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The *DRD3* Ser9Gly Polymorphism Predicted Metabolic Change in Drug-Naive Patients With Bipolar II Disorder

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Abstract: Patients with bipolar II disorder (BDII) have a higher prevalence rate of metabolic disturbance. Whether BDII itself, in addition to its current standard treatment, is a risk factor for metabolic syndrome warrants additional study. The dopamine receptor D3 (*DRD3*) gene, one of the candidate genes for BDII, is also involved in the dopaminergic system. We investigated whether it is related to changes in the metabolic indices of patients with BDII given 12 weeks of standard treatment.

Patients with a first diagnosis of BDII (n = 117) were recruited. Metabolic profiles (cholesterol, triglycerides, fasting serum glucose, body mass index) were measured at baseline and at 2, 8, and 12 weeks. The genotype of the *DRD3* Ser9Gly polymorphism (rs6280) was determined. Multiple linear regressions with generalized estimating equation methods were used.

Seventy-six (65.0%) patients completed the 12-week intervention. Significant differences in triglyceride change were associated with the *DRD3* Ser9Gly genotype ($P = 0.03$). Patients with the Ser/Ser genotype had significantly smaller triglyceride increases and a lower risk of developing metabolic syndrome than did those with the Ser/Gly+Gly/Gly genotype. However, the associations between the DRD3 Ser9Gly polymorphism with changes in triglyceride level become nonsignificant after correcting for multiple comparisons.

We conclude that the *DRD3* Ser9Gly polymorphism is nominally associated with changes in triglycerides and metabolic syndrome after 12 weeks of standard BDII treatment.

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Abbreviations: BD = bipolar disorder, BDII = bipolar II disorder, BMI = body mass index, DBP = diastolic blood pressure, DRD3 = dopamine receptor D3, GEE = generalized estimating equation, HDL = high-density lipoprotein, HDRS = Hamilton Depression Rating Scale, HTN = hypertension, LDL = low-density lipoprotein, MetS = metabolic syndrome, SADS-L = Schedule of Affective Disorder and Schizophrenia-Life Time, SBP = systolic blood pressure, SGAs = second-generation antipsychotics, VPA = valproate, YMRS = Young Mania Rating Scale.

INTRODUCTION

Bipolar II disorder (BDII) is a common mood disorder with a prevalence of approximately 3% to 11%.[1] However, it is believed that BDII is greatly underdiagnosed and frequently misdiagnosed,[1,2] because patients usually seek treatment during depressive episodes but perceive hypomanic episodes as positive experiences.[3,4] More comprehensive research is needed on the clinical presentation of, pathophysiology of, and treatment for BDII.[4,5]

Patients with bipolar disorder (BD) have a higher prevalence rate of metabolic disturbance and obesity than does the general population. It used to be conventional wisdom that people with a pyknic broad-built body were more likely to develop BD.[6,7] With improving economic and living conditions, and with obesity at historically high levels and becoming a major public health

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problem, the association between body build and BD is no longer seriously considered.[8] Nevertheless, the prevalence rates of metabolic disturbance and obesity are still higher in patients with BD than in the international general population.[9] Vancampfort et al,[10] for example, reported that 37.3% of unselected patients with BD have metabolic syndrome (MetS), almost twice the prevalence rate of controls. In Taiwan, 33.9% of patients with BD meet the criteria for MetS, especially those taking second-generation antipsychotics (SGAs).[11] MetS is a cluster of cardiovascular disease and adverse risk factors for type II diabetes, for example, central obesity, impaired glucose metabolism, dyslipidemia, and hypertension (HTN). In addition, in patients with BD, the prevalence of MetS is as high as is the prevalence of obesity, and it is higher than in the general population. Moreover, patients with both MetS and obesity are more likely to have a lifetime history of suicide attempts.[12]

Mood fluctuation in BD might be an independent factor for metabolic disturbances.[13] The striatal dopaminergic system, which is implicated in the pathogenesis of BD,[14] is correlated with body mass index (BMI).[15] In contrast, dopamine agonists have been hypothesized to reverse the metabolic change caused by hyperprolactinemia.[16] In addition to the known etiologies of MetS, such as insulin resistance and central obesity,[16,17] whether the candidate genetic variant of BD involved with the dopaminergic system affects body weight and metabolic profiles warrants additional study.

