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Adiponectine gene +45T/G and +276G/T polymorphism and antipsychotic-induced weight gain

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Abstract: Objective To investigate whether antipsychotic-induced weight gain was associated with adiponectine gene +45T/G and +276G/T polymorphism. **Methods** A case-matched study was done: 85 patients who gained more than 7% of their pre-drug body weight were designed to the study group and 85 patients who gained less than 7% of their pre-drug body weight served as the control group. Ligation diction reaction technique was used to analyze the frequencies of the +276G/T and +45T/G polymorphism of adiponectin gene. **Results** The presence of +276G allele was significantly higher in the study group as compared with the control group. **Conclusion** Subjects with the +276G variant alleles may have a greater risk for weight gain after antipsychotic treatment.

Key words: gene; antipsychotic; schizophrenia; adiponectin

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脂联素基因 +45T/G 和 +276G/T 多态性与抗精神病药物所致体质量增加

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[**摘要**] **目的:** 探讨脂联素基因 +45T/G 和 +276G/T 多态性与抗精神病药物所致体质量增加的相关性。**方法:** 采用病例匹配对照研究,研究组为 85 例服用抗精神病药物后体质量增加≥7% 的精神分裂症患者,对照组为 85 例服用抗精神病药物体质量增加 <7% 的精神分裂症患者,对照组在使用抗精神病药物的种类和治疗时间上与研究组匹配。采用高温连接酶检测反应法对 170 例患者进行了单核苷酸多态性分析。**结果:** 对照组脂联素基因 +276G/T 位点等位基因 G 频率明显高于对照组。**结论:** 脂联素基因 +276G/T 多态性可能与抗精神病药物引起的体质量增加存在关联。

[**关键词**] 基因; 抗精神病药物; 精神分裂症; 脂联素

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Weight gain has long been recognized as the side effects of antipsychotic drugs. The introduction of weight gain by antipsychotic agents has been documented since the introduction of chlorpromazine in the mid-1950's[1]. Weight gain has been considered to be the most troublesome side effect of antipsychotic drug treatment. According to recent studies, up to 50% of patients receiving antipsychotics suffer significant weight gain[2]. Clinical studies indicated that atypical antipsychotics may have a greater potential for inducing weight gain than conventional antipsychotics, and atypical antipsychotics also vary in their propensity to induce weight gain[3-4].

This antipsychotics related side effect not only influences compliance with drug treatment but also inevitably associates with substantial morbidity (diabetes, hypertension, and cardiovascular disease) and mortality. The mechanism underlying weight gain resulting from antipsychotic drugs are complex and not fully elucidated. The substantial differences between individuals in the extent of antipsychotic-induced weight gain suggested that genetic factors may be important[5-6].

However pharmacogenetic data on this issue have been limited and inconsistent. Adiponectin is released by the adiposities to decrease food intake and increase energy expenditure. Some studies have found that patients receiving antipsychotic treatment demonstrate a decrease in adiponectin level[7].

It was reported adiponectin gene are associated with massive obesity. Recent studies have found an association of the +276G/T and +45T/G polymorphism with the plasma adiponectin level[8].

Here, we investigate the role of single nucleotide polymorphism (SNP) +276G/T and +45T/G of adiponectin gene on weight gain induced by antipsychotics in 170 schizophrenic patients.

1 SUBJECTS AND METHODS

1.1 Subjects

It was a case-matched study. Participants were recruited from schizophrenia outpatient between October 2004 and December 2006 in the Mental Health Institute of the Second Xiangya Hospital, Central South University, China. Participants were consistently referred patients, aged 18~60 years, with a first psychotic episode of schizophrenia diagnosed in accordance with criteria set out in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-Ⅳ)[9]. The patients who gained more than 7% of their pre-drug body weight were designed to the study group and were included in our another article[10]. The patients who gained less than 7% of their pre-drug body weight served as the control group. The patients of the control group were matched with which of the study group in the kinds of antipsychotics and duration of antipsychotic treatment. The difference of the 2 groups in duration of antipsychotic treatment was no more than 2 months. The study was approved by the Ethics Committee of the Second Xiangya Hospital and all participants provided written informed consent in accordance with national health and medical research council guidelines.

1.2 Genotyping

Genomic DNA was extracted from whole blood using standard techniques. Ligation diction reaction (LDR) technique was used to analyze the frequencies of the +276G/T and +45T/G polymorphism of adiponectin gene. All SNPs were in Hardy-Weinberg equilibrium.

