Methylenetetrahydrofolate reductase (MTHFR) 677C/T polymorphism is associated with antipsychotic-induced weight gain in first-episode schizophrenia

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BRIEF REPORT

Methylenetetrahydrofolate reductase (MTHFR) 677C/T polymorphism is associated with antipsychotic-induced weight gain in first-episode schizophrenia

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Abstract

Genetic variants of the methylenetetrahydrofolate reductase (MTHFR) gene involved in homocysteine metabolism may be important predictors of antipsychotic drug-induced weight gain (AIWG). We tested whether two functional MTHFR polymorphisms are related to AIWG. Weight gain was studied in two cohorts of first-episode, initially drug-naive schizophrenia patients; Chinese Han (n=182) and Spanish Caucasians (n=72) receiving antipsychotics for 10 wk and 3 months respectively. Blood DNA was genotyped for 677C/T and 1298A/C MTHFR polymorphisms. Patients with the 677 CC genotype had a significantly greater increase in BMI compared to T-allele carriers in both Chinese (p=0.012) and Spanish (p=0.017) samples. The 677C/T MTHFR polymorphism showed an additive effect, but no significant interaction, with the -759C/T HTR2C polymorphism previously associated with AIWG.

These results suggest that the 677C/T MTHFR polymorphism might, along with the -759C/T HTR2C polymorphism and other genetic factors, provide a useful marker for the important and limiting side effect of AIWG.

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Key words: Antipsychotic, genotype, MTHFR polymorphism, schizophrenia, weight gain.

Introduction

Schizophrenia is a severe, complex and chronic disorder, which for many patients is inadequately treated. Antipsychotic drugs can, in many individuals, relieve the positive psychotic symptoms but have various adverse effects; notably several of the drugs can induce a substantial weight gain in susceptible individuals. This weight gain may not only increase treatment noncompliance, but also affect morbidity from metabolic consequences including lipid abnormalities, insulin resistance and diabetes mellitus (Henderson et al., 2000). Patients receiving antipsychotic treatment can develop metabolic abnormalities with increased risk of cardiovascular disease and mortality (Casey et al., 2004; De Hert et al., 2009).

Susceptibility to antipsychotic-induced weight gain varies substantially between individuals in ways that cannot be fully explained by differences between drug effects or other environmental factors. Thus genetic influences are strongly implicated, and associations between many genetic polymorphisms and antipsychotic-induced weight gain have been reported. The most consistently reported genetic factors involved in antipsychotic-induced weight gain include polymorphisms in genes for 5-hydroxytryptamine 2C (5-HT2C), 5-HT2A, adrenergic alpha 2A and melanocortin 4 receptors, as well as leptin and fat mass and obesity associated (FTO) genes (Reynolds, 2012).

Recently, genetic variants of the methylenetetrahydrofolate reductase (MTHFR) gene have been proposed as potential predictors for antipsychotic-induced metabolic side effects (Kuzman and Müller, 2012). MTHFR exerts an important role in folate and homocysteine metabolism by catalysing the reduction of 5,10-methylenetetrehydrofolate to 5-methylenetetrahydrofolate (5-MTHF), which is used in methionine synthesis from homocysteine. The methionine is further converted to S-adenosylmethionine (SAM), which is a major methyl donor in a wide variety of enzymatic processes including the methylation of DNA. MTHFR deficiency can increase serum homocysteine, whereas the decrease in 5-MTHF and SAM causes deficits in DNA methylation, DNA synthesis and repair, and may

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predispose to neurodevelopmental and oncogenic processes, resulting in the development of many disorders including cardiovascular disease, renal failure, cancer and congenital abnormalities (Ueland et al., 2001).

The association of MTHFR polymorphisms with metabolic syndrome has been reported in the general population. Obesity has been associated with MTHFR 1298A/C (Terruzzi et al., 2007) and 677C/T genotypes (Lewis et al., 2006). Carriage of the 677T allele is associated with insulin resistance (Chen et al., 2010; Lunegova et al., 2011). Association of the 677T allele with central obesity, hypertriglyceridemia and low levels of high-density lipoprotein cholesterol (HDL-C) was also reported in the latter study (Lunegova et al., 2011). A replicated study reported that the 677T allele but not the 1298A/C polymorphism of MTHFR was associated with a greater risk of developing metabolic syndrome and the TT genotype was associated with risk of insulin resistance with greater central adiposity induced by antipsychotic treatment (Ellingrod et al., 2008, 2012). Others have reported the association of metabolic syndrome in schizophrenia with the 1298A/C polymorphism in 518 Caucasian patients (van Winkel et al., 2010a). These authors also reported that the 1298C variant was associated with an increased weight and impaired glucose tolerance in 104 Caucasian patients who received antipsychotic treatment for 3 months (van Winkel et al., 2010b). In the present study, we examined the association of the MTHFR 677C/T and 1298A/C polymorphisms with antipsychotic-induced weight gain in first-episode drug-naive patients with schizophrenia.

