ala/Ala or Ala/Val	11 (26.8%)	0.337	I			1 (2.0%)	0.456	I		
		Val/Val	41 (36.3%)		5.936 (0.453–77.715)	0.175		9 (5.9%)		2.848 (0.346–23.430)		0.330
	GSTM1	Present	25 (32.5%)	0.862	I			25 (24.0%)	1.000	I		
		Null	23 (29.9%)		1.181 (0.084–16.568)	0.902		23 (23.2%)		0.948 (0.488–1.843)		0.875
	GSTT1	Present	25 (29.1%)	0.600	I			22 (21.2%)	0.413	I		
		Null	23 (33.8%)		4.903 (0.381–63.157)	0.223		26 (26.3%)		1.458 (0.745–2.853)		0.271
Elevated fasting glucose	SOD2 Val16Ala	Ala/Ala or Ala/Val	12 (29.3%)	0.845	I			11 (22.0%)	0.849	I		
		Val/Val	36 (31.9%)		0.949 (0.059–15.254)	0.971		37 (24.2%)		1.080 (0.496–2.354)		0.846
	GSTM1	Present	27 (35.1%)	0.739	I			26 (25.0%)	0.873	I		
		Null	30 (39.0%)		3.590 (0.276–46.722)	0.329		26 (26.3%)		1.093 (0.550–2.172)		0.799
	GSTT1	Present	33 (38.4%)	0.739	I			24 (23.1%)	0.424	I		
		Null	24 (35.3%)		5.007 (0.421–59.492)	0.202		28 (28.3%)		1.513 (0.754–3.033)		0.244
	SOD2 Val16Ala	Ala/Ala or Ala/Val	16 (39.0%)	0.851	I			11 (22.0%)	0.578	I		
		Val/Val	41 (36.3%)		1.285 (0.088–18.657)	0.854		41 (26.8%)		1.224 (0.544–2.752)		0.625

Notes: *Frequency and percentage indicate those of the metabolic abnormalities for each genotype; †Fisher's exact test; ‡OR (95% CI) and P-values were calculated by logistic regression analysis that included all genotypes, patient-related categorical factors (ie, sex, smoking status, treatment with or without atypical antipsychotics, or inpatient/outpatient status), interactions between genotypes, interactions between genotypes and patient-related factors as fixed effects, and age was included as a random effect.

Abbreviations: CI, confidence interval; GST, glutathione S-transferase; HDL, high-density lipoprotein; MetS, metabolic syndrome; SOD2, superoxide dismutase 2; OR, odds ratio.

Table 3 Association between *GSTM1* genotype and risk of metabolic abnormalities in smokers and nonsmokers among patients with schizophrenia

Parameter	<i>GSTM1</i> genotype	Smokers (n=78)			Nonsmokers (n=76)		
		Frequency (%) ^a	P ^b	OR (95% CI) ^c	Frequency (%) ^a	P ^b	OR (95% CI) ^c
Overweight	Present	14 (33.3%)	0.169	1	20 (57.1%)	0.498	1
	Null	18 (50.0%)		3.202 (1.081–9.480)	20 (48.8%)		0.610 (0.225–1.652)
MetS	Present	11 (26.2%)	0.619	1	5 (14.3%)	1.000	1
	Null	12 (33.3%)		1.629 (0.550–4.828)	6 (14.6%)		0.797 (0.180–3.534)
Abnormal waist circumference	Present	21 (50.0%)	0.367	1	23 (65.7%)	0.109	1
	Null	22 (61.1%)		2.014 (0.750–5.412)	19 (46.3%)		0.336 (0.117–0.968)
Elevated blood pressure	Present	16 (38.1%)	0.493	1	13 (37.1%)	0.642	1
	Null	17 (47.2%)		1.630 (0.579–4.590)	18 (43.9%)		1.182 (0.428–3.263)
Decreased HDL cholesterol	Present	11 (26.2%)	0.062	1	11 (31.4%)	1.000	1
	Null	17 (47.2%)		3.151 (1.062–9.350)	13 (31.7%)		0.852 (0.278–2.609)
Elevated triglycerides	Present	15 (35.7%)	0.810	1	10 (28.6%)	1.000	1
	Null	11 (30.6%)		1.003 (0.331–3.036)	12 (29.3%)		1.144 (0.392–3.342)
Elevated fasting glucose	Present	11 (26.2%)	0.159	1	16 (45.7%)	0.486	1
	Null	15 (41.7%)		1.956 (0.612–6.253)	15 (36.6%)		0.684 (0.248–1.883)

Notes: ^aFrequency and percentage indicate those of the metabolic abnormalities for each genotype; ^bFisher's exact test; ^cOR (95% CI) and P-values were calculated by logistic regression analysis that included the *GSTM1*, *GSTT1*, and *SOD2* genotypes, patient-related categorical factors (ie, sex, treatment with or without atypical antipsychotics, or inpatient/outpatient status) as fixed effects, and age as a random effect.

