

DRD4 48 bp VNTR but not 5-HT_{2C} Cys23Ser receptor polymorphism is related to antipsychotic-induced weight gain

J Popp¹, S Leucht², S Heres² and W Steimer¹

¹Institut für Klinische Chemie und Pathobiochemie, Klinikum rechts der Isar, Technische Universität München, Munich, Germany and ²Psychiatrische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

Correspondence:

Dr W Steimer, Institut für Klinische Chemie und Pathobiochemie, Klinikum rechts der Isar, Technische Universität München, Ismaninger Str 22, München 81675, Germany.
E-mail: W.Steimer@gmx.de

Weight gain is a major side effect of antipsychotic treatment. The antidopaminergic and antiserotonergic effect of antipsychotics may contribute to antipsychotic-induced weight gain. We, therefore conducted a prospective clinical study, to investigate whether the D4 receptor (DRD4) 48 bp (base pair) variable number of tandem repeat (VNTR) polymorphism and the 5-hydroxytryptamine 2C receptor (HT_{2C}) cysteine for serine substitution at position 23 (Cys23Ser) polymorphism may influence weight gain during antipsychotic treatment in a naturalistic setting of 102 Caucasian psychiatric in-patients. Patients suffering from psychotic disorders and treated according to local clinical practice were classified as either homozygous for the shorter alleles of the DRD4 48 bp VNTR polymorphism (<7-fold repeat, group 1) or heterozygous/homozygous for the long allele (7-fold repeat or higher, group 2). HT_{2C} Cys23Ser polymorphism male patients were grouped hemizygous G (Cys) or C (Ser), while female patients were GG, GC or CC and both sexes were evaluated separately. Concerning the DRD4 48 bp VNTR polymorphism the increase in body mass index was significantly less in group 1 (0.38 kg m⁻²; s.d. = 1.04) than in group 2 (0.89 kg m⁻²; s.d. = 1.23; *P* = 0.003). The difference between the genotype groups remained significant in male patients but not in female patients. In contrast, no influence on antipsychotic-induced increase in body weight was observed for the HT_{2C} Cys23Ser polymorphism. These results support the hypothesis that the DRD4 48 bp VNTR polymorphism influences antipsychotic-induced weight gain. Male patients may be more affected than female patients. Due to the limitations of the study (heterogeneity of treatment, pretreatment and concomitant therapy) further studies are required before diagnostic genotyping of the DRD4 48 bp VNTR polymorphism may be useful for individualizing therapy.

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Introduction

One major side effect of treatment with antipsychotic drugs is weight gain.¹ The health consequences of drug-induced weight gain or long-term overweight can be severe. These include a higher risk for hypertension, diabetes mellitus, coronary heart disease and stroke. Furthermore, antipsychotic-induced weight

gain can negatively affect compliance and can, therefore, increase the risk of relapse or worsening of psychotic symptoms. Particularly in Western societies, the existence of negative attitudes toward obesity may further disadvantage patients in terms of reintegration.

Although the field of obesity research is rapidly evolving, little is known about the pathophysiology of antipsychotic-induced weight gain. Monoamines are of particular interest in energy homeostasis, as they act as neurotransmitters in many areas of the central nervous system that have been shown to interact with hunger/satiety regulatory systems.² There is a large body of evidence that dopamine is involved in feeding behavior, however the mechanisms are not yet clear. Drugs such as amphetamines or cocaine that increase dopaminergic transmission lead to a decrease in food intake and weight loss.³ Animal and human studies have shown increased serotonin results in decreased food intake with decreased serotonin having the opposite effect. The 5-hydroxytryptamine 2C receptor (5-HT_{2C}) is of particular interest in weight gain liability due to the obesity and increased feeding observed in 5-HT_{2C} knockout mice.⁴ Furthermore, 5-HT_{2C} antagonists have been shown to increase food intake.⁵ Because antipsychotics are dopaminergic antagonists as well as serotonergic antagonists, one can hypothesize that this mechanism of action might also be responsible for increased food intake. Clozapine and olanzapine are atypical antipsychotics with high affinity to the D4 and HT_{2C} receptor and have been shown to increase body weight substantially.¹ Recently, a patient with a nonfunctional D4 receptor was identified.⁶ He showed extreme adiposity with a body mass index (BMI) of 37 kg m⁻². The D4 and 5-HT_{2C} receptor genes seem, therefore, to be suitable candidate genes for investigating antipsychotic-induced weight gain.