A number of dopaminergic genes have been considered as candidate genes for BD.[17] One of them, the dopamine receptor D3 (*DRD3*) gene, is associated with in treatment response to atypical antipsychotics such as clozapine,[18,19] which frequently caused drug-associated MetS.[20] The *DRD3* gene, on chromosome 3q13.3, is expressed at a relatively high level in the mesolimbic brain regions associated with emotions and behavior, novelty seeking, the reward system, and cognition.[21–24] Therefore, the *DRD3* gene might be important for susceptibility to BD and metabolic change, because mood swings, neurocognitive impairments, and the reward system are all important aspects of BD[25] and are related to appetite change, which affects metabolic parameters. Chiaroni et al[25] suggested that the *DRD3* locus might be involved in a specific endophenotype of BD that consists of clinical characteristics of mania, a low age at onset, and initiation by an acute delusional episode. Our research[26] also suggests an association between the *DRD3* Serine-9-Glycine (Ser9Gly) polymorphism and BDII comorbid with anxiety disorder. Moreover, the receptor protein encoded by the *DRD3* gene is a target site for antipsychotic agents[27] and is efficient for treating BD. The *DRD3* Ser9Gly polymorphism (rs6280) is the most frequently studied variant of the *DRD3* gene that causes a Ser-to-Gly substitution and leads to a significant increase in dopamine-binding affinity.[28] The Gly9 allele of the Ser9Gly polymorphism is associated with significantly greater odds for a treatment response to antipsychotics.[29] It seems that the potential effect of the *DRD3* Ser9Gly polymorphism on the metabolic profile in BDII has never been studied. We hypothesized that the *DRD3* Ser9Gly polymorphism affects metabolic profile changes in patients with BDII after 12 weeks of standard treatment. The *DRD3* Gly/Gly and Ser/Gly genotypes have a significantly higher binding affinity for D3-selective ligand than does the Ser/Ser genotype.[30] These genotypes with a higher binding affinity for clozapine also yield better treatment responses.[18] Therefore, in the current study, we grouped the Ser/Gly and Gly/Gly genotypes together to evaluate changes in metabolic parameters in these 2 groups of genotypes with different binding affinities.

In the present study, to determine whether the *DRD3* Ser9Gly polymorphism predicts posttreatment changes in BMI and metabolic indices, we recruited patients who had been diagnosed with BDII for the first time, and we measured their metabolic parameters changes after they received a standard 12-week pharmacological intervention for BDII.

METHODS

Ethics Statement

The Institutional Review Board for the Protection of Human Subjects at Tri-Service General Hospital and at National Cheng Kung University Hospital approved the research protocol. The methods were carried out following the approved guideline. The study protocol was well explained to each participant before the trial started. After each participant signed written informed consent, blood samples were collected.

Patient Selection

This study is a secondary and subgroup analysis of a clinical trial (Trial registration: NCT01188148 at https://register.clinicaltrials.gov/). The original study was a 12-week trial using randomized, double-blind, controlled design to investigate the add-on effect of memantine on BDII treated using valproate (VPA).[31] As the aim of this study was to explore the association between the *DRD3* gene and changes in metabolic parameters, we chose to analyze only patients who received placebo to stay away from the influence of not routinely used treatment for BDII, add-on memantine. In this way, the present subgroup analysis may make our results more generalizable to daily clinical practice.[32]

The study population was recruited from outpatients and inpatients at Tri-Service General Hospital in Taipei, and at National Cheng Kung University Hospital in Tainan, Taiwan. The inclusion criteria were having a diagnosis of BDII when first evaluated by an attending psychiatrist, then confirmed by a clinical psychologist to verify that the diagnosis met the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), using a structural interview with good inter-rater reliability,[33] the Chinese Version of the Modified Schedule of Affective Disorder and Schizophrenia-Life Time (SADS-L)[34]; whose ethnics are Han Chinese; and aged 18 to 65 years. Patients having psychiatric illness including substance dependence, borderline personality disorder, or dementia were excluded. Patients who were previously medicated with any psychotropic agent or having a history of metabolic diseases were also excluded.

