Lack of Association between Glutathione S-Transferase-M1, -T1, and -P1 Polymorphisms and Olanzapine-Induced Weight Gain in Korean Schizophrenic Patients

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Objective Oxidative stress may be an important pathogenic mechanism in the obesity and metabolic syndrome. The aims of this study was to assess the possible association between the oxidative stress related Glutathione S-Transferase genes (GST-M1, GST-T1, and GST-P1) variants and the olanzapine-induced weight gain in Korean schizophrenic patients.

Methods We categorized 78 schizophrenic patients into two groups the more than 7% weight gain from baseline (weight gain \( \geq 7\% \)) and the less weight gain (weight gain <7%) groups according to weight change between before and after long-term olanzapine treatment (440 ± 288 days). All participants were genotyped for the GST-M1, GST-T1 and GST-P1 genes. Differences in allele frequencies between cohorts with different body weight changes were evaluated by a chi-square analysis and Fisher’s exact test. The multifactor dimensionality reduction (MDR) approach was used to analyze gene-gene interactions.

Results Mean body weight gain was 5.42 kg. There was no difference in the null genotype distribution of GST-M1 and -T1 between subjects with body weight gain \( \geq 7\% \) compared to subjects with body weight gain <7% (p>0.05). No significant difference in GST-P1 genotype and allele frequencies were observed between the groups (p>0.05). MDR analysis did not show a significant interaction between the three GST gene variants and susceptibility to weight gain (p>0.05).

Conclusion These findings do not support a relationship between the genetic variants of three GST genes (GST-M1, -T1 and -P1) and weight gain in Korean schizophrenic patients receiving olanzapine treatment.

Key Words Weight gain, Olanzapine, Polymorphism, Glutathione-S-transferase.

Introduction

Weight gain, as an adverse reaction induced by the use of atypical antipsychotics, is well recognized and has become a serious problem. Weight gain is a major reason for discontinuation or noncompliance with atypical antipsychotics. Obesity and weight gain in adulthood have been associated with significant health complications such as type II diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, obstructive sleep apnea syndrome, respiratory problems and some types of cancer.1 Substantial weight gain may also adversely affect self-esteem, social functioning and physical activity.2 Furthermore, medication-induced weight gain has been associated with a lower quality of life,3,4 and is a leading barrier to continued compliance with psychiatric medications.5,6 In particular, the dibenzodiazepine-derived drugs, clozapine and olanzapine appear to have the greatest weight gain liability. Olanzapine is associated with significant weight gain comparable to that produced by clozapine.7

The underlying mechanisms by which these medications cause weight gain remain unclear. However, there are some pharmacological clues, such as those proposed to involve the histo-
Glutathione-S-transferase (GSTs) are enzymes that have ROS detoxification properties. GSTs also belong to a superfamily of polymorphic enzymes that catalyze the conjugation reaction between reduced glutathione and a variety of xenobiotics including carcinogens, environmental contamination, anti-cancer agents, antibiotics, and products of the oxidative process. The imbalance between ROS and antioxidants is related to insulin resistance in mice and humans. It has been proposed that increased oxidative stress also underlies the pathophysiology of metabolic syndrome. Therefore, functional polymorphisms of GSTs could be considered to be candidate genetic markers for a risk factor of weight gain or metabolic syndrome related to antipsychotic use.

GSTs can be categorized into four main classes: A, M, P, and T. Individuals who are homozygous for the null GST-M1 or GST-T1 allele lack the respective enzyme function. For example, several studies showed the positive correlation between indices of obesity, such as body mass index (BMI) and waist/hip ratio and the markers of oxidative stress such as reduced erythrocyte glutathione. There also has been much interested in the role of free radicals and oxidative stress in the pathogenesis of metabolic syndrome. It was reported that the oxidative stress was related to administration of antipsychotics, which increases dopamine turnover, and leads to excess production of oxidative metabolites in an animal study. Increased production of oxidative metabolites leads to the formation of reactive oxygen species (ROS). Furthermore, ROS-induced mitochondrial dysfunction can lead to disruptions of lipid metabolism, increasing the intracellular lipid content.