The D4 receptor gene contains a 48 bp (base pair) variable number of tandem repeat (VNTR) located in exon 3. It is represented in the third cytoplasmatic loop of the receptor protein that contains 2–10 repeats of a motif of 16 amino acids.⁷ This region is likely to be involved in G-coupling of the protein to its effector systems. The repeat number of the 48 bp sequence seems to affect the pharmacologic activity of this receptor. *In vitro* expression studies showed different properties for the long form (D4.7) and the shorter forms (D4.2, D4.4) with respect to sensitivity for clozapine and spiperone.²

The cysteine by serine substitution in position 23 of the 5-HT_{2C} receptor is caused by a G to C transversion in position 68 of the 5-HT_{2C} receptor gene. As the amino-acid substitution is located in the N-terminal extracellular region of the 5-HT_{2C} receptor, this might have consequences for ligand binding. A recent study has shown that the cysteine for serine substitution at position 23 (Cys23Ser) substitution influences 5-HT_{2C} receptor function *in vitro*, with the Ser23 variant being more active than Cys23 variant.⁸ However the functional *in vivo* effect of this polymorphism remains unclear.^{9,10}

We conducted a prospective clinical study to investigate the association between the DRD4 48 bp VNTR and HT_{2C}

Cys23Ser polymorphism and antipsychotic-induced weight gain in a naturalistic clinical setting of 102 psychotic in-patients of Caucasian origin.

Results

Patient characteristics and medication

A total of 31 patients were released from hospital before day 28 and were, therefore, not included in analysis. No body weight could be measured at day 28 for 9 patients. The remaining 102 patients had an average height of 171.93 cm (s.d. 8.58) and the average weight was 73.83 kg (s.d. 15.12). Fifty-six (54.9%) patients were female. The average age was 37.54 years (s.d. 13.70), the average severity of illness (Clinical Global Impression, CGI 1) on admission to hospital 6.06 (s.d. 0.91). Fifty-six (54.9%) patients were smokers. Antipsychotics used included olanzapine, risperidone, amisulpride, quetiapine, clozapine, flupentixol, ziprasidone, haloperidol, perazin, pipamperon, chlorprothixen, zuclopentixol, promethazin, levomepromazin, prothipentyl, sertindole and fluspirilene (listed from most frequently to least frequently used; Table 1). During the 4 weeks the 102 patients received 180 antipsychotic prescriptions (combinations per patient possible), 33 patients additionally received antidepressants, 68 patients sedatives and 17 patients mood stabilizers. Forty-nine (48.0%) patients received an antipsychotic medication prior to admission to hospital.

DRD4 48 bp VNTR polymorphism and weight gain

The most frequently detected allele of the 48 bp VNTR of the D4 receptor was the fourfold repeat allele (69.6%; 142/204

Table 1 Antipsychotic medication (combinations per patient possible)

<i>Antipsychotic medication (combinations per patient possible)</i>	n
<i>Atypical antipsychotics</i>	130
Olanzapine	35
Risperidone	32
Amisulpride	22
Quetiapine	16
Clozapine	16
Ziprasidone	9
<i>Low- and medium-potency antipsychotics</i>	28
Perazin	7
Pipamperon	7
Chlorprothixen	3
Zuclopentixol	3
Promethazin	3
Levomepromazin	3
Prothipentyl	2
<i>High-potency antipsychotics</i>	22
Haloperidol	9
Flupentixol	11
Fluspirilene	1
Sertindol	1

alleles), followed by the sevenfold repeat allele (14.2%; 29/204), the twofold repeat allele (13.2%; 27/204) and the threefold repeat allele (2.0%; 4/204). The fivefold and eightfold repeat alleles were each detected once (0.5%). No 6-fold, 9-fold or 10-fold repeat allele could be detected in the study population. The genotype distribution of the 102 patients is shown in Table 2. In total 74/102 patients (72.5%) were classified as homozygous for the S alleles, 26/102 were heterozygous (25.5%) and only 2 patients were homozygous for the L alleles (Table 2). Altogether 74 patients were grouped to genotype group 1, 28 to group 2 (Table 2).

