Multiple Genetic Factors in Olanzapine-Induced Weight Gain in Schizophrenia Patients: A Cohort Study

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Objective: One of the clinically significant adverse effects of olanzapine treatment is weight gain, which shows substantial inter-individual differences and may be influenced by genetic variation. The aim of this investigation was identification of genetic risk factors associated with olanzapine-induced weight gain.

Method: Inpatients with DSM-IV-TR schizophrenia (N = 164) were administered olanzapine for 8 to 24 (mean ± SD = 17.9 ± 9.4) weeks. The clinical background, body mass index (BMI), and clinical response to olanzapine were investigated. Twenty-one loci of diverse candidate genes encoding dopamine, serotonin (5-HT), histamine, and adrenergic receptors, tumor necrosis factor-alpha, ghrelin, adiponectin, and peroxisome proliferator-activated receptor gamma-2, were analyzed. The study was conducted from June 2001 to June 2003 at 4 psychiatric hospitals in Japan.

Results: BMI increased by a mean ± SD 4.3 ± 10.7% after treatment with olanzapine (mean ± SD dose = 15.5 ± 5.8 mg/day). Olanzapine-induced weight gain correlated negatively with baseline BMI and positively with clinical global improvement and the length of olanzapine treatment ($p < .0001$), but it did not correlate with the daily dose of olanzapine, concomitant antipsychotics, sex, age, or smoking. Four genetic variants, the 102T allele of *HTR2A*, the 825T allele of *GNB3*, the 23Cys allele of *HTR2C*, and the 64Arg/Arg genotype of *ADRB3*, were significantly associated with olanzapine-induced weight gain. Stepwise regression analysis revealed that the baseline BMI predicted 12.5% of the weight gain, and the 2 latter genetic factors added 6.8%. The patients with double and triple genetic risk factors showed 5.1% and 8.8% BMI increases, respectively, during olanzapine treatment, whereas the patients with a single or no risk factor showed approximately a 1% BMI increase.

Conclusions: We identified genetic variants of 5-HT_{2A} and 5-HT_{2C} receptors, the G-protein beta-3 subunit, and the adrenergic receptor beta-3, as genetic risk factors for olanzapine-induced weight gain, and they showed additive genetic effects on weight gain.

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Atypical antipsychotics have the advantage of producing fewer adverse extrapyramidal and hormonal effects than typical antipsychotics. The American Psychiatric Association Practice Guideline[1] recommends prescribing atypical antipsychotics as the first treatment for schizophrenia. However, atypical antipsychotics also have some disadvantages, including apparently increased risks for weight gain and development of metabolic syndrome,[2] which could interfere with treatment adherence, damage the quality of life, and increase mortality. Among the atypical antipsychotics, clozapine and olanzapine may induce these side effects most frequently. A recent Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study[3] revealed that a weight gain of 7% or more was found in 30% of schizophrenic patients treated with olanzapine at doses of 7.5 to 30 mg/day, and the amount of weight gain induced by olanzapine was much greater than that induced by quetiapine, risperidone, or ziprasidone. Clinical observation of substantial inter-individual differences in drug-induced weight gain implies that genetic components may be involved, but the precise genetic mechanisms remain unclear. Several previous studies suggested a possibility of predicting antipsychotic-induced weight gain by individual genetic testing.[4–6] In Japan, olanzapine has the most potential to induce weight gain among antipsychotics, because clozapine is still not available. Accordingly, we measured weight changes in schizophrenic patients after treatment with olanzapine and examined the genetic association with multiple candidate genes. For

this purpose, we examined diverse genes as candidates: genes encoding dopamine (*DRD2*), serotonin (*HTR2A, HTR2C,* and *HTR6*), and histamine receptors (*HRH1, HRH2,* and *HRH3*) were selected because of the pharmacologic profile of olanzapine, and genes encoding molecules related to appetite, feeding, and obesity, i.e., tumor necrosis factor-alpha and its receptors, ghrelin, adiponectin, peroxisome proliferator-activated receptor gamma (*PPARG*), and fatty acid amide hydrolase (*FAAH*), a synthetase of endogenous cannabinoids, were also examined. We also examined genes previously reported to be associated with clozapine-induced weight gain, i.e., the synaptosomal-associated protein 25 kDa (*SNAP25*) and the G protein beta-3 subunit (*GNB3*) genes.[7–9]