Although the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition criteria imposed a 4-day duration criterion for hypomanic episode, a 2-day duration of hypomania was supported by current epidemiologic data samples[35,36] as being more prevalent in the community. Therefore, in the current study, we implemented the 2-day minimum for hypomania when diagnosing BDII.

Study Design

After enlisting in this study, the patients were administered with open-label use of valproic acid [500 and 1000 mg daily (50–100 μg/mL in plasma)]. Accompanying medication was narrowed to benzodiazepines (lorazepam; up to 8 mg/day) for insomnia, agitation, or irritability and fluoxetine (up to 20 mg/day) for depression. The doses were adjusted according to each patient's clinical manifestations and tolerance. In the event of side effect intolerance or worsening of clinical symptoms, the

patients were withdrawn early from the study. After the introduction of pharmacological treatment, the patients' metabolic profiles, including BMI, lipid profile [cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL)], waist circumference, blood pressure, and fasting serum glucose levels, were measured at baseline and at 2, 8, and 12 weeks. The Young Mania Rating Scale (YMRS)[35] and the Hamilton Depression Rating Scale (HDRS)[36,37] were used to assess severity of mood symptoms. Trained and experienced research psychiatrists assessed the clinical ratings of YMRS and HDRS at baseline and at each visit when metabolic profiles were assessed.

The diagnosis of MetS was defined according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) guidelines and the Asian criteria for abdominal obesity: plasma triglycerides (after 8-hour fasting) $\geq$ 150 mg/dL); low HDL cholesterol with fasting HDL cholesterol $\leq$40 mg/dL in men and $\leq$50 mg/dL in women; previously diagnosed HTN or HTN defined as systolic blood pressure (SBP) $\geq$130 or diastolic blood pressure (DBP) $\geq$85 mm Hg; or hyperglycemia, defined as fasting plasma glucose $\geq$100 mg/dL or previously diagnosed type 2 diabetes; and abdominal obesity, defined as a waist circumference $\geq$90 cm in men or $\geq$80 cm in women.

Ten milliliters of whole blood were withdrawn from the antecubital vein of each patient. DNA was extracted from the lymphocytes. The genotyping of the *DRD3* Ser9Gly polymorphism was done at baseline using a modified protocol described elsewhere.[38] The laboratory analyst who performed and recorded the genotyping was blinded to the patients' diagnoses.

Statistical Analysis

SPSS 18 for Windows, Chicago: SPSS Inc. was used for all statistical analyses. Significance was set at $P < 0.05$. The demographic and clinical characteristics of the patients were compared between different genotype groups at baseline and endpoint using independent *t* tests for continuous variables and χ^2 tests for categorical variables. When the sample size in each cell was less than 5, Fisher exact probability tests were used instead of χ^2 tests. We performed quality control on all the metabolic parameters (BMI, lipid profile, fasting serum glucose level, blood pressure, and waist circumference) to check for outliers using box plot and Q-Q plot. We found outliers in the variables of "Fasting Plasma Glucose" and "Triglyceride," presenting positive skew. We therefore transformed these variables to normal distribution by taking log $(x+1)$ of these variables, and then performed further statistical analysis. The metabolic parameters before and after pharmacological treatment were repeatedly measured. To evaluate the possible association of the *DRD3* Ser9Gly polymorphism with changes in metabolic parameters and symptom severity, we implemented a multiple linear regression model. The generalized estimating equation (GEE)[39] is a statistical method using multiple linear regression for repeated-measures studies, which is able accommodate randomly missing data.[40] We used GEE analysis to investigate whether the *DRD3* Ser9Gly polymorphism predicts changes in the metabolic profiles controlling for concomitant medication (fluoxetine use and plasma valproic acid levels), time effects (treatment period from baseline to week 12), gender, and age. All the variables, after transformation by taking log $(x+1)$, fit the normality assumption for GEE. Seven models ran with each outcome (metabolic parameters: BMI, triglycerides, HDL-C, etc.) as a dependent variable. To check the validity of GEE model, we used the Quasi-Akaike Information Criterion (QIC) method. In each model, the interaction of the *DRD3* Ser9Gly Ser/Ser genotype and the treatment course, main effects of the *DRD3* Ser9Gly genotypes, treatment course, gender, age, valproic acid level, and fluoxetine were included as independent variables; patients with the *DRD3* Ser9Gly Ser/Gly + Gly/Gly genotypes were the reference group. The interactive variable (genotype $\times$ treatment duration) reflects the effect of the genotype on the dependent variable (e.g., BMI, triglyceride) after the entire treatment course in the assessed GEE model without considering the time effect (the treatment course). In the GEE model, the moderators included age and gender, and the mediators included the drug used valproic acid or fluoxetine.