A substantial weight gain was observed in the study population 28 days after admission to hospital with a mean increase of body weight of 1.56 kg (s.d. = 3.26) and a mean increase of BMI of 0.53 kg m⁻² (s.d. = 1.11). When comparing the two genotype groups, increase in BMI was significantly less in group 1 than in group 2. In all 102 patients, homozygotes for the shorter alleles showed an increase in BMI of 0.38 kg m⁻² (s.d. = 1.04) compared to an increase of 0.89 kg m⁻² (s.d. = 1.23) in patients heterozygous or homozygous for the longer alleles (*P* = 0.003) (Figure 1). The calculated effect size (mean BMI increase group 1–mean BMI increase group 2/s.d.) was 0.49. According to Cohen¹¹ this can be interpreted as a medium effect size. Weight gain in group 1 was lower (1.14 kg; s.d. = 3.09) than in group 2

(2.69 kg; s.d. = 3.5, corresponding effect size: 0.50). In a subgroup analysis, the difference of increase in BMI between the two genotype groups was only statistically significant in male patients (group 1: increase in BMI = 0.39 kg m⁻² (s.d. = 1.07); group 2: increase in BMI = 1.30 kg m⁻² (s.d. = 0.75); *P* = 0,005) but not in female patients (group 1: increase in BMI = 0.38 kg m⁻² (s.d. = 1.03); group 2: increase in BMI = 0.58 kg m⁻² (s.d. = 1.44); *P* = 0,130) (Figure 1). However, female patients displayed a similar trend. The two patients homozygous for the L allele showed the biggest (1.37 kg m⁻², s.d. = 1.25) increase in BMI 28 days after admission to hospital indicating a possible gene-dose effect.

In the total population, there was no significant difference between the two genotype groups with regard to BMI at admission to hospital, age, severity of illness (CGI 1) at admission to hospital, fraction of smokers, fraction of patients with antipsychotic treatment at admission to hospital and gender (Table 3).

A multiple linear regression with increase in BMI during 4 weeks of treatment as the dependent variable and age, sex, smoking, baseline BMI, previous antipsychotic treatment and the genotype group as the independent variables revealed that smoking (*P* = 0.014), genotype group (*P* = 0.033) and interaction of smoking and genotype group (*P* = 0.006) had significant effects on the increase of BMI.

Table 2 D4 receptor 48 bp repeat genotypes and genotype group classification

D4 receptor 48 bp repeat genotype	n	%	Genotype group
2/2	3	2.9	1
2/4	16	15.7	1
2/5	1	1.0	1
3/4	3	2.9	1
4/4	51	50.0	1
2/7	4	3.9	2
3/7	1	1.0	2
4/7	20	19.6	2
4/8	1	1.0	2
7/7	2	2.0	2

Genotype group 1: <7-fold repeat of the 48 bp repeat of D4 receptor.
Genotype group 2: ≥7-fold repeat of the 48 bp repeat of D4 receptor.

Table 3 Patient characteristics

	Group 1 (n = 74)	Group 2 (n = 28)	P-value
BMI at admission to hospital (kg m ⁻²)	25.57 (s.d. = 5.34)	24.85 (s.d. = 4.33)	0.925
Age at admission to hospital (years)	37.5 (s.d. = 13.6)	37.6 (s.d. = 14.2)	0.960
Severity of illness at admission to hospital (CGI 1)	6.07 (s.d. = 0.87)	6.04 (s.d. = 1.02)	0.836
Percentage of smokers	55.4 (41/74)	53.6 (15/28)	1.000
Percentage of females	54.1 (40/74)	57.1 (16/28)	0.826
Percentage of patients with antipsychotic medication at admission to hospital	51.4 (38/74)	39.3 (11/28)	0.193

Abbreviations: BMI, body mass index; CGI, Clinical Global Impression.
Genotype group 1: <7-fold repeat of the 48 bp repeat of D4 receptor.
Genotype group 2: ≥7-fold repeat of the 48 bp repeat of D4 receptor.

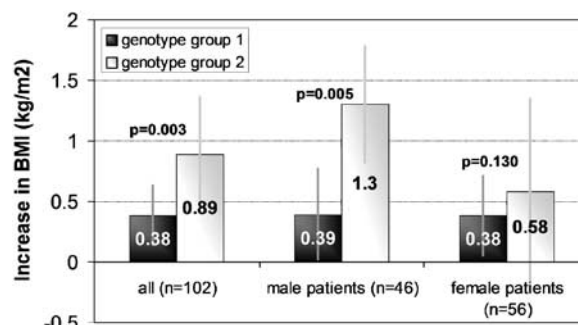


Figure 1 D4 48 bp repeat polymorphism and increase in BMI. Genotype group 1: <7-fold repeat of the 48 bp repeat of D4 receptor. Genotype group 2: ≥7-fold repeat of the 48 bp repeat of D4 receptor. BMI, body mass index calculated as body weight in kg divided by the square of the height in meters. Indicated are mean and *P*-values and 95% confidence intervals.

