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TNF-α −308 G>A polymorphism and weight gain in patients with schizophrenia under long-term clozapine, risperidone or olanzapine treatment

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ABSTRACT

Atypical or second-generation antipsychotics (SGAs) are associated with excessive body weight gain (BWG) and other components of metabolic syndrome. Among all SGAs, clozapine and olanzapine are known to cause the most significant weight gain, followed by risperidone and quetiapine. The genetic variant of tumor necrosis factor α (*TNF-α*), −308 G>A polymorphism (rs1800629), has been implicated in clozapine-induced BWG in several studies. We hypothesized that *TNF-α* −308 G>A polymorphism has a general effect on SGA-induced BWG. The present study was conducted to examine the association between *TNF-α* −308 G>A polymorphism and BWG during treatment for schizophrenia using a variety of second generation antipsychotics (SGAs). A total of 500 patients with schizophrenia treated with clozapine ($n = 275$), olanzapine ($n = 79$) or risperidone ($n = 146$) for an average of 49.9 months were recruited. Subjects with an increase in weight of more than 7% from the baseline before the current SGA treatment to the weight at the survey point were defined as having BWG. The association between *TNF-α* −308 G>A polymorphism and BWG was studied, and the effect of non-genetic factors such as baseline BMI, SGA treatment duration and SGA type on the association was controlled by logistic regression. The results revealed that there was no significant association between BWG and *TNF-α* −308 G>A polymorphism (GG/GA/AA or GG/GA+AA) in each separate SGA group or collectively. These findings suggest that *TNF-α* −308 G>A polymorphism does not play a major role in SGA-induced weight gain.

Despite numerous benefits offered by second-generation antipsychotics (SGAs), there have been rising concerns that certain medications are associated with increased risks of metabolic syndrome – obesity, glucose intolerance, and dyslipidemia and hypertension. Weight gain is an important issue not only because of its association with other components of metabolic syndrome but also immediate concerns regarding quality of life and drug compliance [18]. Among all SGAs, clozapine and olanzapine are known to cause the most significant weight gain, followed by risperidone and quetiapine [20]. A meta-analysis showed that after at least 10 weeks of treatment, clozapine produced a weight gain of 4.45 kg, olanzapine 4.15 kg and risperidone 2.10 kg [2].

The mechanisms of SGA-related weight gain are not well understood and a large body of evidence points to a significant role played by genetic factors. In a review article, Correll and Malhotra summarized three categories of genes of great interest: (1) genes involved in the metabolism and bioavailability of antipsychotic medications, (2) genes coding for receptors modulated by antipsychotics, and (3) genes involved in molecular pathways associated with obesity [6], such as tumor necrosis factor alpha (TNF-α). TNF-α is a multifunctional pro-inflammatory cytokine that is widely expressed and exerts as autocrine, paracrine and endocrine at different concentrations. It is produced and secreted by adipose tissue and plays an important role in both normal weight regulation and drug-induced weight gain. Hotamisligil first linked TNF-α to obesity and insulin resistance by showing increased production of *TNF-α* mRNA and protein in adipose tissue in obese or type II diabetes rodents [13]. A similar correlation of TNF-α with obesity and insulin resistance was later established in human subjects [12,13]. In contrast to its effects on weight gain, TNF-α has also been shown to have catabolic and antiadipogenic effects on adipocytes. Kern et al. identified a positive correlation between *TNF-α* mRNA in adipose tissue and BMI; such a correlation disappeared when BMI>45 [14]. Kras et al. proposed that TNF-α at a physiological level exerts anabolic effects, while

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at the supraphysiological level TNF-α produces metabolic effects [16].

The association between antipsychotic-induced weight gain and increased TNF-α or soluble TNF receptors level has been established in the literature. Antipsychotics relevant to prominent weight gain such as clozapine and olanzapine were observed to significantly increase the serum TNF-α level [8,15,21]. Antipsychotics less relevant to weight change have also been shown not to interfere with the TNF-α system [19]. However, the temporal relationship between change in body weight and TNF-α level is controversial [25]. In a recent study, Kluge et al. showed that the TNF-α level increased with BMI under treatment with olanzapine and clozapine. The early activation of the TNF-α system observed in the study also implied a causal role in weight gain [15].

Regarding the notable relevance between the TNF-α system and antipsychotic-induced weight gain, genetic variants in the *TNF-α* gene have been investigated in detail over the past decade. The *TNF-α* gene is located on human chromosome 6p21.3 and contains a large number of polymorphisms. Among those, the −308 G>A polymorphism (rs1800629) in the promoter region has become a candidate of interest in recent years with regards to antipsychotics-induced weight gain. Previous studies identified that the −308 A polymorphism was associated with a higher transcriptional rate as compared with −308 G [1,27]. However, some studies have shown that TNF-α expression is cell-specific: while the −308 A allele increased TNF-α expression in a lymphocyte-derived B-cell line [14], it might cause decreased expression in leukocytes and SHSY-5Y neuroblastoma cells [9,22]. The −308 G>A polymorphism has been shown to be associated with obesity and insulin resistance from previous data [4,17]. There have been several studies investigating the association between the −308 G>A polymorphism and clozapine-induced weight gain. However, the findings of these studies are inconsistent. Basile et al. reported a non-significant twofold increase in weight gain with the −308 A/A genotype than G/G and G/A genotypes in patients after 6 weeks of clozapine treatment [3]. In contrast, two other studies observed that patients with the G/G genotype tend to experience more weight gain than those of the other two genotypes after 6 weeks or 4 months of clozapine treatment [24,28]. In our previous study, in which 55 patients with refractory schizophrenia were recruited, we found that G/G carriers had a significantly greater weight gain than A allele carriers during 8 years of clozapine treatment [26]. However, the sample size was small and only six −308 A allele carriers were recruited. In the present study, we further examined the association between −308 G>A polymorphism and weight gain induced by a variety of SGAs, including clozapine, risperidone and olanzapine, in a larger population consisting of 500 patients with schizophrenia.