Abbreviations: CI, confidence interval; GST, glutathione S-transferase; HDL, high-density lipoprotein; MetS, metabolic syndrome; OR, odds ratio.

the statistical power with a larger effect size (ie, an OR of 3.0 and 4.0) in the smokers with schizophrenia. When the OR was fixed at 3.0 and 4.0 in the 78 smokers with schizophrenia, the statistical power of the associations between genotype and risk of metabolic abnormalities was 55%–66% and 72%–82%, respectively. The respective percentages are shown in Supplementary Table 6.

Association between genotype and incidence of metabolic abnormalities in age/sex-matched controls

None of the *GSTM1*, *GSTT1*, or *SOD2* genotypes examined was individually associated with the incidence of overweight, metabolic syndrome, or abnormalities in each component of the metabolic syndrome in controls (Table 2). To compare the results in patients with schizophrenia, we assessed the effects of *GSTM1* genotype on the risks of being overweight, having a large waist circumference, and on the HDL cholesterol levels separately in smokers and nonsmokers, and also examined the effects of combinations of the *GSTM1* and *GSTT1* genotypes on the risk of decreased HDL cholesterol. The *GSTM1* null genotype was not associated with the incidence of overweight, an abnormal waist circumference, or a decreased HDL cholesterol level among smokers and nonsmokers (Table 5). The risk of a decreased HDL cholesterol level was not significantly different in subjects with the *GSTM1* null/*GSTT1* present, *GSTM1* present/*GSTT1* null, and *GSTM1* null/*GSTT1* null genotypes compared with those with the *GSTM1* present/*GSTT1* present genotype (Table 5).

Discussion

The present study showed that none of the *GSTM1*, *GSTT1*, and *SOD2* genotypes examined were independent risk factors for metabolic abnormalities in patients with schizophrenia. On the other hand, when the possible associations between genotype and risk of metabolic abnormalities were analyzed, while also paying careful attention to the associations with other patient characteristics, the present study demonstrated the possible impact of the *GSTM1* null genotype on metabolic abnormalities in patients with schizophrenia.

In this study, we found that the risks of being overweight and having a decreased HDL cholesterol level were significantly higher in subjects with the *GSTM1* null genotype than in those with the present genotype among smokers with schizophrenia (Table 3). The findings of the present study are in line with another recent study showing that the *GSTM1* null genotype was associated with a tendency toward a higher BMI and decreased HDL cholesterol in patients

Table 4 Frequency distribution of combinations of *GSTM1* and *GSTT1* genotypes in schizophrenic subjects with metabolic abnormalities

Parameter	<i>GSTM1</i> genotype	<i>GSTT1</i> genotype	Frequency (%) ^a	P ^b	OR (95% CI) ^c	P ^c
Overweight	Present	Present	20 (40.8%)	0.660	I	
	Null	Present	20 (54.1%)		2.032 (0.824–5.012)	0.124
	Present	Null	14 (50.0%)		1.789 (0.656–4.876)	0.256
	Null	Null	18 (45.0%)		1.475 (0.600–3.626)	0.398
MetS	Present	Present	7 (14.3%)	0.252	I	
	Null	Present	10 (27.0%)		2.297 (0.751–7.028)	0.145
	Present	Null	9 (32.1%)		2.778 (0.843–9.147)	0.093
	Null	Null	8 (20.0%)		1.830 (0.568–5.898)	0.311
Abnormal waist circumference	Present	Present	25 (51.0%)	0.449	I	
	Null	Present	21 (56.8%)		1.225 (0.512–2.929)	0.649
	Present	Null	19 (67.9%)		1.997 (0.730–5.464)	0.178
	Null	Null	20 (50.0%)		1.024 (0.432–2.429)	0.957
Elevated blood pressure	Present	Present	18 (36.7%)	0.651	I	
	Null	Present	15 (40.5%)		1.290 (0.517–3.221)	0.586
	Present	Null	11 (39.3%)		1.252 (0.449–3.496)	0.668
	Null	Null	20 (50.0%)		1.825 (0.735–4.533)	0.195
Decreased HDL cholesterol	Present	Present	12 (24.5%)	0.021	I	
	Null	Present	20 (54.1%)		3.599 (1.409–9.193)	0.007
	Present	Null	10 (37.5%)		1.535 (0.533–4.419)	0.427
	Null	Null	10 (25.0%)		0.919 (0.337–2.505)	0.869
Elevated triglycerides	Present	Present	12 (24.5%)	0.180	I	
	Null	Present	13 (35.1%)		1.882 (0.702–5.043)	0.209
	Present	Null	13 (46.4%)		2.813 (0.972–8.140)	0.057
	Null	Null	10 (25.0%)		1.425 (0.507–4.004)	0.501
Elevated fasting glucose	Present	Present	17 (34.7%)	0.845	I	
	Null	Present	16 (43.2%)		1.482 (0.580–3.783)	0.411
	Present	Null	10 (35.7%)		1.399 (0.479–4.088)	0.540
	Null	Null	14 (35.0%)		1.036 (0.399–2.688)	0.942