METHOD

Patients

To avoid selection bias, all patients enrolled in this study fulfilled the following criteria: (1) had schizophrenia diagnosed by DSM-IV-TR criteria, (2) were more than 18 years and less than 70 years old, (3) were inpatients of a certain psychiatric hospital for the entire period of olanzapine treatment, (4) underwent treatment with olanzapine for 8 weeks or more (maximum 24 weeks) as an add-on to previous antipsychotics without changing other medicines, (5) had no physical disease that affected body weight or appetite, e.g., diabetes mellitus or gastrointestinal disease, and (6) gave written informed consent to participate in the study. One hundred sixty-four schizophrenic patients (100 men and 64 women) fulfilled the above conditions. Their mean age was 51.8 (SD 10.9) years. The dosage of olanzapine was determined by the attending psychiatrist. The antipsychotics most frequently administered concomitantly with olanzapine were risperidone, haloperidol, bromperidol, zotepine, and chlorpromazine. Mood stabilizers were administered to 47 patients (28.7%), and antidepressants were administered to 4 patients (2.4%). Body weight before and after treatment with olanzapine was measured once a month. We also examined clinical variables—height, daily dose of olanzapine, length of olanzapine treatment, concomitant antipsychotic (haloperidol-equivalent dose) treatment, number of cigarettes smoked daily, and the clinical efficacy of olanzapine using the Clinical Global Impressions-Improvement scale (CGI-I). This study was approved by the Ethics Committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences. The study was conducted from June 2001 to June 2003. Participating hospitals were Jikei Hospital and Okayama University Hospital (Okayama, Japan), Fukuyama Jinpuso Hospital (Fukuyama, Japan), and Kibougaoka Hospital (Tsuyama, Japan).

Genotyping

Genomic DNA was extracted from peripheral venous blood using a standard method. Twenty-one polymorphisms of 17 genes were selected as candidate loci based on previous reports that showed a possible genetic association with olanzapine- or clozapine-induced weight gain. Genes that are known to be involved in appetite and obesity and the pharmaceutical effects of olanzapine were also examined. The loci examined were the *Taq*1A polymorphism of the dopamine D2 receptor gene (*DRD2*), the -308G/A and -857C/T polymorphisms of the tumor necrosis factor-alpha gene (*TNFA*), the 36A/G polymorphism of the TNFA receptor 1A gene (*TNFRSF1A*), the 196Met/Arg polymorphism of the TNFA receptor 1B gene (*TNFRSF1B*), the 449Leu/Ser polymorphism of the histamine receptor H1 gene (*HRH1*), the -1018G/A polymorphism of the H2 receptor gene (*HRH2*), the 332Ser/Ser polymorphism of the H3 receptor gene (*HRH3*), the 102T/C polymorphism of the serotonin receptor 2A gene (*HTR2A*), the 23Cys/Ser and -759C/T polymorphisms of the serotonin receptor 2C gene (*HTR2C*), the 267T/C polymorphism of the serotonin receptor 6 gene (*HTR6*), the Try64Arg polymorphism of the beta 3 adrenergic receptor gene (*ADRB3*), the Leu72Met polymorphism of the ghrelin gene (*GHRL*), the G276T polymorphism of the adiponectin gene (*ADIPOQ*), the Pro12Ala polymorphism of the *PPARG* gene, the 401C/T, 1065T/G, and 1069T/C polymorphisms of the *SNAP25* gene, the C825T polymorphism of the *GNB3* gene, and the Pro129Ther polymorphism of the *FAAH* gene. Genotyping was determined by a restriction fragment length polymorphism method or TaqMan SNP Genotyping Assays (Applied Biosystems, Foster City, Calif.) under conditions blind to the clinical data.