A total of 500 inpatients with chronic schizophrenia of Yuli Veterans Hospital, the largest psychiatric hospital in Taiwan with approximately 2500 inpatients, were enrolled in this study. A consensus diagnosis for each patient was made according to the Diagnostic and Statistical Manual-IV criteria for schizophrenia based on the data collected from an interview, clinical observation, and medical records by two certified psychiatrists. All patients had been treated with an SGA (clozapine: 275, olanzapine: 79, and risperidone: 146 subjects) for at least 3 months. Patients with the following conditions were excluded: history of mood disorder, organic mental disorder, exposure to abused substances, neurological illness, diabetes mellitus, and those aged over 65 years or under 18 years. The clinical variables measured included sex, age, duration of treatment and SGA dosage at survey. Body weight was measured at initiation (baseline) and at the survey. All patients were ethnic Chinese, were continuously hospitalized and received diets from a central kitchen. Alcohol consumption was prohibited on all wards. These conditions ensured optimal control of drug treatment compliance and fasting status to allow assessment of metabolic parameters. According to earlier reports [5], body weight gain (BWG) was defined as an increase of more than 7% from the baseline body weight during treatment with the current SGA. This study was reviewed and approved by the Ethics Review Committee of Yuli Veterans Hospital and was carried out in accordance with the principles of the Declaration of Helsinki. The study was described in full to all patients, and informed consent was obtained before blood withdrawal.

Genomic DNA was extracted from the peripheral blood cells of the study patients. Determination of the genotype of the *TNF-α* −308 G>A polymorphism (rs1800629) for each patient was conducted according to the method of Tsai et al. [24], and was carried out by researchers who were strictly blind to the clinical information of the patients.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) V10.0. Categorical data were analyzed using the χ^2 test or Fisher's exact test if necessary. Differences in the means of continuous variables between groups were evaluated using Student's *t*-test or one-way ANOVA. The criterion for significance was set as a *p*-value lower than 0.05 for tests involving demographic and clinical data. Logistic regression analyses for the association of *TNF-α* −308 G>A polymorphism with BWG were conducted and baseline BMI, duration of current SGA exposure and types of SGA drugs were entered as covariates.

The 500 recruited patients with schizophrenia were treated with clozapine ($n = 275$), olanzapine ($n = 79$) or risperidone ($n = 146$) for a mean of treatment duration of 49.9 months (range: 4–120 months). Using a cutoff level of 7% to define patients with BWG, we found that 37.8% (189 of 500) of the patients met this criterion. The demographic and clinical information and the genotype distribution of *TNF-α* −308 G>A of the patients with or without BWG are shown in Table 1. There was no significant difference in the mean age or gender distribution between the two groups. However, the patients with BWG had a higher baseline BW, higher baseline BMI and longer SGA treatment duration and a higher proportion of concomitant mood stabilizer use than those without BWG (Table 1, all *p*-values < 0.05). The case numbers of individual SGAs in the patients with or without BWG also differed significantly: the BWG group had a higher proportion of patients under clozapine treatment; in contrast, the number of patients treated with risperidone in the non-BWG was significantly higher than that in the BWG group (Table 1, $p = 0.005$). The distribution of *TNF-α* −308 G>A genotype did not deviate significantly from HWE in the BWG ($p = 0.105$) or the non-BWG ($p = 0.394$) group. The BWG percentages in the individual genotype groups were: GG = 4.2 ± 15.7%; GA = 5.9 ± 18.2%; AA = −3.0 ± 10.1%. Because there were only three subjects with the −308 AA genotype (Table 1), we also grouped the subjects with GA or AA types as the A-allele group (GA+AA) in the subsequent genotypic and regression analyses.

There was no significant association between BWG and *TNF-α* −308 G>A polymorphism (GG/GA/AA or GG/GA+AA) in the SGA-treated patients (Table 1). The association of the polymorphism and BWG during SGA treatment remains insignificant according to logistic regression analysis in which the baseline BMI, duration of current SGA treatment, SGA class and the use of mood stablizers were entered as covariates ($p = 0.893$). Stratifying the patients according to the SGA, neither the binary outcome (BWG or non-BWG) nor the quantitative outcome (BMI change and percentage change in BW) showed a significant association with the *TNF-α* polymorphism (data not shown).

The results of this study indicate that, for our sample, there was no significant association between *TNF-α* −308 A polymorphism and SGA-induced weight gain in patients with schizophrenia treated with clozapine, olanzapine or risperidone. The present study was not able to replicate the findings of our previous study, in