Notes: ^aFrequency and percentage indicate those of the metabolic abnormalities for each genotype; ^bFisher's exact test; ^cOR (95% CI) and P-values were calculated by logistic regression analysis that included combinations of the *GSTM1* and *GSTT1* genotypes, *SOD2* genotypes, patient-related categorical factors (ie, sex, treatment with or without atypical antipsychotics, or inpatient/outpatient status) as fixed effects, and age as a random effect.

Abbreviations: CI, confidence interval; GST, glutathione S-transferase; HDL, high density lipoprotein; MetS, metabolic syndrome; OR, odds ratio; *SOD2*, superoxide dismutase 2.

Table 5 Association of *GSTM1* genotype with risk of metabolic abnormalities in smokers and nonsmokers and association of combinations of *GSTM1* and *GSTT1* genotypes among age/sex-matched controls

Subjects	Parameter	Genotype	Frequency (%) ^a	P ^b	OR (95% CI) ^c	P ^c
Smokers (n=43)	Overweight	<i>GSTM1</i> present	5 (23.8%)	0.457	I	
		<i>GSTM1</i> null	3 (13.6%)		0.566 (0.106–3.036)	0.507
	Abnormal waist circumference	<i>GSTM1</i> present	5 (23.8%)	1.000	I	
		<i>GSTM1</i> null	5 (22.7%)		1.568 (0.275–8.941)	0.613
	Decreased HDL cholesterol	<i>GSTM1</i> present	1 (4.8%)	0.607	I	
		<i>GSTM1</i> null	3 (13.6%)		2.782 (0.228–33.873)	0.422
Nonsmokers (n=160)	Overweight	<i>GSTM1</i> present	21 (25.3%)	1.000	I	
		<i>GSTM1</i> null	20 (26.0%)		1.010 (0.490–2.081)	0.979
	Abnormal waist circumference	<i>GSTM1</i> present	24 (28.9%)	0.399	I	
		<i>GSTM1</i> null	28 (36.4%)		1.540 (0.755–3.140)	0.235
	Decreased HDL cholesterol	<i>GSTM1</i> present	3 (3.6%)	1.000	I	
		<i>GSTM1</i> null	3 (3.9%)		1.147 (0.220–5.981)	0.871
All (n=203)	Decreased HDL cholesterol	<i>GSTM1</i> present/ <i>GSTT1</i> present	2 (4.0%)	0.919	I	
		<i>GSTM1</i> null/ <i>GSTT1</i> present	3 (5.6%)		1.230 (0.190–7.962)	0.828
		<i>GSTM1</i> present/ <i>GSTT1</i> null	2 (3.7%)		0.773 (0.100–5.968)	0.805
		<i>GSTM1</i> null/ <i>GSTT1</i> null	3 (6.7%)		1.763 (0.273–11.379)	0.551

Notes: ^aFrequency and percentage indicate those of the metabolic abnormalities for each genotype; ^bFisher's exact test; ^cOR (95% CI) and P-values were calculated by logistic regression analysis that included the *GSTM1* and *GSTT1* genotypes (or combinations of the *GSTM1* and *GSTT1* genotypes), *SOD2* genotypes, and sex as fixed effects, and age as a random effect.

Abbreviations: CI, confidence interval; GST, glutathione S-transferase; HDL, high-density lipoprotein; OR, odds ratio; *SOD2*, superoxide dismutase 2.

who underwent coronary angiography.⁴² Additionally, the interactive effects of current smoking and *GSTM1* null genotype on development of type 2 diabetes, nonalcoholic fatty liver disease, and several cancers have been reported in the general population.^{27,30,43,44} The findings of the present study also suggest that the *GSTM1* null genotype, in combination with current smoking, could be associated with the risks of being overweight and having decreased HDL cholesterol in patients with schizophrenia.

In this study, we found that the risk of an abnormal waist circumference was lower in nonsmoking schizophrenic subjects with the *GSTM1* null genotype (Table 3). The *GSTM1* null genotype is reported to be one of the potential risk factors for various smoking-related diseases.^{27–30,43} In this study, among smokers with schizophrenia, the risks of being overweight and having a decreased HDL cholesterol level were significantly higher in subjects with the *GSTM1* null genotype (Table 3). It is thus possible that some nonsmoking patients harboring the high-risk *GSTM1* null genotype might have stopped smoking or made other lifestyle modifications, which may have led to the lower risk of abdominal obesity. In fact, the frequency of the *GSTM1* null genotype tended to be higher in nonsmokers than in smokers with schizophrenia (53.9% versus 46.2%; see Supplementary Table 7). However, because we could not obtain information about these lifestyle-related factors, including past smoking status, from the patients in the present study, the association between the *GSTM1* null genotype and the lower risk of an abnormal waist circumference in nonsmokers with schizophrenia needs to be confirmed in a longitudinal study incorporating a collection of detailed lifestyle information.