Statistical Analysis

The body mass index (BMI) of patients was calculated as body weight (kg) divided by the square of the height (m^2). The phenotype used was the percent change of BMI. The relationships of the BMI change with the clinical variables of age, baseline BMI, daily dose of olanzapine, period of olanzapine treatment, CGI-I score, daily haloperidol-equivalent dose of concomitant antipsychotics, and number of cigarettes smoked daily were examined by the Spearman rank correlation test. Effects of sex and each genotype on BMI change were examined by Kruskal-Wallis test or Mann-Whitney test. Stepwise linear regression analysis was used to establish the potential confounding effects of age, baseline BMI, daily dose of olanzapine, duration of olanzapine treatment, daily haloperidol-equivalent dose of concomitant antipsychotics, and number of cigarettes smoked daily and to estimate the magnitude of a certain genotype effect on variation of olanzapine-induced weight change.

Statistical analyses were done with Statview software version 4.5J (Adept Scientific, Inc., Acton, Mass.).

RESULTS

Body weight increased by a mean ± SD 4.3 ± 10.7% after treatment with olanzapine at a mean ± SD daily dose of 15.5 ± 5.8 mg for a mean ± SD duration of 17.9 ± 9.4 weeks. The weight change induced by olanzapine showed substantial inter-individual differences. Thus, 51.7% patients showed weight gain (defined as +3% or more), 28.0% patients showed no weight change (defined as within ≤ 3%), and 17.1% showed weight loss (defined as –3% or more). An apparent weight gain, defined as 7% or more weight increase, was observed in 31.1% patients, and a prominent weight gain, defined as 10% or more weight increase, was observed in 14.6% patients.

Several clinical variables showed significant correlation with the olanzapine-induced weight gain. The BMI at baseline was inversely correlated with olanzapine-induced weight gain ($p < .0001$, $\rho = –0.324$), indicating that patients with a lower BMI tended to gain weight during olanzapine treatment, whereas patients with a higher BMI tended to lose weight during olanzapine treatment. We also found that CGI-I score ($p < .0001$, $\rho = 0.322$) and duration of olanzapine treatment ($p < .0001$, $\rho = 0.344$) correlated positively with weight gain after treatment with olanzapine. On the other hand, the daily dose of olanzapine ($p = .64$), daily haloperidol-equivalent dose of concomitant antipsychotics ($p = .10$), age ($p = .67$), sex ($p = .75$), or number of cigarettes smoked daily ($p = .80$) did not correlate with olanzapine-induced weight change. Concomitant treatment of mood stabilizers (carbamazepine, lithium carbonate, or valproate) did not affect olanzapine-induced weight change, because the patients with mood stabilizer ($N = 47$) and without ($N = 117$) showed a mean ± SD weight change of 4.7 ± 13.3% and 4.1 ± 11.2%, respectively.