Baseline BMI showed a trend toward influencing increase in BMI ($P=0.060$). Age, sex and previous antipsychotic treatment did not have significant effects on increase in BMI during the 4 weeks of treatment.

Surprisingly, smokers showed a greater increase in BMI (0.76 kg m^{-2} , s.d. = 1.03) than nonsmokers (0.24 kg m^{-2} , s.d. = 1.16; $P=0.018$).

HT_{2C} Cys23 Ser polymorphism and weight gain

Concerning the HT_{2C} Cys23Ser polymorphism, 82.6% (38/46) of the male patients were hemizygous G (Cys) and 17.4% (8/46) C (Ser) hemizygous. In total 69.6% (39/56) of the female patients showed the G/G genotype and 30.4% (17/56) carried at least one C allele. No significant difference in increase in BMI after 4 weeks of treatment in either male or female patients could be measured between the different genotype groups. In Cys-hemizygous men ($n=38$) the increase in BMI was 0.64 Kg m^{-2} (s.d. = 1.12) compared to 0.55 Kg m^{-2} (s.d. = 0.85) in Ser-hemizygous ($n=8$) ($P=0.701$), and Cys-homozygous women ($n=39$) showed an increase in BMI of 0.44 Kg m^{-2} (s.d. = 1.21) compared to 0.42 Kg m^{-2} (s.d. = 1.04) in women with other genotypes.

Treatment response

In the whole study population, mean CGI (item 1) severity of illness at admission to hospital was 6.06 (s.d. = 0.91) and 5.14 (s.d. = 1.22) 4 weeks thereafter. The reduction in severity of illness was statistically significant ($P<0.0001$) ($n=98$; CGI could not be evaluated in four patients). No association was found between the DRD4 48 bp VNTR polymorphism and response (group 1: 58.6% (41/70) responders, group 2: 50.0% (14/28) responders; $P=0.503$) as well as between the HT_{2C} Cys23Ser polymorphism and response (Cys-hemizygote men: 55.9% (19/34) responders, Ser-hemizygote men: 50.0% (4/4) responders; $P=1.00$; Cys-homozygote women: 61.5% (24/39) responders; other women: 47.1% (8/17) responders; $P=0.384$).

In general there was no tendency toward a correlation with response, but response was only measured by a simple rating scale.

Materials and methods

Patients

Over a period of 24 months, 142 patients suffering from schizophrenia (-like) illness (International Classification of Diseases (ICD)-10: F2 diagnosis) were included in the one-center double-blind study. 98 patients suffered from schizophrenia (ICD-10: F 20), 33 from schizoaffective disorder (ICD-10: F 25) and 11 from other psychotic disorders (1 × ICD-10: F21; 3 × ICD-10: F22; 7 × ICD-10: F23). The patients were treated according to local clinical practice with various antipsychotics and at the discretion of the psychiatrist. Change in antipsychotic treatment, combination of antipsychotics or augmentation of dose of antipsychotics was possible. Sedatives, mood stabilizers, antidepressants and nonpsychotropic medication were allowed as co-medication. Patients were informed of the

aims of the study and gave written consent. The study was approved by the Institutional Review Board (Technische Universität München, Germany) and followed the principles of the Helsinki declaration.

Body weight was measured on admission to hospital and 4 weeks thereafter (day 28). Patients were psychopathologically evaluated by clinical global impression scores (item 1) (severity of illness) at admission to hospital and 4 weeks later. Response was evaluated using CGI (item 2) (improvement) score 4 weeks after admission to hospital.

Patients under 18 years of age were excluded from the study. Other exclusion criteria were drug or alcohol abuse (primary diagnosis), dementia, pregnancy and lactation.

Blood sampling and genotyping

A volume of 2.7 ml of ethylenediaminetetraacetic acid blood was taken from every patient. DNA extraction was performed with the Wizard Genomic DNA Purification Kit (Promega, Mannheim, Germany) according to the instructions of the manufacturer. Genotyping of the DRD4 48 bp VNTR polymorphism was performed slightly modified from Cohen *et al.*¹² using polymerase chain reaction followed by agarose gel electrophoresis and visualization by ethidium bromide. Genotyping of the HT_{2C} Cys23Ser polymorphism was performed slightly modified from Lappalainen *et al.*⁹ using polymerase chain reaction followed by enzymatic digestion, agarose gel electrophoresis and visualization by ethidium bromide.

