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No association of antipsychotic agent-induced weight gain with a DA receptor gene polymorphism and therapeutic response[1]

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ABSTRACT

AIM: To investigate whether there is an association of antipsychotic agent-induced weight gain with the *Taq*I A polymorphism of dopamine D2 receptor (DRD2) gene and therapeutic response to antipsychotic treatment in schizophrenia. **METHODS:** Genotyping was performed using the PCR-RFLP techniques in a total of 117 first-episode Chinese Han schizophrenic patients (mean age 26±8 a; 58 male, 59 female). Moreover, the measurements were finished either for baseline weight and body mass index (BMI) or for changed weight and BMI 10 weeks after antipsychotic treatment. The Positive and Negative Symptom Scale (PANSS) was used for the evaluation of the improvement of clinical psychotic symptoms. **RESULTS:** There was an average increase in body weight of (3±3) kg or (6±6) % of baseline weight with a changed range of -7 kg–12 kg or -7.8 %–32.4 % 10 weeks after treatment, and the change in the BMI was associated with the baseline BMI and patients' age (P=0.0001; P=0.03; respectively). However, there was no significant difference in distribution of allelic frequencies (χ^2=0.65, v1, P>0.05) and genotype (χ^2=1.47, v2, P>0.05) between the subgroups, and the change in BMI was not associated with genotypes of DRD2. Furthermore, there was no relationship of the therapeutic response to antipsychotic treatment with changed BMI in the patients (P>0.05). **CONCLUSION:** The *Taq*I A polymorphism of DRD2 gene is therefore unlikely to play an important role in antipsychotic agent-induced weight gain, a side effect of antipsychotic treatment. Furthermore, increase in body weight is unlikely to be prediction of therapeutic response to antipsychotic treatment in schizophrenia.

INTRODUCTION

Weight gain during treatment with antipsychotic agents, particularly "atypical" antipsychotics has been emerging as a new "extrapyramidal side effect" (EPS) and a significant obstruction to effective therapy of schizophrenia. Furthermore, weight gain has substantial implications in terms of drug compliance, and has inevitable consequences in increases in morbidity and mortality[1]. The underlying mechanisms of antipsychotic agent-induced weight gain are multifactorial and

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certainly remain unclear. Several lines of evidences implicate an important role for the dopamine D2 receptor (DRD2) in the regulation of food intake and energy metabolism. DRD2 antagonists enhanced appetite while DRD2 agonists greatly normalized hyperphagia and weight gain in genetically obese female mice[2]. Previous studies have revealed significant interindividual variation of the DRD2 density in human striatum by positron emission tomography (PET) with a lower density in obese individuals as shown by negative correlation between DRD2 density and the body mass index (BMI) in a white population[3]. Further studies have demonstrated that the lower DRD2 binding in the striatum of normal subjects was associated with the A1 allele of the *Taq*I polymorphism of DRD2 gene[4]. Furthermore, the A1 allele was associated with BMI in Caucasians[5] and with increased markers of peripheral subcutaneous obesity in Chinese non-diabetic hypertensive patients[6]. Therefore, it has prompted us to investigate whether the A1 allele of the *Taq*I polymorphism of the DRD2 gene is associated with antipsychotic agent-induced weight gain, and whether weight gain is an indicator of responses of antipsychotic treatment in first-episode schizophrenic patients.

MATERIALS AND METHODS

Subjects The subjects were Chinese Han inpatients referred to the Department of Psychiatry, Nanjing Brain Hospital, Nanjing Medical University, China. The inclusive criteria were as follows: (1) All patients met criteria for a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM IV). (2) The patients were experiencing their first psychotic episode and were antipsychotic agent-naive. (3) The patients had no other mental diseases and neurological diseases, no eating disorder, obesity, diabetes, hypertension and those of family history, and no drug substance and alcoholism. (4) Antipsychotic treatment had been received according to normal clinical practice for 10 weeks. (5) All subjects gave informed written consent for participation in the study, which had been approved by the Hospital Ethical Committee, in accordance with the Declaration of Helsinki.

Subjects were weighed and height was measured on admission they were weighed every week subsequently. BMI was calculated for each patient. All patients received dietetically balanced hospital meals (daily energy intake for men: 2500 kcal; for women: 2200 kcal) occasionally supplemented by gifts (usually fruit) by their relatives, and had the opportunity for 1-h physical exercises each day. To assess and evaluate improvement of clinical psychotic symptoms and therapeutic response to antipsychotic treatment, all patients were rated using the Positive and Negative Symptom Scale (PANSS) in the day of admission, then subsequently assessed every two weeks following antipsychotic treatment by the senior psychiatrists (YZJ, SJ), who had trained specially for the operation of PANSS. The improvement after antipsychotic agent treatment was expressed by percentage improvement as shown by (the baseline total PANSS scores or subscoresthe – 10 weeks total PANSS scores or 10 weeks subscores)/ baseline total PANSS scores or subscores.