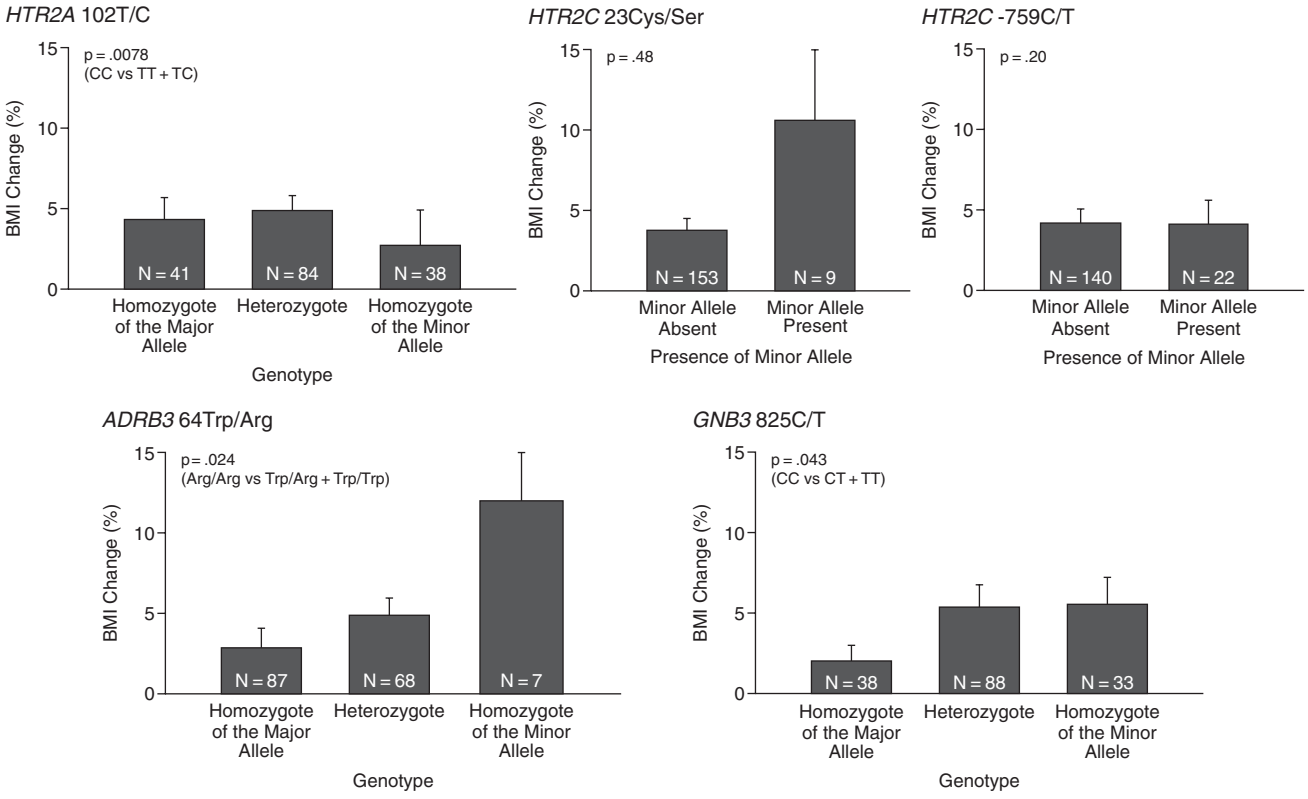
Among the 21 polymorphisms examined, the 449Leu/Ser polymorphism of the *HRH1* gene and the 401C/T polymorphism of the *SNAP25* gene were monomorphic in the Japanese subjects, and the -308G/A polymorphism of the *TNFA* gene and the 96Met/Arg polymorphism of the *TNFRSF1B* gene showed that the minor genotype group had an N less than 5, which could not be applied to the Kruskal-Wallis test or the Mann-Whitney test. Accordingly, genotypes of the other 17 polymorphisms were analyzed for association with olanzapine-induced weight changes. Significant associations of olanzapine-induced weight gain were found with the 102T/C polymorphism of the *HTR2A* gene ($z = –2.659$, $p = .0078$), the 64Trp/Arg polymorphism of the *ADRB3* gene ($z = –2.256$, $p = .024$), and the 825C/T polymorphism of the *GNB3* gene ($z = –2.019$, $p = .043$; Figure 1). Thus, the patients who were homozygous for the 64Arg allele of the *ADRB3* gene or those who were heterozygous or homozygous for the 825T allele of the *GNB3* gene showed a significantly greater weight gain after olanzapine treatment than those who were not. In contrast, patients with the 102C/C genotype of the *HTR2A* gene showed a significantly lower weight gain than those without it. In other words, having the 102T allele of *HTR2A*, a major allele, was a risk factor for olanzapine-induced weight gain. Similar to the results of the Spearman rank correlation test, stepwise regression analysis revealed that the baseline BMI predicted olanzapine-induced weight gain, whereas age, dose of olanzapine, duration of olanzapine treatment, haloperidol-equivalent dose of concomitant antipsychotics, and number of cigarettes smoked daily did not. Table 1 shows that the mean ± SD coefficient of the baseline BMI was –0.98 ± 0.21. Stepwise regression analysis also revealed that possession of the 23Ser allele of the *HTR2C* gene and the 64Arg/64Arg genotype of the *ADRB3* gene predicted olanzapine-induced weight gain, and their mean ± SD coefficients were 9.1 ± 3.4 and 9.0 ± 3.6, respectively.