Specificity of published primers was confirmed by standard BLAST search. The length of PCR products and DNA products after enzymatic digestion and gel electrophoresis were compared with results from a self-developed software tool that predicts the length of PCR/enzymatic digestion products based on GenBank sequences. Each run was performed with positive controls and a water control to rule out false positive findings. Genotyping was reproduced repeatedly by several members of our team.

Statistical analysis

The patients' BMI was calculated as body weight in kilograms divided by the square of the height in meters (kg m^{-2}). Patients were rated as responders if their illness improved according to CGI (item 2) very much (score 1) or much (score 2), and as nonresponders if their illness improved minimally (score 3), was unchanged (score 4), minimally worse (score 5), much worse (score 6) or very much worse (score 7). Statistical analysis was performed using SPSS 12.0.1 for Windows. Differences of the mean were analyzed with the Mann-Whitney *U*-test. Fisher's exact test was used for comparisons of prevalence between the groups. *P*-values are always given two-tailed. A multiple stepwise linear regression analysis was used to establish the potential influence of age, sex, smoking, baseline BMI, previous antipsychotic treatment and the genotype on increase in BMI during the 4 weeks.

On the basis of the functional consequences of the DRD4 48 bp VNTR polymorphism, alleles were grouped in short (S; <7-fold repeat) and long (L; ≥7-fold repeat) as described

in a previous study.¹³ For statistical analysis, patients were placed in one of two genotype groups. Genotype group 1 consisted of patients homozygous for the short alleles and genotype group 2 of individuals heterozygous or homozygous for the long alleles.

As the 5-HT_{2C} receptor gene is located on the X chromosome, we made separate analyses for the two sexes. Male patients were grouped hemizygous G (Cys) or C (Ser), while female patients were GG, GC or CC.

Discussion

The results of our study do not support a possible association of the HT_{2C} Cys23Ser polymorphism with antipsychotic-induced weight gain in psychiatric in-patients. This is in accordance with a previously reported negative result in clozapine-treated German patients¹⁴ and a report by Basile *et al.*¹⁵ who assessed the association of clozapine-induced weight gain with nine candidate gene polymorphisms, including the HT_{2C} Cys23Ser polymorphism. In contrast, there is significant evidence that the HT_{2C} Cys23Ser polymorphism plays a role in body weight regulation *per se*. The Ser23 allele was found to be associated with weight loss in teenage girls¹⁶ and was also associated with the diagnosis of anorexia nervosa.¹⁷ Also, the findings of Praszak-Riederer *et al.*¹⁸ provide evidence that the HT_{2C} Cys23Ser polymorphism mediates severity of weight regulation disturbances in female patients with seasonal affective disorder (SAD). Therefore, missing slight but existing effects cannot be ruled out due to sample size and other limitations of our study discussed later.

Despite the above mentioned negative results, the HT_{2C} receptor remains an interesting structure implicated in antipsychotic-induced weight gain. Several studies investigated a HT_{2C} -759 C/T polymorphism in the promotor region which may alter the expression of the receptor. It was repeatedly shown that this receptor may contribute to variability of antipsychotic-induced weight gain.^{19–24} This was also confirmed in a recently published meta-analysis.²⁵

The DRD4 48 bp VNTR polymorphism affected treatment-induced weight gain in the studied population of schizophrenic inpatients. Patients homozygous for the short alleles showed a significantly lower increase in weight and BMI than others.

In a subgroup analysis, the difference of increase in BMI between the two genotype groups was statistically significant only in male patients. Most clinical studies found male patients treated with atypical antipsychotics to be at higher risk for weight gain than female patients.^{26–28} However, one study reported female patients to be at higher risk²⁹. The different risk for weight gain could in part be explained by hormonal differences and differential interaction of the hormones with receptors including DRD4.³⁰ This may also explain a possible different impact of the DRD4 48 bp VNTR polymorphism on antipsychotic-induced weight gain in male and female patients. However, further studies are necessary to confirm this idea.