The present study shows that the risk of decreased HDL cholesterol was significantly higher in subjects with the *GSTM1* null/*GSTT1* present genotypes, but not in those with the *GSTM1* present/*GSTT1* null and *GSTM1* null/*GSTT1* null genotypes, compared with the *GSTM1* present/*GSTT1* present genotypes (Table 4). These findings suggest that the *GSTM1* null, rather than the *GSTT1* null, genotype might be associated with the risk of having decreased HDL cholesterol levels in patients with schizophrenia. The *GSTT1* null genotype, especially in combination with the *GSTM1* null genotype, has been reported to be associated with the risk of cardiovascular or metabolic disease in the general population.^{27–29,44} The frequency of nonsmoking tended to be higher in subjects with the *GSTM1* null/*GSTT1* null genotypes (57.5%) compared with those having the other combinations (32.1%–53.1%) in the present study (see Supplementary Table 4), which might be related to the lack

of an association between the *GSTM1*/*GSTT1* double null genotypes and the metabolic abnormalities observed in this study. Nevertheless, larger studies are required to elucidate the influence of the *GSTT1* null genotype and/or combination with the *GSTM1* null genotype on the risk of metabolic abnormalities in patients with schizophrenia.

A previous study of 78 Korean patients with schizophrenia demonstrated that there were no differences in the null genotype distribution of *GSTM1* and *GSTT1* between subjects with a body weight gain $\geq 7\%$ compared with subjects with a body weight gain $< 7\%$ after long-term olanzapine treatment.³⁷ However, the level of lipid peroxidation appears to be significantly higher after treatment with typical antipsychotics,⁴⁵ and a significant increase in lipid peroxidation was observed after long-term treatment with clozapine, ziprasidone, and risperidone, but not with olanzapine, in the rat brain.⁴⁶ The patients in the present study were treated with olanzapine, as well as with other atypical and typical antipsychotics, and/or combinations of these agents, whereas patients were excluded if they took antipsychotics other than olanzapine in the Korean study.³⁷ Therefore, we speculate that levels of systemic reactive oxygen species might have been higher in the patients included in the present study than in those in the Korean study, resulting in the significant effects of the *GSTM1* null genotype on the metabolic abnormalities in patients with schizophrenia observed in the present study.

SOD2 also plays crucial roles in antioxidant defense mechanisms.³¹ The Val16Ala polymorphism has been linked to cardiovascular disease and to type 2 diabetes and its complications in the general population, but studies so far have yielded conflicting results.^{28,29,33} In the present study, we did not find any significant associations between the *SOD2* genotype and the risks of being overweight and having metabolic syndrome in patients with schizophrenia or controls. Although further study is required to elucidate this relationship in a larger number of subjects, it is possible that the *SOD2* Val16Ala polymorphism as a risk factor by itself is not strong enough to demonstrate a significant association with metabolic abnormalities in patients with schizophrenia.

This investigation has some potential limitations. First, the power of the samples in the analyses ranging from 32% to 90% (Supplementary Table 6) and the small number of subjects were major limitations. Therefore, the present study may not have had enough power to clarify whether *GSTM1*, *GSTT1*, and *SOD2* polymorphisms are independent risk factors for metabolic abnormalities in patients with schizophrenia, and a type 1 error cannot be excluded. Specifically, when effect size (ie, OR) is fixed at 2.0 with a

statistical power of 0.80, a sample size of 322–540 patients would be needed to determine the effects of the *SOD2* genotype before any definitive conclusions can be drawn. Further, the prevalence of overweight and metabolic syndrome was low in the controls (Table 1), which might have contributed to our results showing that none of the polymorphisms was associated with metabolic abnormalities in the controls. Second, this was a cross-sectional study that had only one assessment for metabolic abnormalities, and several potential covariates associated with overweight and metabolic syndrome could not be included, such as dietary habits, physical activity levels, past smoking status, duration of illness, and treatment and schizophrenic symptoms. Therefore, as in any study examining genotype-phenotype relationships, replication of the current findings is required.