To test the effects of multiple genetic risks on olanzapine-induced weight gain, the patients were divided by the numbers of genetic risk factors found in the present study, which were defined as presence of the 102T allele of the *HTR2A* gene, the 23Ser allele of the *HTR2C* gene, the 64Arg/Arg genotype of the *ADRB3* gene, and the 825T allele of the *GNB3* gene. Twelve patients had no genetic risk factor, 49 patients had 1, 87 patients had 2, 13 patients had 3 genetic risk factors, and no patient had all 4 genetic risk factors. The patients with double or triple genetic risk factors showed 5.1% and 8.8% BMI increases after olanzapine treatment, respectively, whereas the patients with a single or no genetic risk factor showed approximately a 1% BMI increase (Figure 2).

DISCUSSION

The present study design was retrospective, but we tried to minimize the sampling bias by enrolling all subjects without physical disorders, e.g., diabetes mellitus or gastrointestinal disease, who were treated with olanzapine for at least 8 weeks. In addition, only inpatients were enrolled to avoid the effects of free access to food, e.g., soft drinks or midnight snacks. Under these conditions, more than half the patients showed weight gain after treatment with olanzapine, and about 30% of patients showed a weight gain of 7% or more, a ratio similar to that reported by the CATIE study.[3] Among clinical variables, the baseline BMI, clinical effectiveness of olanzapine therapy as measured by CGI-I scores, and duration of olanzapine treatment correlated with olanzapine-induced weight gain. Patients with a lower baseline BMI and those who showed better clinical response showed a greater weight gain. These results were consistent with previous

Figure 1. Effects of Polymorphisms on Olanzapine-Induced Weight Gain[a]



[a]Vertical bars indicate the standard error.
Abbreviation: BMI = body mass index.

clozapine studies.[10–12] On the other hand, age, sex, dose of olanzapine, dose of concomitant antipsychotics, and smoking did not influence olanzapine-induced weight gain. Unexpectedly, no effect of the daily dose of olanzapine on weight gain was found, but this result was consistent with previous studies reporting that the daily dose of clozapine did not affect clozapine-induced weight gain.[13,14]

We found that having the 102T allele of the *HTR2A* gene, the 825T allele of the *GNB3* gene, the 23Cys allele of the *HTR2C* gene, or the 64Arg/Arg genotype of the *ADRB3* gene were positive genetic risk factors for olanzapine-induced weight gain. Stepwise regression analysis revealed that a clinical variable, baseline BMI, predicted 12.5% of the weight gain, and the 2 latter genetic factors, the 23Cys allele of the *HTR2C* gene and the 64Arg/Arg genotype of the *ADRB3* gene, added 6.8%. The coefficient value of these 2 genetic factors was about 9.

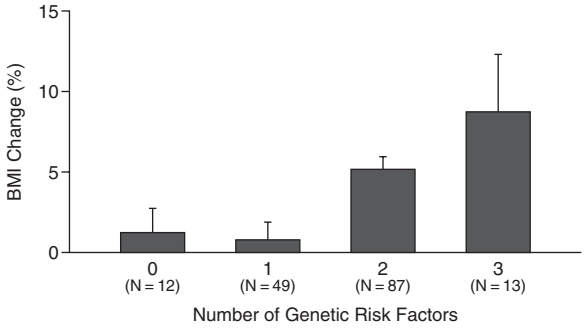
The serotonin system is involved in regulation of appetite and food intake, and increasing and decreasing serotonin levels result in attenuated and enhanced feeding behaviors, respectively, in animals and humans.[15] These effects of serotonin on feeding may be mediated in part via the serotonin 2 family receptors, 5-HT_{2A} and 5-HT_{2C}. In previous studies of 5-HT_{2A} receptors, specific agonists of 5-HT_{2A} receptors decreased the neuropeptide Y-induced hyperphagia[16] and 5-HT_{2A} receptor antagonists reduced serotonin-induced hypophagia.[17] We found that the 102T/C polymorphism of the *HTR2A* gene was associated with olanzapine-induced weight gain, and the 102T allele, a major one, was a risk for excess weight gain. The 102T/C polymorphism is a silent one, but it is in complete linkage disequilibrium with the promoter -1438G/A polymorphism, and the T allele is associated with higher expression of 5-HT_{2A} receptors in the brain.[18] Olanzapine may be more efficient in antagonizing 5-HT_{2A} receptors in individuals with the T allele of *HTR2A* because they presumably have a higher 5-HT_{2A} receptor density in the brain, which results in olanzapine-induced weight gain. On the other hand, 5-HT_{2C} receptor agonists reduced food consumption and weight,[19] 5-$HT_{2A/2C}$ receptors antagonists caused a marked increase in feeding,[20] and 5-HT_{2C}–deficient mice showed increased feeding and obesity.[21] Basile et al.[5] reported for the first time that the nonsynonymous polymorphism Cys23Ser of *HTR2C* showed a tendency, although not a statistically significant one, to be associated with clozapine-induced weight gain.