To adjust for multiple comparisons, the Bonferroni method was used. The power analysis was done using G-Power 3,[41,42] and the effect-size conventions were determined on the basis of Buchner et al.[41]

RESULTS

The trial ran from August 1, 2008, to July 31, 2012. The first patient was recruited on August 25, 2009, and the last enrolled patient finished on May 30, 2012. One hundred seventeen patients were recruited and assigned to the Placebo group. All the recruited patients were first diagnosed BDII, never administered with mood stabilizers or antipsychotics in the past.

At baseline, 117 patients were assessed. Finally, 76 (65.0%) patients completed the 12-week pharmacological treatment and metabolic profile follow-up; the other 41 patients dropped out. The genotype and allele distributions of the *DRD3* Ser9Gly polymorphism of patients at baseline were Ser/Ser, Ser/Gly, Gly/Gly: 56.4% versus 35.0% versus 8.5% and Ser/Gly: 74% versus 26%. The genotype distributions of the *DRD3* Ser9Gly polymorphisms at baseline were in Hardy–Weinberg equilibrium (Chi = 0.966, $P = 0.325$). We divided the study population into 2 genotype subgroups: the Ser/Ser and the Ser/Gly + Gly/Gly of the *DRD3* Ser9Gly polymorphism. The demographic and clinical characteristics, and the metabolic parameters between the 2 subgroups, were similar in all patient groups at baseline. At the endpoint, patients with the Ser/Gly + Gly/Gly genotype had a higher level of triglycerides (Table 1).

In addition, the frequency of MetS at the endpoint was significantly ($P = 0.03$) higher in the Ser/Gly + Gly/Gly group (11.4%) than in the Ser/Ser group (0%). Three of the 10 patients with MetS at baseline dropped out at the end and were lost to follow-up. Four of the 5 patients with the Ser/Ser genotype and MetS at baseline did not have MetS at the endpoint, and 1 patient was lost to follow-up. Therefore, none with the Ser/Ser genotype had MetS at the endpoint. Two of the 5 patients with the Ser/Gly + Gly/Gly genotypes and MetS at baseline still had MetS at the endpoint, 2 patients were lost to follow-up, and only 1 patient did not have MetS at the endpoint. In addition, 2 patients with the Ser/Gly + Gly/Gly genotypes who did not have MetS at baseline developed MetS at the endpoint. Therefore, at the endpoint, 4 patients with the Ser/Gly + Gly/Gly genotypes had MetS. By excluding patients who dropped out before the endpoint, we found that there was still no significant difference in the prevalence of MetS at baseline, but that the significant difference ($P = 0.036$) at the endpoint remained. Therefore, although the dropout rate was high, the change in the incidence of MetS in patients with different genotypes of the *DRD3* Ser9Gly polymorphism was still significant.

TABLE 1. Mean HDRS Score, YMRS Score, and Cytokine and Metabolic Profiles Before and After Pharmacological Treatment