Conclusion

The results of the present study suggest that the *GSTM1* null genotype, in combination with smoking status or *GSTT1* genotype, may be associated with the risk of metabolic abnormalities in Japanese patients with schizophrenia. Although these results need to be confirmed in further investigations with larger samples, our findings provide new insight for continued work in this area.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary tables

Table S1 Demographic and clinical characteristics according to *GSTM1* genotype in patients with schizophrenia and controls

	Schizophrenia (n=154)			Controls (n=203)		
	<i>GSTM1</i> present genotype	<i>GSTM1</i> null genotype	<i>P</i> ^a	<i>GSTM1</i> present genotype	<i>GSTM1</i> null genotype	<i>P</i> ^a
Number ^b	77 (50.0%)	77 (50.0%)	–	104 (51.2%)	99 (48.8%)	–
Age (years)	47.5±14.8	52.9±15.4	0.027	52.6±9.2	52.1±8.8	0.701
Male ^c	41 (53.2%)	39 (50.6%)	0.872	58 (55.8%)	59 (59.6%)	0.670
Smoker ^c	42 (54.5%)	36 (46.8%)	0.420	22 (22.2%)	21 (20.2%)	0.735
Height (cm)	161.8±8.4	161.5 ± 8.5	0.844	162.4±9.5	163.4±8.3	0.436
Weight (kg)	66.1 ± 13.9	64.1±13.3	0.360	60.6±11.6	62.9±10.0	0.127
BMI (kg/m ²)	25.1±4.2	24.4±4.0	0.297	22.9±3.3	23.5±3.1	0.136
Overweight ^c	34 (44.2%)	38 (49.4%)	0.628	26 (25.0%)	23 (23.2%)	0.870
Metabolic syndrome ^c	16 (20.8%)	18 (23.4%)	0.846	9 (8.7%)	6 (6.1%)	0.595
Waist circumference (cm)	87.3±12.4	84.9±11.3	0.203	82.2±8.3	83.5±7.8	0.260
Systolic blood pressure (mmHg)	123.0±14.5	128.8±17.9	0.027	116.6±16.8	117.7±15.7	0.642
Diastolic blood pressure (mmHg)	75.9±10.4	77.7±13.4	0.345	71.4±11.1	74.4±10.8	0.056
High-density lipoprotein (mg/dL)	53.9±15.1	50.3±13.9	0.122	65.2±16.4	65.9±18.2	0.768
Triglycerides (mg/dL)	151.4±119.1	146.5±156.6	0.828	122.1±104.1	119.8±68.1	0.851
Fasting blood glucose (mg/dL)	102.9±36.7	103.1±27.6	0.974	95.2±18.8	97.4 ± 21.5	0.437
Outpatients ^c	50 (64.9%)	43 (55.8%)	0.323	–	–	–
Treatment with AAP(s) ^c	54 (70.1%)	58 (75.3%)	0.588	–	–	–

Notes: Data expressed as the mean ± standard deviation; ^a*P*-values were determined by Student's *t*-test or Fisher's exact test; ^bvalues in parentheses indicate percentages in patients with schizophrenia and controls, respectively; ^cvalues in parentheses indicate percentages among the subjects with each genotype.

Abbreviations: AAP(s), atypical antipsychotics except for aripiprazole; BMI, body mass index; GST, glutathione S-transferase.

Table S2 Demographic and clinical characteristics according to *GSTT1* genotype in patients with schizophrenia and controls

	Schizophrenia (n=154)			Controls (n=203)		
	<i>GSTT1</i> present genotype	<i>GSTT1</i> null genotype	<i>P</i> ^a	<i>GSTT1</i> present genotype	<i>GSTT1</i> null genotype	<i>P</i> ^a
Number ^b	86 (55.8%)	68 (44.2%)	–	104 (51.2%)	99 (48.8%)	–
Age (years)	50.1±15.0	50.4±15.7	0.904	51.6±9.4	53.1±8.5	0.233
Male ^c	46 (53.5%)	34 (50.0%)	0.746	64 (61.5%)	53 (53.5%)	0.259
Smoker ^c	42 (48.8%)	36 (52.9%)	0.630	26 (25.0%)	17 (17.2%)	0.229
Height (cm)	160.6±8.1	163.0±8.6	0.080	163.9±8.0	161.8±9.7	0.087
Weight (kg)	64.2±12.8	66.3±14.5	0.324	62.6±10.3	60.8±11.4	0.235
BMI (kg/m ²)	24.8±4.1	24.8±4.0	0.969	23.2±2.9	23.1±3.4	0.852
Overweight ^c	40 (46.5%)	32 (47.1%)	1.000	24 (23.1%)	25 (25.3%)	0.745
Metabolic syndrome ^c	17 (19.8%)	17 (25.0%)	0.442	5 (4.8%)	10 (10.1%)	0.184
Waist circumference (cm)	85.6±12.1	86.8±11.8	0.529	83.1±7.6	82.6±8.6	0.648
Systolic blood pressure (mmHg)	125.0±16.9	127.1±16.0	0.447	117.5±16.5	116.8±16.0	0.775
Diastolic blood pressure (mmHg)	75.6±10.9	78.3±13.2	0.157	73.3±11.3	72.4±10.7	0.531
High-density lipoprotein (mg/dL)	53.1±16.1	50.9±12.5	0.335	64.1±16.7	67.1±17.7	0.215
Triglycerides (mg/dL)	134.8±93.9	166.9±179.3	0.184	125.0±101.6	116.8±71.6	0.508
Fasting blood glucose (mg/dL)	101.3±23.1	105.2±41.3	0.467	95.7±17.7	96.9±22.4	0.662
Outpatients ^c	55 (64.0%)	38 (55.9%)	0.324	–	–	–
Treatment with AAP(s) ^c	61 (70.9%)	51 (45.5%)	0.591	–	–	–