Table 1. Forward Stepwise Regression Analysis of Clinical and Genetic Risk Factors for Olanzapine-Induced Weight Gain

Response Variable	Step	r^2	p Value	Regressors	Coefficient
Weight change (% BMI)	1	0.125	< .0001	Baseline BMI	–0.997
	2	0.160	< .0001	Baseline BMI	–0.999
				Ser23 of *HTR2C*	8.683
	3	0.193	< .0001	Baseline BMI	–0.984
				Ser23 of *HTR2C*	9.128
				Arg/Arg of *ADRB3*	8.994

Abbreviation: BMI = body mass index.

Figure 2. Dose Effects of Number of Genetic Risk Factors for Olanzapine-Induced Weight Gain[a]*



[a]Vertical bars indicate the standard error.
*p = .006.
Abbreviation: BMI = body mass index.

Subsequent studies showed no significant association between the Cys23Ser polymorphism and clozapine-induced weight-gain in Caucasian[22] and Chinese[23] people with schizophrenia. However, the present study revealed that the 23Ser allele of the *HTR2C* gene was a significant risk factor for olanzapine-induced weight gain, at least in Japanese schizophrenia patients. In contrast, C795T, another polymorphism of *HTR2C*, was shown to be associated with antipsychotic-induced weight gain in Caucasian and Chinese but not Japanese schizophrenia patients. Thus, the –795T allele, which has been shown to reduce transcription of the gene to 60%,[24] was a negative risk for antipsychotic-induced weight gain in the first episode of schizophrenia in Han Chinese patients treated mainly with risperidone and chlorpromazine[25] or clozapine alone[13] or Caucasian patients treated with several antipsychotics[26] or olanzapine.[26,27] These findings were not supported by several other studies of the same populations treated with clozapine,[28–30] and the present study examined Japanese patients treated with olanzapine.

The adrenergic receptor beta-3 plays a key role in the regulation of energy balance through stimulation of lipid mobilization and thermogenesis in adipose tissue,[31] and the Arg64 variant allele of the *ADRB3* gene has been linked to overweight, lower resting metabolic rate, and insulin resistance.[32–34] We found that patients with the homozygote of the Arg64 variant showed significantly higher weight gain after olanzapine treatment compared to those without it. Tsai et al.[35] did not find this effect of the Arg64 variant for clozapine treatment in patients with treatment-resistant schizophrenia in a Han Chinese population. However, only 1 out of 87 patients in their sample had the Arg64 homozygote. Therefore, this inconsistency may be the result of lower statistical power in their study.