Genomic DNA extraction and genotyping of DRD2 Genomic DNA was extracted from 5 mL aliquots of edetic acid-anticoagulated venous blood using Nucleon BACC Kits (Nucleon-Biosciences, Scotland, UK). Genotyping by the PCR-RFLP technique was performed strictly blind to the clinical status of patients and according to the method as previously described by Grandy[7] with a pair of primers 971: 5'-CCG TCG ACG GCT GGC CAA GTT GTC TA-3' and 5014: 5'-CCG TCG ACC CTT CCT GAG TGT CAT CA-3'. The digestion products of the restriction endonuclease *Taq*I were analyzed following electrophoresis in 3 % agrose gel stained with ethidium bromide. The 310 bp PCR product named A1 allele was left uncut while the A2 allele was cut into 130 bp and 180 bp.

Statistical analysis All statistical analyses were performed using SPSS 10.0 for Windows. The χ^2-goodness-of-fit test was used to test the distribution of genotypes for deviations from Hardy-Weinberg equilibrium. *Chi*-square was used to compare allele and genotype frequencies between the patients' subgroups. Differences in clinical variables or in PANSS scores between groups were evaluated with Student's *t*-test for independent samples, analysis of variance (ANOVA), or nonparametric tests for independent samples (Mann-Whitney U and Kruskal-Wallis H tests). Values are given as mean±SD. The association of weight gain (indicated by change in BMI at 10 weeks) with the DRD2 genotype or therapeutic responses (indicated by reduced PANSS scores) were examined by multivariate regression of stepwise multiple regression using potential confounding variables (age, gender, duration of illness, baseline BMI, antipsychotic dosage) to be adjusted simultaneously.

RESULTS

(1) A total of 117 first-episode patients with schizophrenia were recruited for the present study, including 58 male and 59 female. Clinical demographic features and assessment of PANSS of the schizophrenic patients are shown in Tab 1. There was no significant difference in the terms of age, age of onset, duration of illness, proportion of antipsychotic prescribed, antipsychotic day dose (mg chlorpromazine equivalents), total PANSS scores and positive and general psychopathology subscores admission, and total PANSS and subscores percentage improvement after 10 weeks treatment between male and female patients. However, it is obvious that there were significant differences in the terms of baseline body weight, baseline BMI, negative scores before treatment, and day dosage of antipsychotics between the gender subgroups. Initial antipsychotic agent treatment primarily consisted of monotherapy with chlorpromazine [n=66; (322±74) mg] or resperidone [n=43; (4±0.5) mg]; eight patients received clozapine (n=4), fluphenazine (n=3), or sulpiride (n=1). Treatment was reviewed after approximately 6 weeks and changed where necessary.

(2) With all patients as a whole, the subjects gained an average of (3±3) kg in weight, or (6±6) % of their baseline body weight at 10 weeks after treatment of antipsychotic agents. There was no significant difference in change in body weight and change in BMI at 10 weeks between male and female patients (Tab 1) and between chlorpromazine-treated and risperidone treated groups [(4±3) kg *vs* (3±4) kg or (1.3±1) kg/m^2 *vs* (1.2±1.5) kg/m^2]. When the patients were examined individually, however, it was observed that change in body weight varied greatly (ranging from –7 kg to 12 kg and from –7.8 % to +32.4 %).

Tab 1. Clinical demographic features and PANSS scores of schizophrenic patients. Mean±SD. [a] $P>0.05$, [b] $P<0.05$, [c] $P<0.01$ *vs* female patients.

Features	All patients (n=117)	Male patients (n=58)	Female patients (n=59)
Age/a	26±8	26±7[a]	27± 8
Age of onset/a	25±7	25±7[a]	25±8
Duration of illness/a	1.5±1.2	1.5±1.3[a]	1.4±1.2
CPZ doses/mg	332±74	350±86[c]	293±44
Baseline weight/kg	60±11	66±11[c]	55±8
Baseline BMI/kg·m^2	22±3.0	22±3[c]	21±2.8
Changed BMI/kg·m^2	1.2±1.2	1.1±1.3	1.2±1.2
Total PANSS	97±14	97±13[a]	97±15
Positive scores	28±8	28±8[a]	28±7
Negative scores	19±7	20±8[b]	18±7
General scores	50±7	49±6[a]	51±8
Changed PANSS/%	49±10	50±12	48±9
Changed positive/%	56±14	58±15	55±13
Changed negative/%	39±14	40±15	38±12
Changed general/%	47±11	48±12	47±10