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GSTs can be categorized into four main classes: A, M, P, and T. Individuals who are homozygous for the null GST-M1 or null GST-T1 allele lack the respective enzyme function. GST-P1 is an important GST isoform. Depending on the GST-P1 polymorphisms, Ile-to-Val changes in the amino acid sequence of the protein may alter the activity of the enzyme. Recently there was the finding that GST-P1 Val variant possesses five-fold more enzymatic activity to some metabolites in GST-P1 Ile/Val or Ile/Ile. Therefore, we hypothesized that the null alleles of GST-M1, -T1, and the Ile allele of GST-P1 may increase the formation of ROS and then, the disruptions of lipid metabolism, increasing the intracellular lipid content, leading to the risk of weight gain. We sought to characterize the genetic polymorphisms in the GST-M1, T1, and -P1 genes in schizophrenic patients with and without weight gain in a genetically homogenous Korean population. To date there has been no study of antipsychotic-induced weight gain associated with GST genes yet. We therefore performed the first study of antipsychotic-induced weight gain associated with GST gene variants. We also investigated whether gene-gene interactions among GST-M1, -T1, and -P1 gene polymorphisms could be correlated with olanzapine-induced weight gain in our sample.

### Methods

**Subjects**

A total of 103 schizophrenic patients were enrolled from the three collaborating hospitals of Korea University Hospital. All subjects were examined by trained psychiatrists using the Korean version of the Structured Clinical Interview for DSM-IV, leading to a diagnosis based on DSM-IV criteria. Exclusion criteria included evidence of other psychiatric, medical, or neurological illness; family history of diabetes or eating disorder; and age over 65 or under 18 years. Application of these criteria resulted in the exclusion of 25 patients. All the subjects were ethnic Koreans, and some findings from these subjects have been reported previously. Written informed consents were obtained, and the study protocol was approved by the Ethics Committee of the Korea University Hospital.

Seventy-eight subjects were weighed prior to starting olanzapine and again after long-term treatment at least 3 months (440±288 days). The dosage was adjusted individually according to clinical judgment. We controlled the use of drugs other than olanzapine. Medications such as antipsychotics, mood stabilizers, and antidepressants were avoided during the study, because of their potential effects on weight change. However, we combined the use of benzodiazepines or anticholinergics as needed. No subject had received olanzapine or clozapine prior to the present study. The mean daily dose of olanzapine at the end-point examination was 14.05 mg (standard deviation=5.1 mg).

Other clinical variables that were measured in the study were gender, age, olanzapine treatment duration and dosages, and previous antipsychotics dosages (expressed as chlorpromazine equivalents). Changes in body weight and BMI during the treatment were also calculated.

**Genotyping**

Genetic polymorphism analyses for the GSTM1 and GSTT1 genes were determined using the multiplex polymerase chain reaction (PCR) with modifications of the previously described method. The appropriate fragment of the GST gene for the GSTM1 and GSTT1 alleles was amplified with specific primers from human genomic deoxyribonucleic acid (DNA). The following primers were used in the PCR reaction: GSTM1, (sense) 5'-GAACCTCCCTGAAAAGCTAAAGC-3' and (antisense) 5'-GTGGA-GCTCAATAATACGTGG-3'; GSTT1, (sense) 5'-TTCCTTACTGGTCCTCACATCTC-3' and (antisense) 5'-TCACCGGATCATGGCCAGCA-3'. PCR was performed in a total volume of 30 L containing 100 μg genomic DNA, 5 M of each primer, 2.5 mM deoxyribonucleoside triphosphates, 1.5 mM MgCl₂, 100 mM Tris- HCl, and 1 U thermostable Taq DNA polymerase with a GeneAmp PCR system 2700 (Applied Biosystems, Foster, CA, USA). The amplification conditions were initial denaturation at 94°C for 5
min, followed by 35 cycles of denaturation at 94°C for 45 sec, annealing at 59°C for 50 sec, extension at 72°C for 1 min, and a final extension step at 72°C for 10 min. The PCR amplification products (GSTM1: 215 bp, GSTT1: 480 bp) were then separated electrophoretically on an ethidium bromide-stained 2% agarose gel.