The polymerase chain reaction (PCR) were carried out on the ABI 9600 (Applied Biosystems, USA) in a total volume of 20μL containing 20 ng genomic DNA, 10 mmol/L Tris-HCl (pH7.4), 50 mmol/L KCl, 2.0 mmol/L $MgCl_2$, 200 mmol/L dNTPs, 0.5μmol/L Primers, and 1U Taq DNA polymerase. The cycling protocol consisted of denaturation at 94℃ for 15 min, followed by 30~35 cycles at 95 ℃ for 30 s, 50 ℃~65 ℃ for 1 min, 64 ℃ for 1 min, and a final extension at 64 ℃ for 10 min.

LDR for each subject was carried out in a final volume of 20 μL containing 20 mmol/L Tris-HCl

(pH 7.6), 25 mmol/L potassium acetate, 10 mmol/L magnesium acetate, 10 mmol/L DTT, 1 mmol/L NAD, 0.1% Triton X-100, 2 μL of Multi-PCR product, 1 pmol of each discriminating probe, 0.5 μL of 40 U/mL Taq DNA ligase (New England Biolabs, USA). The LDR was performed with 40 cycles of 94 ℃ for 30 s and 50 ℃ for 2 min.

Following the LDR reaction, the solution was diluted to obtain 1 μL LDR reaction product, 1 μL ROX and 1 μL loading buffer. The mixture was then analyzed by the ABIPRISM 3730 DNA Sequencer (Applied Biosystems, USA).

1.3 Statistical analysis

All analyses were conducted by using the Statistical Package for Social Sciences, version 11.5 (SPSS Inc.). A χ^2 analysis (Fisher's exact test) was conducted comparing whether or not there were differences in the allele frequencies of all SNPs between the 2 groups. The difference was considered statistically significant if a 2-tailed P value was less than 0.05.

2 RESULTS

A total of 170 eligible patients were included in this study. Eighty-five patients were assigned to the study group and control group respectively. Sixty-one patients were female in the study group and 49 patients were female in the control group. The age in the study and control groups were (23.4 ± 5.3) years and (22.7 ± 4.8) years, respectively. The 2 treatment groups did not differ significantly on demographic or clinical characteristics (Tab. 1).

The alleles frequencies of +276G and +276T alleles were 80.6% and 19.4% for the study group, 68.2% and 31.8% for the control group (Tab. 2). The presence of the +276G allele was significantly higher in study group as compared with the control group ($P < 0.01$, Tab. 2).

The alleles frequencies of +45T and +45G alleles were 67.1% and 32.9% for the study group, and 70.6% and 29.4% for the control group (Tab. 2). There were not significant differences in the 2 groups in the presence of the +45T or +45G ($P > 0.05$, Tab. 2).

Tab. 1 Demographic and clinical characteristics of the 170 participants

Patient variables	Study group (n = 85)	Control group (n = 85)	Test Statistic	P
Age (year)	23.4 ± 5.3	22.7 ± 4.8	0.976	0.383
Female [No (%)]	61.0(71.7)	49.0(57.6)	0.082	0.964
Duration of disease (months)	6.9 ± 3.1	7.4 ± 3.6	0.625	0.582
Weight of pre-drug treatment (kg)	54.7 ± 10.23	55.6 ± 11.14	0.223	0.644

Tab. 2 Distribution of +276G allele and +45T allele in the 2 groups

	Adiponectin gene +276G/T		Adiponectin gene +45T/G	
	Presence of +276G allele	Presence of +276T allele	Presence of +45T allele	Presence of +45G allele
Study group	137	33	114	56
Control group	116	54	120	50
χ^2	6.812		0.496	
P	0.009		0.482	

3 DISCUSSION

This study is the first as a case-matched study to report association of weight gain induced by antipsychotic with the polymorphisms of adiponectin gene +276G/T and +45T/G.

The findings indicated that allele +276G of adiponectin gene was associated with antipsychotic-induced significant weight gain. The physiological mechanism behind this genetic finding could be through the effect of the adiponectin SNPs on adiponectin levels. Adiponectin, an adipocyte-derived hormone, is considered one of the main peripheral signals that affects food intake and body weight[11]. Leptin also directly influences insulin resection, could involved in the development of diabetes in obese subjects with insulin resistance and improves glucose metabolism by increasing insulin sensitivity.

In the study, we found that the +45T/G polymorphism of the adiponectin gene did not show evidence of association with antipsychotic induced weight gain. These results did not consist with some previous reports[12-14].

The limitation of the study was that additional factors did not be taken into consideration such as exercise and diet. Because it was not a perspective study we did not monitor the diet and exercise of these patients.

In summary, our results suggest that the +276G/T polymorphism of adiponectin gene were associated with antipsychotic induced weight gain. Subjects with the +276G variant alleles may have a greater risk for weight gain after antipsychotic treatment.

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