(3) Allele and genotype frequencies of the subjects for the *Taq*I A polymorphism in DRD2 gene were shown in Tab 2. The genotypic distributions in all patients as a whole group (χ^2=5.25, v2, P=0.07), and in the male patients (χ^2=3.39, v2, P=0.18) and the female patients (χ^2=2.1, v2, P=0.35) as separate groups were all consistent with the Hardy-Weinberg equilibrium. We observed no significant differences in the distributions of allelic frequencies and genotype between the subgroups as shown in Tab 2. Moreover, there were no significant differences either in clinical demographic characteristics (with one expectation of day dosage A1A1 *vs* A2A2, P<0.05) and the change in weight and BMI 10 weeks after antipsychotic treatment between the genotypic groups; however, as compared with A2A2 genotype groups, A1 allele groups had significant improvement only on positive symptoms of schizophrenia, which had been discussed in another study of association of DRD2 polymorphism with treatment response of antipsychotic agents (Tab 3).

(4) The degrees of weight gain, expressed as change in BMI at 10-week treatment with antipsychotics were compared between genotype groups by regression analysis of stepwise models. When the DRD2 genotype, age, gender, duration of illness, baseline BMI, antipsychotic dosage, baseline PANSS, and percentage improvement of PANSS were entered into the regression analysis as independent variables, we observed significant associations of weight gain with baseline BMI (P=0.0001) when all patients were considered as a whole group, but the rest of the variables, including the DRD2 genotype and PANSS percentage improvement, were removed from the model. Repeating statistical analysis with restricted subgroups indicated that the association of weight gain with baseline BMI remained in males (P=0.03), females (P=0.0001), patients receiving initial and continuing antipsychotic treatment with only chlorpromazine or risperidone (both P=0.0001), and patients with BMI between 17.0 and 23.0 kg/m^2 (ie, excluding underweight and overweight subjects[8,9];

Tab 2. Distributions of allele frequencies and genotype of DRD2 gene between the subgroups of schizophrenic patients.

Subgroups	*n*	Allele		Genotype		
		A1	A2	A1A1	A1A2	A2A2
All patients	117	0.44	0.56	0.14 (0.19)	0.60 (0.49)	0.26 (0.31)
Male	58	0.46	0.54[1)]	0.12 (0.18)	0.60 (0.48)	0.28 (0.34)[2)]
Female	59	0.45	0.55[1)]	0.15 (0.2)	0.59 (0.5)	0.25 (0.3)[2)]
Weight <7 %	67	0.44	0.56[3)]	0.16 (0.19)	0.55 (0.49)	0.28 (0.31)[4)]
Weight >7 %	50	0.43	0.57[3)]	0.10 (0.18)	0.66 (0.49)	0.24 (0.32)[4)]

The genotype distribution according to a Hardy-Weinberg equilibrium is shown in parentheses.
[1)] the male patients *vs* the female patients (χ^2=0.007, *v*1, *P*=0.93) all *P*>0.05
[2)] the male patients *vs* the female patients (χ^2=0.27, *v*2, *P*=0.87)
[3)] the patients gained weight <7 % *vs* >7 % at 10 weeks (χ^2=0.006, *v*1, *P*=0.94)
[4)] the patients gained weight <7 % *vs* >7 % at 10 weeks (χ^2=1.62, *v*2, *P*=0.44)

Tab 3. Comparison of clinical features and PANSS scores between genotype groups in schizophrenic patients. Mean±SD. [a]*P*>0.05, [b]*P*<0.05 *vs* A2A2.

Features	Genotype groups			
	A1A1	A1A2	A1A1+A1A2	A2A2
	n=16	*n*=70	*n*=86	*n*=31
Age/a	26±9[a]	27±8	27±8	26±7
Age of onset/a	25±9[a]	25±8	25±8	24±7
Duration/a	1.4±1.2[a]	1.4±1.1	1.4±1.1	1.7±1.4
Male:female	7:9	35:35	42:44	16:15
CPZ dose/mg·d^{-1}	297±62[b]	323±69	318±68	332±87
Baseline weight/kg	60±9[a]	60±11	60±11	62±12
Baseline BMI/kg·m^{-2}	22±3[a]	22±3	21±3	22±3
Changed weight	2±4[a]	3±3	3±3	3±4
Changed BMI	0.6±1.3[a]	1.2±1.2	1.1±1.2	1.2±1.4
PANSS score	95±19[a]	97±14	96±17	100±11
PANSS/%	48±11[a]	48±11	48±11	51±8
Positive/%	54±16[b]	55±15[b]	55±15[b]	60±9
Negative/%	37±16[a]	39±14	39±14	38±12
General/%	48±10[a]	47±11	47±11	48±10

n=75, *P*=0.002); moreover, in this last subgroup, patients' age was also associated with weight gain (*P*=0.03).