A PCR-based assay was used to detect the GSTP1 polymorphism on exon 5.10 The primer sequences for GSTP1 exon 5 were (sense) 5’-GAGGAAACTGAGACCCACTGAG-3’ and (antisense) 5’-AGCCCTTTTCTTTGTTACGCC-3’. A typical PCR reaction was performed in a 25 μL volume containing 1× PCR buffer, 3.0 mM MgCl₂, 0.25 mM dNTPs, 1.5 units of Taq polymerase, and 0.3 mM of primers GSTP1 exon 5. The DNA chains were denatured by incubation at 94°C for 5 min, followed by 35 cycles of 94°C for 30 sec, then 60°C for 30 sec, and 72 °C for 30 sec, followed by a final extension step at 72°C for 5 min. A 424-bp DNA fragment was amplified for exon 5 and followed by 3 h of digestion with 4 units of BsmAI for exon 5 (New England Biolabs, Beverly, MA, USA). The fragments were separated on a 3% agarose gel stained with ethidium bromide. The Ile/Ile, Ile/Val and Val/Val genotypes yielded two bands (292 and 132 bp), four bands (292, 222, 132 and 70 bp), and three bands (222, 132 and 70 bp), respectively.

### Statistical analyses

Differences in allele frequencies between groups with different body weight changes were evaluated by a chi-square analysis and Fisher’s exact test. The association of genotype with weight gain and change in BMI was tested with Student’s t-test. All of the analyses were performed using standard software (Statistical Package for the Social Sciences for Windows), and p values smaller than 0.05 were considered statistically significant. The multifactor dimensionality reduction (MDR) approach was designed to detect gene-gene interactions in the presence or absence of main effects in case-control studies in human genetics.11-13 MDR has been shown to have high power for detecting interactions in a wide range of simulated data.15-17 MDR has also been used to identify interactions in common complex diseases.10-19 MDR is a non-parametric, model-free approach, making it a unique tool for identifying interactions. MDR categorizes all genetic data into 2 groups, “high risk” and “low risk”, by comparing all single loci and all multilocus combinations and then categorizing each genotype as either “high risk” or “low risk” on the basis of the ratio of cases to controls having that genotype. MDR ultimately selects one genetic model, either single or multilocus, that predicts phenotype with the greatest success. To evaluate the predictive ability of the model, prediction error was calculated using 10-fold cross-validation. The result is a set of models, one for each model size considered. From these models, a final model is chosen on the basis of minimization of prediction error and maximization of cross-validation consistency (CVC) (number of times a particular set of factors is identified across the cross-validation subsets). Statistical significance is determined empirically by permuting the case and control labels 1,000 times. The use of permutations to generate p values eliminates the problem of multiple testing. The MDR analysis was carried out using version 1.1.0 of the MDR software package (http://www.epistasis.org).

### Results

There were no differences in age (45.24±11.24 years vs. 47.41±11.43 years, t=0.83, p=0.41), sex (male/female, 25/12