Notes: Data expressed as the mean ± standard deviation; ^a*P*-values were determined by Student's *t*-test or Fisher's exact test; ^bvalues in parentheses indicate percentages in patients with schizophrenia and controls, respectively; ^cvalues in parentheses indicate the percentages among the subjects with each genotype.

Abbreviations: AAP(s), atypical antipsychotics except for aripiprazole; BMI, body mass index; GST, glutathione S-transferase.

Table S3 Demographic and clinical characteristics according to *SOD2* genotype in patients with schizophrenia and controls

	Schizophrenia (n=154)			Controls (n=203)		
	Val/Val	Ala/Val, Ala/Ala	P ^a	Val/Val	Ala/Val, Ala/Ala	P ^a
Number ^b	113 (73.4%)	41 (26.6%)	–	153 (75.4%)	50 (24.6%)	–
Age (years)	49.5±15.2	52.2±15.6	0.334	52.4±9.0	52.3±8.8	0.993
Male ^c	59 (52.2%)	21 (51.2%)	1.000	88 (57.5%)	29 (58.0%)	1.000
Smoker ^c	57 (50.4%)	21 (51.2%)	1.000	34 (22.2%)	9 (18.0%)	0.690
Height (cm)	162.0±8.4	160.8±8.5	0.417	163.0±9.2	162.4±8.2	0.688
Weight (kg)	65.7±13.4	63.6±14.1	0.406	61.9±11.1	61.2±10.3	0.711
BMI (kg/m ²)	24.9±4.1	24.4±4.0	0.526	23.2±3.1	23.2±3.4	0.996
Overweight ^c	55 (48.7%)	17 (41.5%)	0.469	34 (22.2%)	15 (30.0%)	0.261
Metabolic syndrome ^c	24 (21.2%)	10 (24.4%)	0.666	11 (7.2%)	4 (8.0%)	0.765
Waist circumference (cm)	86.7±11.6	84.8±12.9	0.391	82.8±8.0	83.1±8.5	0.827
Systolic blood pressure (mmHg)	124.6±15.5	129.5±18.7	0.142	117.3±15.7	116.8±17.8	0.856
Diastolic blood pressure (mmHg)	76.5±11.4	77.7±13.5	0.573	72.9±11.1	72.6±10.9	0.858
High-density lipoprotein (mg/dL)	51.3±14.0	54.4±16.2	0.231	65.0±17.4	67.1±16.7	0.460
Triglycerides (mg/dL)	150.7±148.4	144.3±108.7	0.802	119.8±72.3	124.7±125.8	0.732
Fasting blood glucose (mg/dL)	102.6±31.2	104.2±35.7	0.780	96.9±21.0	94.4±17.2	0.447
Outpatients ^c	69 (61.1%)	24 (58.5%)	0.853	–	–	–
Treatment with AAP(s) ^c	84 (74.3%)	28 (68.3%)	0.540	–	–	–

Notes: Data expressed as the mean ± standard deviation; ^aP-values were determined by Student's t-test or Fisher's exact test; ^bvalues in parentheses indicate percentages in patients with schizophrenia and controls, respectively; ^cvalues in parentheses indicate the percentages among the subjects with each genotype.

Abbreviations: AAP(s), atypical antipsychotics except for aripiprazole; BMI, body mass index; *SOD2*, superoxide dismutase.

Table S4 Demographic and clinical characteristics according to the combination of *GSTM1* and *GSTT1* genotypes in the overall population of patients with schizophrenia