	Baseline			After 12 wks		
Total Number	117			76		
***DRD3* Ser9Gly Genotypes (Ser/Ser, Ser/Gly, Gly/Gly) (%)**	66/41/10 (56.4%/35.0%/8.5%)			41/27/8 (53.9%/35.5%/10.5%)		
***DRD3* Ser9Gly Genotypes**	**Ser/Ser (n = 66)**	**Ser/Gly + Gly/Gly (n = 51)**	***t* or χ^2, *P***	**Ser/Ser (n = 42)**	**Ser/Gly + Gly/Gly (n = 34)**	***t* or χ^2, *P***
Gender (male/female) (n)	33/33	31/20		23/19	23/11	1.310, $P = 0.25$
Age, mean (SD), y	29.9 ± 10.8	30.9 ± 11.6	0.990, $P = 0.32^{\S}$	32.1 ± 12.2	29.5 ± 10.8	0.160, $P = 0.69^{\S}$
HDRS score, mean (SD)	18.5 ± 5.7	20.3 ± 4.7	0.170, $P = 0.68^{\S}$	9.3 ± 6.5	9.1 ± 5.9	0.190, $P = 0.66^{\S}$
YMRS score, mean (SD)	9.9 ± 4.4	8.3 ± 4.4	0.460, $P = 0.50^{\S}$	5.0 ± 2.6	5.2 ± 3.2	0.530, $P = 0.47^{\S}$
BMI, mean (SD), kg/m^2	23.1 ± 4.5	23.6 ± 5.4	0.490, $P = 0.49^{\S}$	24.0 ± 4.3	24.1 ± 5.2	0.690, $P = 0.41^{\S}$
Fasting plasma glucose, mean (SD), (mg/dL)	88.1 ± 13.1	92.1 ± 21.3	1.081, $P = 0.28^{\dagger,\S}$	82.1 ± 9.7	93.6 ± 38.9	1.774, $P = 0.08^{\dagger,\S}$
Triglyceride, mean (SD), mg/dL	82.2 ± 37.2	93.3 ± 59.6	0.876, $P = 0.38^{\dagger,\S}$	83.7 ± 38.7	120.2 ± 89.9	2.115, $P = 0.04^{*,\dagger,\ddagger}$
Cholesterol (total), mean (SD), mg/dL	178.6 ± 38.9	180.8 ± 29.7	2.800, $P = 0.096^{\S}$	177.8 ± 31.1	193.0 ± 40.0	2.350, $P = 0.13^{\S}$
HDL-C, mean (SD), mg/dL	60.9 ± 16.0	54.7 ± 15.5	0.086, $P = 0.77^{\S}$	60.9 ± 15.4	54.2 ± 16.5	0.019, $P = 0.89^{\S}$
LDL-C, mean (SD), mg/dL	108.2 ± 32.3	112.1 ± 27.9	0.440, $P = 0.51^{\S}$	105.8 ± 28.0	123.5 ± 32.9	1.180, $P = 0.28^{\S}$
Waist circumference, mean (SD), cm	79.3 ± 11.9	82.5 ± 13.3	0.320, $P = 0.58^{\S}$	82.0 ± 11.9	83.9 ± 13.4	0.140, $P = 0.71^{\S}$
Systolic blood pressure, mean (SD), mm Hg	112.8 ± 17.1	117.1 ± 15.3	0.660, $P = 0.42^{\S}$	111.8 ± 14.2	117.3 ± 17.4	2.320, $P = 0.13^{\S}$
Diastolic blood pressure, mean (SD), mm Hg	73.5 ± 11.6	74.0 ± 11.9	0.010, $P = 0.94^{\S}$	71.9 ± 11.1	73.3 ± 10.7	0.110, $P = 0.74^{\S}$
Depakine level, mean (SD), mg/L	0	0	N/A	71.8 ± 21.0	58.9 ± 26.7	0.470, $P = 0.50^{\S}$
Metabolic syndrome (n) (%)	5 (7.6%)	5.0 (9.8%)	0.180, $P = 0.75$	00 (0%)	4.0 (11.4%)	6.00, $P = 0.03^{*}$

HDRS = Hamilton Depression Rating Scale, SD = standard deviation, VPA = valproate, YMRS = Young Mania Rating Scale.
$^{*}P < 0.05$.
$^{\dagger}P$ value using data transformed by log(x + 1) to normalize distribution.
‡After Bonferroni correction for multiple comparison (P values times by 13 tests), $P = 0.49$.
§After Bonferroni correction for multiple comparison (P values times by 13 tests), all the P values equal to 1.

TABLE 2. Association of the *DRD3* Ser9Gly Polymorphism With Changes in Metabolic Profiles From Baseline After 12 Wks of Follow-Up in Patients With BP-II

	Association of the *DRD3* Ser9Gly Polymorphism and Changes in Metabolic Profiles					
	B	**95% CI**	**SE**	***P***	***QIC***	***P*‡**
BMI	0.01	−0.33 to 0.35	0.17	0.97	3712.26	1.00
Triglycerides	−0.04	−0.07 to −0.004	0.02	0.03*,†	22.86	0.20
HDL-C	0.24	−1.48 to 1.96	0.88	0.79	36,726.89	1.00
Fasting serum glucose	−0.02	−0.04 to 0.05	0.01	0.15†	17.09	1.00
Waist size	0.15	−1.31 to 1.61	0.74	0.84	21,662.50	1.00
Systolic blood pressure	−0.64	−3.59 to 2.31	1.50	0.67	34,920.07	1.00
Diastolic blood pressure	−0.15	−2.11 to 1.85	0.02	0.88	17,784.26	1.00