**Table 1. GSTs genotype frequencies in subjects with weight gain <7% and weight gain ≥7%**

| Genotypes         | Weight gain <7% (N=37) | Weight gain ≥7% (N=41) | χ², p-value | OR (95% CI) |
|-------------------|------------------------|------------------------|-------------|-------------|
| GST-M1 Wild       | 18 (48.6)              | 17 (41.5)              | χ²=0.41, p=0.52 | OR=0.75 (0.31-1.83) |
| Null              | 19 (51.4)              | 24 (58.5)              |             |             |
| GST-T1 Wild       | 15 (40.5)              | 17 (41.5)              | χ²=0.007, p=0.93 |             |
| Null              | 22 (59.5)              | 24 (58.5)              | OR=1.04 (0.42-2.57) |             |
| GST-M1/GST-T1 Both wild | 7 (18.9) | 5 (12.2) | χ²=0.76, p=0.69 |             |
| Either null       | 19 (51.4)              | 24 (58.5)              |             |             |
| Both null         | 11 (29.7)              | 12 (29.3)              |             |             |
| GST-P1 Ile/Ile    | 26 (70.3)              | 26 (63.4)              | χ²=0.52, p=0.77 |             |
| Ile/Val           | 9 (24.3)               | 13 (31.7)              |             |             |
| Val/Val           | 2 (5.4)                | 2 (4.9)                |             |             |

GST: glutathione S-transferase, OR: odds ratio, CI: confidence interval
Table 2. Summary of multifactor dimensional reduction results

| Model          | Training accuracy | Testing accuracy | p-value* | CVC†  |
|----------------|-------------------|------------------|----------|-------|
| GST-P1         | 0.5514            | 0.4490           | 0.8281   | 6/10  |
| GST-M1 and -P1 | 0.5838            | 0.4320           | 0.8281   | 9/10  |
| GST-M1, T1, and P1 | 0.5950            | 0.3816           | 0.9453   | 10/10 |

*1,000-fold permutation test, †cross-validation consistency. GST: glutathione S-transferase, CVC: cross-validation consistency.

found that some of the side effects of antipsychotic drug are related to oxidative stress and to the level of ROS that is controlled by antioxidant such as glutathione. Kuzuya et al. reported that there was the association between glutathione peroxidase 1 (GPX1) 198Leu variants and central obesity in men. They also reported that CT/TT genotypes were associated with the higher prevalence of metabolic syndrome in men. Therefore, they speculated that these association suggested that a weaker antioxidant defense system or greater oxidative stress might be a causative factor for obesity. In addition to GPX1, it was reported that defective glutathione peroxidase 3 (GPX3) expression in adipose tissue is associated with reduced systemic GPX activity and increased oxidative stress in obesity. Lee et al. proposed that local ROS accumulation in the adipose tissue of obesity could be expanded into systemic oxidative stress by the vicious cycle wherein increasing local ROS accumulation suppresses adipose GPX3 expression. Although there was no previous study reporting the association between the GSTs and weight gain and we also found no evidence of the association between the GST polymorphism of glutathione and olanzapine-induced weight gain, it is possible that glutathione and its related enzymes are associated with obesity and metabolic complication such as metabolic syndrome.

This study had several limitations. First, its long-term nature made complete control over the use of drugs impossible. Therefore, we could not exclude the effects of different dosages and combining medications (e.g., benzodiazepine and benzotriphenine), although the drugs used (regarding olanzapine dosage) did not differ significantly among genotype groups. Furthermore, most patients had received other antipsychotics before olanzapine treatment, and hence we could not exclude the effects of prior medication. Second, the duration of medication was not the same for all subjects in our sample. However, we do not believe that this would have a significant effect, since the duration of olanzapine treatment did not differ between the genotype groups and we checked the final body weight at least 3 months later in all patients. Previous studies have found that weight was mainly gained during the first 6–8 weeks of olanzapine therapy. It is also reported that there was the association between the -759C/T polymorphism of the 5-HT2C receptor gene with early phase (after 4 weeks of treatment) weight gain induced by antipsychotic treatment in Korean schizophrenic patients. Third, the long-term nature of this study prevented us from assessing or controlling caloric intake (e.g., caloric count and meal refusals). Fourth, the relatively small sam-
ple limits the generalizability of our findings.

Future studies should employ larger samples and control the use of medication. In addition, the possible involvement of as-yet-uncovered gene(s) that influence susceptibility to olanzapine-induced weight gain should be evaluated, as well as the possibility of gene-gene and gene-environment interactions.

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