<i>GSTM1</i> and <i>GSTT1</i> genotypes	<i>M1</i> present/ <i>T1</i> present	<i>M1</i> null/ <i>T1</i> present	<i>M1</i> present/ <i>T1</i> null	<i>M1</i> null/ <i>T1</i> null	P ^a
Number ^b	49 (31.8%)	37 (24.0%)	28 (18.2%)	40 (26.0%)	–
Age (years)	49.2±15.1	51.3±15.1	44.6±13.9	54.4±15.7	0.064
Male ^c	28 (57.1%)	18 (48.6%)	13 (46.4%)	21 (52.5%)	0.802
Smokers ^c	23 (46.9%)	19 (51.4%)	19 (67.9%)	17 (42.5%)	0.203
Height (cm)	161.1±7.8	160.0±8.6	163.1±9.4	163.0±8.2	0.332
Weight (kg)	64.4±13.1	63.9±12.7	69.2±15.0	64.4±14.0	0.381
BMI (kg/m ²)	24.7±4.1	24.9±4.3	25.8±4.2	24.0±3.7	0.338
Overweight ^c	20 (40.8%)	20 (54.1%)	14 (50.0%)	18 (45.0%)	0.660
Metabolic syndrome ^c	7 (14.3%)	10 (27.0%)	9 (32.1%)	8 (20.0%)	0.252
Waist circumference (cm)	85.5±12.3	85.8±12.0	90.7±12.2	84.1±10.8	0.142
Systolic blood pressure (mmHg)	123.2±16.3	127.4±17.7	122.6±11.1	130.2±18.2	0.144
Diastolic blood pressure (mmHg)	74.8±10.3	76.6±11.6	77.8±10.4	78.8±14.9	0.463
High-density lipoprotein (mg/dL)	56.0±15.8	49.2±15.8	50.2±13.5	51.3±12.0	0.132
Triglycerides (mg/dL)	128.8±75.7	142.8±114.3	191.0±165.0	150.0±188.9	0.299
Fasting glucose (mg/dL)	99.4±23.7	103.9±22.4	109.1±52.3	102.4±31.9	0.652
Outpatients ^c	31 (63.3%)	24 (64.9%)	19 (67.9%)	19 (47.5%)	0.284
Treatment with AAP(s) ^c	36 (73.5%)	25 (67.6%)	18 (64.3%)	33 (82.5%)	0.308

Notes: Data expressed as the mean ± standard deviation; ^aP-values were determined by analysis of variance or Fisher's exact test; ^bvalues in parentheses indicate percentages in *GSTM1* present/*T1* present, *M1* null/*T1* present, *M1* present/*T1* null, *M1* null/*T1* null genotypes, respectively; ^cvalues in parentheses indicate percentages among the subjects with each genotype.

Abbreviations: AAP(s), atypical antipsychotics except for aripiprazole; BMI, body mass index; *GST*, glutathione S-transferase.

Table S5 Demographic and clinical characteristics according to the combination of *GSTM1* and *GSTT1* genotypes in the overall population of controls

<i>GSTM1</i> and <i>GSTT1</i> genotypes	<i>M1</i> present/ <i>T1</i> present	<i>M1</i> null/ <i>T1</i> present	<i>M1</i> present/ <i>T1</i> null	<i>M1</i> null/ <i>T1</i> null	<i>P</i> ^a
Number ^b	50 (24.6%)	54 (26.6%)	54 (26.6%)	45 (22.2%)	–
Age (years)	51.8±9.2	51.4±9.6	53.3±9.2	52.9±7.6	0.679
Male ^c	30 (60.0%)	34 (63.0%)	28 (51.9%)	25 (55.6%)	0.676
Smoker ^c	12 (24.0%)	14 (25.9%)	9 (16.7%)	8 (17.8%)	0.618
Height (cm)	163.4±8.1	164.4±8.0	161.4±10.6	162.2±8.7	0.333
Weight (kg)	62.4±10.1	62.8±10.6	58.9±12.7	63.0±9.4	0.177
BMI (kg/m ²)	23.3±3.1	23.2±2.8	22.4±3.4	24.0±3.3	0.123
Overweight ^c	13 (26.0%)	11 (20.4%)	13 (24.1%)	12 (26.7%)	0.872
Metabolic syndrome ^c	3 (6.0%)	2 (3.7%)	6 (11.1%)	4 (8.9%)	0.487
Waist circumference (cm)	84.1±7.5	82.2±7.6	80.5±8.7	85.1±7.9	0.023
Systolic blood pressure (mmHg)	118.9±17.4	116.2±15.7	114.6±16.1	119.6±15.6	0.371
Diastolic blood pressure (mmHg)	73.2±11.6	73.5±11.2	69.8±10.4	75.4±10.4	0.075
High-density lipoprotein (mg/dL)	63.0±16.8	65.1±16.7	67.3±15.8	66.9±20.0	0.583
Triglycerides (mg/dL)	134.9±129.4	115.8±66.4	110.3±72.5	124.6±70.4	0.515
Fasting glucose (mg/dL)	93.9±8.6	97.4±23.2	96.5±24.7	97.5±19.6	0.790

Notes: Data expressed as the mean ± standard deviation. ^a*P*-values were determined by analysis of variance or Fisher's exact test; ^bvalues in parentheses indicate percentages in *GSTM1* present/*T1* present, *M1* null/*T1* present, *M1* present/*T1* null, and *M1* null/*T1* null genotypes, respectively; ^cvalues in parentheses indicate the percentages among subjects with each genotype.

Abbreviations: BMI, body mass index; GST, glutathione S-transferase.