DISCUSSION

To our knowledge, this is the first study on the association of *Taq*I polymorphism of the DRD2 gene with antipsychotic agent-induced weight gain in first-episode schizophrenic patients. We observed no significant differences in the distribution of allelic frequencies and genotype between weight gain >7 % and <7 % groups[8,9]. Furthermore, antipsychotic agent-induced weight gain was associated neither with A1 allele of *Taq*I polymorphism of the DRD2 gene nor with the improvement of clinical psychotic symptoms in schizophrenic patients. In addition, weight gain is unlikely to be indicators of therapeutic response to antipsychotic treatment in the present study.

In this prospective study of 117 first-episode inpatients with schizophrenia attending a normal clinical practice, we observed 42 % of patients treated with antipsychotics (major chlorpromazine or risperidone) for 10 weeks gained a significant amount of weight, 23 % patients gained more than 10 % of their initial body weight, and 19 % gained more than 7 % of initial body weight. There was no significant difference in weight change between chlorpromazine- and risperidone- treated groups with the average weight gain (3.7±2.9) kg and (3±4) kg, respectively. However, the change in BMI varied widely with 20 % patients showing no change in weight or (11 %) even losing their body weight with average (2.8±1.8) kg. The baseline BMI was significantly associated with weight gain, also age was inversely correlated with weight gain in "normal weight group"[8,9] (including baseline BMI from 17.0 to 23.0 kg·m^{-2}) but not other clinical variables with gained weight including drug dosage. Kelly[10] found the young patients increased in body weight average 8.17 kg with treatment of risperidone for 4 months. This demonstrated that the patients who were of lower weight and younger at the start of treatment were more likely to gain significantly more weight after antipsychotic admission. This is consistent with most previ-

ous studies[1,11], Thereby, this will be important for selection of antipsychotic agent and prevention of weight gain, particularly for early onset, adolescent patients. In addition, the weight gain was not associated with clinical improvements (as measured by percentage improvement PANSS scores) at 10 weeks, which was in contrast with early studies but consistent with most of recent studies[12]. The present study further supports that weight gain is unlikely to be an indictor of the improvement of clinical symptoms and of efficacy of antipsychotic treatment in schizophrenia.

Although we observed no association of *Taq*I A polymorphism of DRD2 with antipsychotic agent-induced weight gain in schizophrenia, a variety of changes in body weight in schizophrenics after treatment may indicate the contribution of a genetic factor to the susceptibility. In fact, the underlying mechanisms of antipsychotic agent-induced weight gain also involves other neurotransmissions[13], for example 5-HT receptors, and/or relates to an interaction of the genotype of candidate genes with the environment resulting in the development of obesity. It is therefore important for the assessment of an individual's risk of developing greater weight gain to analyze other candidate genes. We have been determining candidate genes related to antipsychotic agent-induced weight gain in the patients. Interestingly, we observed a significant association of a polymorphism in the promoter region of 5-HT_{2C} receptor gene with weight gain[14]. However, no interaction was found between the $5HT_{2C}$ and DRD2 genes on weight gain in the patients. The difference in the allelic type of functional polymorphisms of 5-HT_{2C} can affect the promoter activity and even the expression of neurotransmitters, and thus contributes to risk of weight gain in schizophrenia. Antipsychotic drug-induced weight gain (obesity) is a serious adverse effect in schizophrenia, which decreases compliance and increases health risks. However, losing weight is such a difficult task, particularly for schizophrenic patients with cognitive dysfunction. Prevention and management of weight gain in the first place is therefore most important, by selecting antipsychotic drugs according to the potential of drug-induced side effects, efficacy, and pharmacogenetic profile.

In conclusion, the present study demonstrated no significant difference in the prevalence of the A1 allele of *Taq*I polymorphism of the DRD2 gene between greater weight gain patients and those of "normal weight" group either in the first-episode, drug naive period or in following antipsychotic treatment. Therefore, there is no stronger evidence that the DRD2 gene is linked to antipsychotic drug-induced weight gain in schizophrenia. Combined with our previous study regarding a significant association of polymorphism in the promoter region of the 5-HT_{2C} receptor gene with weight gain in the schizophrenic patients, it is suggested that the 5-HT_{2C} receptor, even the serotonin system, might be more important than the dopamine system in the regulation of antipsychotic drug-induced weight gain.

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