Metabolic parameters are dependent variables. Independent variable shown here is the interaction of *DRD3* Ser9Gly Ser/Ser genotype and treatment course, using *DRD3* Ser9Gly Ser/Gly + Gly/Gly genotypes as reference group. Other covariables are *DRD3* Ser9Gly genotypes, treatment course, gender, age, depakine level, and use of fluoxetine.

B = standardized coefficient, BMI = body mass index, BP-II = bipolar disorder II, CI = confidence interval, HDL-C = high-density lipoprotein cholesterol, QIC = Quasi-Akaike's Information Criterion, SE = standard error.

*$P < 0.05$.

†P value using data transformed by log (x + 1) to normalize distribution.

‡P value corrected by Bonferroni correction for multiple comparison (P values times by 7 tests).

A multiple linear regression analysis of the association between the *DRD3* Ser9Gly polymorphism and changes in the metabolic parameter scores before and after the 12 weeks of treatment showed that the *DRD3* Ser9Gly polymorphism was significantly ($P = 0.03$) associated with the changes in triglyceride levels (Table 2; Figure 1). Patients with the Ser/Ser genotype had a significantly smaller increase in triglycerides than did patients with the Ser/Gly + Gly/Gly genotype. However, the *DRD3* Ser9Gly polymorphism was not associated with changes in other metabolic parameters (Table 2). After correcting for multiple comparisons, the associations between the *DRD3* Ser9Gly polymorphism with changes in triglyceride levels become nonsignificant.

For multiple regression analysis in a sample of 117 patients in the present study, the power was 0.33 to detect a small effect; to detect medium and large effects, the power was 0.99. The effect-size for the multiple regression model ($\alpha = 0.05$) was set at 0.02 for small effect, 0.15 for medium effect, and 0.35 for large effect, determined according to Buchner et al.[41]

DISCUSSION

In the association analysis of the *DRD3* Ser9Gly polymorphisms and changes of metabolic parameters, we found preliminary evidence that, in patients with BDII, the *DRD3* gene influences changes in triglyceride levels, one of the key criteria of MetS. The genotype distribution of the *DRD3* Ser9Gly polymorphism in the current study is comparable to patients with schizophrenia[43] and healthy individuals[44] in other studies from the Han Chinese population. Patients with the Ser/Ser genotype had a significantly smaller increase in triglyceride level than did those with the Ser/Gly + Gly/Gly genotype. Furthermore, after 12 weeks of follow-up, significantly fewer patients with the Ser/Ser genotype than with the Ser/Gly + Gly/Gly genotype had MetS. However, the *DRD3* Ser9Gly polymorphism was not related to changes in other metabolic parameters. We therefore hypothesize that, after 12 weeks of standard BDII treatment, patients with the *DRD3* Ser9Gly

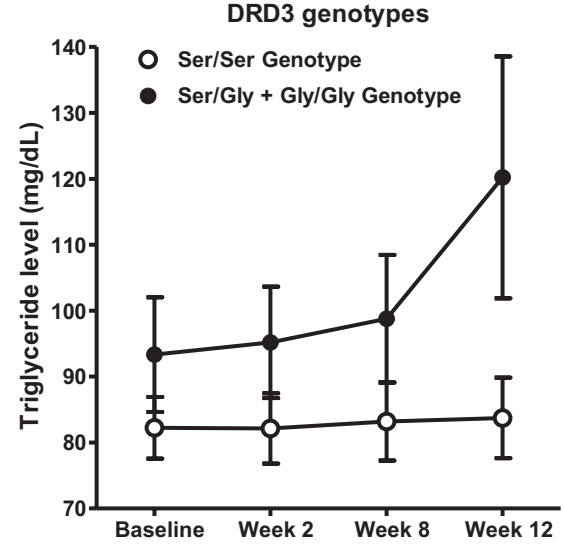

FIGURE 1. Changes in the triglyceride level of patients with different genotypes of the *DRD3* Ser9Gly polymorphism after 12 weeks of standard treatment for bipolar II disorder. (The error bars represent the standard error of the mean).