In clinical studies it was further shown that, in addition to gender, age, cigarette smoking and baseline BMI may influence antipsychotic-induced weight gain. There is a well known inverse association between tobacco smoking and body weight or weight gain.^{31,32} Thin individuals and lower age groups are more likely to gain weight than heavy individuals.^{2,33} The two genotype groups studied in our population did not differ regarding age, number of smokers and gender ($P > 0.05$). However, in a regression analysis we showed that smoking was significantly associated with weight gain during the 4 weeks of antipsychotic treatment. To our surprise, smokers showed the highest increase in BMI. This could possibly be explained by smoking cessation or decrease in number of smoked cigarettes during hospitalization. Decrease in smoking could lead to weight gain *per se* but could also lead to a decrease of activity of cytochrome CYP1A2 which is inducible by cigarette smoking.³⁴ As several antipsychotics are at least partially metabolized by CYP1A2, reduced smoking may lead to higher drug concentrations leading to a more intense drug-induced weight gain. Baseline BMI showed a trend toward influencing increase in BMI. The fraction of patients with antipsychotic treatment on admission to hospital, age and sex did not influence the obtained results significantly. Unfortunately we were not able to determine duration and dose of antipsychotic treatment before admission to hospital, so that a possible influence of pretreatment on antipsychotic-induced weight gain cannot be ruled out.

Recently, Levitan *et al.*³⁵ showed an association between the hypo functional 7-repeat allele of the DRD4 48 bp VNTR polymorphism with weight gain and obesity in women with SAD: Binge eating as reason for weight gain suggests that a dopamine dependent food reward process might be involved. Such mechanisms may have influenced the results of our study and further studies should include indices of eating behavior in order to clarify the nature of the obtained results.

Van Tol and colleagues first reported different properties for the long (D4.7) and shorter forms (D4.2, D4.4) of the DRD4 48 bp VNTR polymorphism with respect to sensitivity for clozapine and spiperone.² Additionally the 7-fold repeat has been related to poorer response to dopamine stimulating drugs and is suggested to be associated with less functional dopamine transmission.³⁶ Therefore, one may hypothesize that dopaminergic neurotransmission of the hypofunctional long form (D4.7) may be more easily blocked by antipsychotics leading to increased eating and weight gain. However, most antipsychotics display low affinities to the DRD4 receptor. It, therefore, remains unclear if the observed association of the DRD4 48 bp VNTR polymorphism with antipsychotic-induced weight gain is due to a direct influence on receptor targeting by antipsychotics or a yet unknown mechanism.

There are a number of limitations to our study. Inclusion criteria were very broad and patients were treated with various antipsychotics in different combinations and various doses leading to nonhomogeneously treated cohorts. Co-medication may also have influenced the increase in body weight. With respect to the heterogeneity of our study we

cannot rule out a false positive finding concerning the DRD4 48bp VNTR polymorphism. Further studies with larger homogenous patient samples, monotherapy and a fixed dosage regimen are necessary to confirm the obtained results. However, detecting effects under these naturalistic 'clinical conditions' could support their possible clinical relevance. Moreover, patients in our study were hospitalized throughout and the weight gain was observed under more controlled and similar conditions than in an outpatient setting (standardized hospital food, daily routine, exercise and so on). As antipsychotic therapy is long term, studies that investigate the influence of the dopamine DRD4 48bp VNTR polymorphism on antipsychotic-induced weight gain over a longer period of time should be performed. Although the literature shows the greatest increase in body weight upon initiation of treatment, a plateau is reached in most cases after 10 weeks to 2 years.^{37,38} Also, it has been reported that an early increase in BMI appears to be a predictor for long-term weight gain with olanzapine³⁹ may lead to metabolic syndrome and seems to be irreversible by discontinuation or change of treatment. Therefore, an indicator or marker for patients at risk would be extremely valuable.⁴⁰

To our knowledge, this is the first prospective pharmacogenetic study pertaining to the DRD4 48bp VNTR polymorphism that supports the potential role of the investigated polymorphism in predicting patient susceptibility to body weight gain as a major side effect of antipsychotic treatment. One prior study failed to find a correlation between D4 receptor polymorphisms and clozapine-related weight gain. However, this study was retrospective and had a completely different scope. Weight gain was not the primary target, no concrete data was given and the lack of correlation is merely mentioned.⁴¹ Should our results be confirmed, diagnostic laboratories may wish to offer genotyping prior to initiation of therapy and assist clinicians in choosing an optimal therapeutic regimen. Keeping patients at risk on a strict diet or treating them with antipsychotics known to cause less weight gain could prevent consequences such as decreased compliance or cardiovascular morbidity and mortality. We observed a moderate to large effect size of the DRD4 48bp VNTR polymorphism on antipsychotic-induced increase in BMI and weight gain. Nevertheless, due to the complexities and multiple potential interactions between the mechanism of action of antipsychotics and energy homeostasis, it is likely that not a single gene or polymorphism, but a variety of genes, are involved in the genetic susceptibility of weight gain induced by antipsychotics.

Duality of Interest

None declared.

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