The *GNB3* gene is another attractive candidate for antipsychotic-induced weight change, because the C825T polymorphism of *GNB3* has been associated with obesity in a general population[36,37] and patients with obesity-related disorders, hypertension, coronary disease,[38–40] and postpregnancy weight retention.[41] The C825T polymorphism of *GNB3* was silent when located on exon 10, but it affected splicing, and the 825T allele increased the occurrence of a splice variant that enhanced G-protein signaling.[42,43] Functional data have shown that the 825T allele of the gene decreased the lipolytic response of adipose tissue to catecholamines.[44,45] In addition, clozapine administration has been shown to increase the GNB3 level in the rat striatum.[46] We found that patients with the 825T allele showed a significantly greater weight gain after olanzapine treatment than did those with the 825C homozygote. The present finding was consistent with previous studies. Wang et al.[9] reported that Chinese schizophrenia patients with the 825T homozygote showed greater weight gain after clozapine treatment, although this finding was not consistent with a study that examined Chinese treatment-resistant patients.[35] Bishop et al.[8] reported that Caucasian schizophrenia patients with the TT genotype showed a greater tendency to gain weight during olanzapine treatment and a better response to treatment.

We found that 4 genetic variants of 21 candidate loci were risk factors for weight gain due to treatment with olanzapine in schizophrenic patients. Because all of the previous studies, except for that by Basile et al.,[5] examined only 1 or 2 genes for antipsychotic-induced weight gain, the effects of multiple genetic risk factors for this adverse effect were unknown. We reexamined individual genetic profiles, and analyzed the relationships between a number of genetic factors and weight gain. We found that the patients with double or triple genetic risk factors showed significantly greater weight gain during

olanzapine treatment than the patients with a single or no genetic risk factor. The findings seem reasonable and very important for enabling clinical practitioners to predict the risk of obesity due to olanzapine treatment. However, the patients with only 1 genetic risk factor did not show weight gain. This fact may seem to be inconsistent with the results of the primary analysis. Among 49 patients with a single genetic risk factor, 25 patients had the 102T allele of *HTR2A*, 23 patients had the 825T allele of *GNB3*, and 1 patient had the 64Arg/Arg genotype of *ADRB3*. Therefore, 25 patients with the 102T allele of *HTR2A* also had the 825C/C genotype of *GNB*, which was a negative risk factor for olanzapine-induced weight gain, and 23 patients with the 825T allele of *GNB3* also had the 102C/C genotype of the *HTR2A*, which was a negative risk factor for olanzapine-induced weight gain. Such a combination of a risk factor and a negative risk factor in the patients with single genetic risk may offset weight gain.

LIMITATIONS

Some limitations of the present study must be considered. Olanzapine was administered in addition to previously prescribed antipsychotics. Although the doses of the concomitant antipsychotics were fixed during this study, and stepwise regression analysis did not detect any effect of the concomitant antipsychotics on olanzapine-induced weight change, the possibility of additive or synergistic effects of olanzapine should be taken into account. The subjects enrolled were inpatients, because hospital admission can make it easier to control compliance with olanzapine administration, measure weight precisely in identical conditions, and control the total diet. Nevertheless, this restriction may overlook some factors associated with appetite. In clinical observation, patients treated with olanzapine sometimes showed enhanced appetite and hyperphagia or binge consumption of food and soft drinks that resulted in overweight. The present study design could not detect genetic factors of olanzapine-induced weight gain due to such mechanisms. Our sample size, 164 patients, was relatively large when compared to previous studies examining this issue but not large enough to dismiss the possibility of type I and II errors. Especially, the 2 genetic risks found in the present study, the 23Cys allele of the *HTR2C* gene and the 64Arg/Arg genotype of the *ADRB3* gene, were found in only 9 and 7 patients in this cohort, respectively, which may be too small a sample to exclude a possibility of type I error. Thus, our findings must be replicated in larger samples.

CONCLUSIONS

Four genetic variants of 5-HT_{2A} and 5-HT_{2C} receptors, the G-protein beta-3 subunit, and the adrenergic receptor beta-3, appear to be genetic risk factors for olanzapine-induced weight gain. Multiple risk factors have additive effects on weight gain. If these findings can be replicated in larger studies, clinicians will have a new tool to help them predict which patients will be most susceptible to olanzapine-induced weight gain.

Drug names: carbamazepine (Carbatrol, Equetro, and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproate (Depacon and others), ziprasidone (Geodon).

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