Ser/Gly + Gly/Gly genotype are at a higher risk for higher triglyceride levels and for MetS than are those with the Ser/Ser genotype.

The current study showed that the *DRD3* Ser9Gly polymorphism, the candidate genetic variant of BD involved in the dopaminergic system, might affect changes in metabolic profiles. Such an association between the *DRD3* Ser9Gly polymorphism and metabolic profiles in BDII or other disorders has never been studied in the past. The relationship between the dopamine system and MetS, however, has been reported: the striatal dopaminergic system is apparently involved in regulating BMI.[15] Dopamine is a mediator of feeding behavior: an increase in dopamine signaling promotes feeding behavior, but a decrease represses it.[45] In addition, dopamine neurons are frequently targets of hormones such as leptin and insulin, both of which regulate the homeostatic system.[46] Global dopamine D2 receptor knockout female mice are reported[47] to eat more and have more adipose tissue than mice with the normal density of dopamine D2 receptors. In the current study, patients with the Gly allele, which increases dopamine binding affinity,[28] had a greater risk for MetS and an increase in triglycerides after 12 weeks of standard BDII therapy. It is possible that the increased dopamine-binding affinity of those patients might also have caused them to increase their food intake. However, because we did not record the dietary habits of each patient, this hypothesis requires additional investigation.

Nevertheless, we found no significant association between the *DRD3* Ser9Gly polymorphism and other metabolic parameters. This agrees with the study by Soma et al,[48] who reported no association between the *DRD3* Ser9Gly polymorphism and essential HTN. In addition, unlike other studies, we analyzed this association between the *DRD3* Ser9Gly polymorphism and changes in metabolic profiles in a longitudinal rather than a cross-sectional study. Moreover, we focused on drug-naive patients with BDII undergoing initial short-term pharmacological intervention. Additional evaluations of the association between the *DRD3* Ser9Gly polymorphism and longer-term metabolic changes are warranted.

Physical inactivity and eating habits might be the main behavioral risk factors for MetS.[49] Significant correlations have been reported between obesity and comorbid binge-eating disorder and health habits in BD.[50] Therefore, it is important to regularly monitor a patient's MetS status and provide prompt lifestyle interventions that encourage greater physical activity and less overeating. Whether these lifestyle behaviors are associated with genetics or the underlying psychology of BD requires additional study.

Our study has some limitations. First, the power of the current study is low for a small effect. We would need about 395 participants (more than 3 times the current sample size) for sufficient power (0.8) detect a small effect (0.02). In addition, the associations between the *DRD3* Ser9Gly polymorphism with changes in triglyceride level become nonsignificant after correcting for multiple comparisons. Second, the correlation between the gene and metabolic indices might be obscured by the medication permitted in the study. Although we tried to limit concomitant treatment medication to only 3 drugs (lorazepam, fluoxetine, and valproic acid) and adjust for its use in our linear regression analysis, our results should still be taken with caution. In addition, other possible confounders such as socioeconomic class, education level, dietary habits, drug adherence, and daily activities and the energy they required were not adjusted for. Third, the 2-day hypomania criteria used in the present study is not widely agreed. Our positive finding might not be generalizable to patients with BDII diagnosed using the DSM-IV-TR criterion of a 4-day duration for hypomania. Finally, the current study only followed the metabolic change after 12-week of pharmacological intervention. A longer-term follow-up of metabolic changes in our patients is needed in future investigation.

In conclusion, the present study results support that the *DRD3* gene affects changes in triglyceride levels and in the frequency of MetS after 12-week of standard treatment in drug-naive bipolar II patients. Those with the Gly allele might be vulnerable to an increased risk for a high level of triglyceride and for MetS. Our finding provides initial evidence that the dopamine system is related to metabolic disturbance. However, the exact mechanism of the *DRD3* gene's effects on metabolic parameters warrants additional analysis. We hypothesize that knowledge of how the *DRD3* Ser9Gly polymorphism affects changes in triglyceride levels will be clinically useful for reminding clinicians to more closely monitor and control metabolic parameters in patients being treated for BDII.

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