Table S6 Statistical power of associations between the genotypes and risk of metabolic abnormalities in patients with schizophrenia and smokers with schizophrenia at a significance (alpha) level of 0.05 (two-tailed) and adequate effect sizes (ie, odds ratios 2.0, 3.0, and 4.0) based on the sample size of the study and observed frequencies of the genotypes and metabolic abnormalities

	All patients with schizophrenia (n=154)						Smokers with schizophrenia (n=78)	
	<i>GSTM1</i> null genotype		<i>GSTT1</i> null genotype		<i>SOD2</i> Val/Val genotype		<i>GSTM1</i> null genotype	
	OR 2.0	OR 3.0	OR 2.0	OR 3.0	OR 2.0	OR 3.0	OR 3.0	OR 4.0
Overweight	56%	90%	55%	90%	46%	83%	63%	81%
MetS	43%	75%	41%	75%	32%	56%	55%	72%
Abnormal waist circumference	56%	90%	55%	90%	49%	85%	66%	82%
Elevated blood pressure	55%	89%	55%	89%	45%	79%	63%	81%
Decreased HDL cholesterol	52%	87%	51%	87%	40%	73%	62%	78%
Elevated triglycerides	50%	85%	49%	85%	39%	70%	57%	76%
Elevated fasting glucose	53%	88%	53%	88%	42%	76%	59%	76%

Notes: Frequencies of *GSTM1* null, *GSTT1* null, and *SOD2* Val/Val genotypes were fixed as 50.0%, 44.2%, and 73.4%, respectively, and those of overweight, MetS, abnormal waist circumference, elevated blood pressure, decreased HDL cholesterol, elevated triglycerides, and elevated fasting glucose were fixed as 47%, 22%, 55%, 41%, 34%, 31%, and 37%, respectively.

Abbreviations: MetS, metabolic syndrome; HDL, high density lipoprotein; GST, glutathione S-transferase; *SOD2*, superoxide dismutase 2; OR, odds ratio.

Table S7 Demographic and clinical characteristics according to the *GSTM1* genotypes in smokers and nonsmokers among patients with schizophrenia

	Smokers (n=78)			Nonsmokers (n=76)		
	<i>GSTM1</i> present genotype	<i>GSTM1</i> null genotype	<i>P</i> ^a	<i>GSTM1</i> present genotype	<i>GSTM1</i> null genotype	<i>P</i> ^a
Number ^b	42 (53.8%)	36 (46.2%)	–	35 (46.1%)	41 (53.9%)	–
Age (years)	45.5±13.8	52.7±15.3	0.033	49.9±15.7	53.2±15.7	0.371
Male ^c	29 (69.0%)	27 (75.0%)	0.620	12 (34.3%)	12 (29.3%)	0.805
Height (cm)	163.9±8.4	164.1±8.75	0.893	159.3±7.9	159.3±7.6	0.969
Weight (kg)	66.8±15.5	67.7±13.8	0.796	65.3±11.8	61.0±12.1	0.121
BMI (kg/m ²)	24.7±4.3	25.0±3.86	0.751	25.7±4.0	24.0±4.1	0.071
Overweight ^c	14 (33.3%)	18 (50.0%)	0.169	20 (57.1%)	20 (48.8%)	0.498
Metabolic syndrome ^c	11 (26.2%)	12 (33.3%)	0.619	5 (14.3%)	6 (14.6%)	1.000
Waist circumference (cm)	87.1±13.6	87.1±11.1	0.985	87.7±11.0	83.0±11.3	0.076
Systolic blood pressure (mmHg)	122.3±13.5	127.3±15.7	0.132	123.8±15.8	130.2±19.8	0.131
Diastolic blood pressure (mmHg)	75.6±11.2	77.0±11.4	0.582	76.3±9.4	78.4±15.0	0.481
High-density lipoprotein (mg/dL)	53.5±15.8	45.8±13.6	0.026	54.5±14.6	54.2±13.1	0.931
Triglycerides (mg/dL)	156.7±105.6	172.2±205.0	0.670	145.1±134.9	124.0±93.2	0.426
Fasting blood glucose (mg/dL)	97.2±21.6	106.3±34.9	0.164	109.8±48.6	100.3±19.0	0.252
Outpatients ^c	29 (69.0%)	23 (63.9%)	0.640	21 (60.0%)	20 (48.8%)	0.363
Treatment with AAP(s) ^c	30 (71.4%)	31 (86.1%)	0.170	24 (68.6%)	27 (65.9%)	1.000

Notes: Data expressed as the mean ± standard deviation; ^a*P*-values were determined by Student's *t*-test or Fisher's exact test; ^bvalues in parentheses indicate the percentages in smokers and nonsmokers, respectively; ^cvalues in parentheses indicate the percentages among the subjects with each genotype.

Abbreviations: AAP(s), atypical antipsychotics except for aripiprazole; BMI, body mass index; GST, glutathione S-transferase.

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