Methods

Study population

Two cohorts of first-episode, initially antipsychotic drug-naive patients with schizophrenia receiving treatment according to normal clinical practice were studied; one main sample of Chinese Han (n=182) and a replication sample of Spanish Caucasians (n=72). All patients gave written informed consent to the procedure of the study, which was approved by local ethical committees. Height and weight to determined body-mass index (BMI) were measured on initiation of antipsychotic drug treatment and after 8 or 10 wk (Chinese cohort) or 3 months (Spanish cohort) and weight gain was determined by change in BMI over the treatment period. Initial antipsychotic drug treatment for Chinese Han patients consisted primarily of chlorpromazine (n=60) risperidone (n=114); eight patients received clozapine, fluphenazine or sulpiride. Patients in the Spanish cohort received primarily risperidone (n=21) or olanzapine (n=22) and two received both; others had quetiapine (n=10), haloperidol (n=8) or ziprasidone (n=6) with three not receiving antipsychotics. In this group, as with a subsample of the Chinese cohort (Reynolds et al., 2002), association of the -759C/T polymorphism of HTR2C with weight gain had previously been identified (Templeman et al., 2005). These results were also included in a combined analysis with the MTHFR findings.

Genotyping of MTHFR polymorphisms

Genomic deoxyribonucleic acid (DNA) was isolated from blood using standard techniques and was genotyped for MTHFR 677C/T (rs1801133) and 1298A/C (rs1801131) using TaqMan® SNP genotyping assays: assay ID C_1202883_20 and C_850486_20, respectively (Applied Biosystems, USA). The PCR conditions consisted of initial denaturation at 95 °C for 10 min, followed by 40 cycles of 95 °C for 15 s and 60 °C for 1 min. Assays were run on a Step One Plus Real-Time PCR System (Applied Biosystems, USA).

Statistical analysis

All statistical analysis of results was performed using SPSS version 18.0. Data were expressed as mean±S.D. Stepwise linear regression was used to determine the potential confounding effects of baseline BMI and age on antipsychotic-induced weight gain. Analysis of variance was used to determine the association between MTHFR genotypes and weight gain. Statistical significance was assumed for p values less than 0.05. The main Chinese cohort of 182 subjects had approximately 90% power to identify a significant genotype difference for a medium effect size of 0.5.

Results

Clinical characteristics and genotype results

The 182 (83 men, 99 women) Chinese Han patients had a mean age 26.24±7.35 years. The genotype distribution for 677C/T MTHFR was as follows: CC (n=54), TT (n=28), and CT (n=94), six samples failing genotyping, and for 1298A/C was AA (n=114), CC (n=5), and AC (n=56) with seven samples failing genotyping. On regression analyses, baseline BMI but not age had a significant confounding effect on weight gain after 8–10 wk treatment (F=24.189, p<0.001), whereas age had a significant confounding effect on baseline BMI (F=11.036, p=0.001). Therefore, the subsequent analyses were performed with adjustment for age or baseline BMI as covariates.

The second study sample of 72 (53 men, 19 women) Spanish patients had a mean age of 25.35±6.80 years. The 677C/T genotype distribution was CC (n=20), TT (n=13), and CT (n=36) and the 1298A/C genotypes were AA (n=45), CC (n=3), and AC (n=21) with three samples failing genotyping. On regression analysis, age but not baseline BMI had a significant confounding effect on weight gain at 3 months (F=7.026, p=0.010). Therefore, the subsequent analysis was performed with adjustment for age as a covariate.

Table 1. Sociodemographics, baseline body mass index (BMI) and change in BMI among methylenetetrahydrofolate reductase (MTHFR) 677C/T and 1298A/C genotypes in Spanish and Chinese Han samples. Data are expressed as Mean±S.D.

	MTHFR 677C/T genotype				MTHFR 1298A/C genotype			
	CC	CT	TT	p^*	AA	AC	CC	p^*
Chinese Han sample	n=54	n=94	n=28		n=114	n=56	n=5	
Age	25.04±6.84	26.21±7.18	28.45±8.60	0.136	26.54±7.77	25.61±6.61	27.20±5.54	0.710
Gender M/F (%male)	25/29 (46.3%)	57/65 (46.7%)	13/15 (46.4%)	0.998	53/61 (46.5%)	24/32 (42.9%)	4/1 (80%)	0.279
Baseline BMI (kg/m^2)	20.99±2.69	21.43±2.77	21.92±3.53	0.607	21.47±3.06	21.20±2.59	21.78±1.51	0.895
Change BMI (kg/m^2)	1.58±1.25	0.92±1.15	1.43±1.10	**0.003**	1.27±1.24	1.04±1.18	1.63±0.94	0.228
Spanish sample	n=20	n=36	n=13		n=45	n=21	n=3	
Age	27.60±8.34	24.25±5.69	23.92±6.96	0.168	25.36±7.36	24.76±6.38	25.00±1.73	0.949
Gender M/F (%male)	14/6 (70.0%)	29/7 (80.6%)	9/4(69.2%)	0.578	32/13 (71.1%)	17/4 (81%)	3/0(100%)	0.412
Baseline BMI (kg/m^2)	21.44±3.78	22.06±3.70	22.29±4.01	0.780	21.92±3.62	21.99±4.16	21.45±3.76	0.973
Change BMI (kg/m^2)	2.86±1.53	2.09±1.44	1.85±1.81	**0.049**	2.18±1.66	2.46±1.52	2.03±0.99	0.807

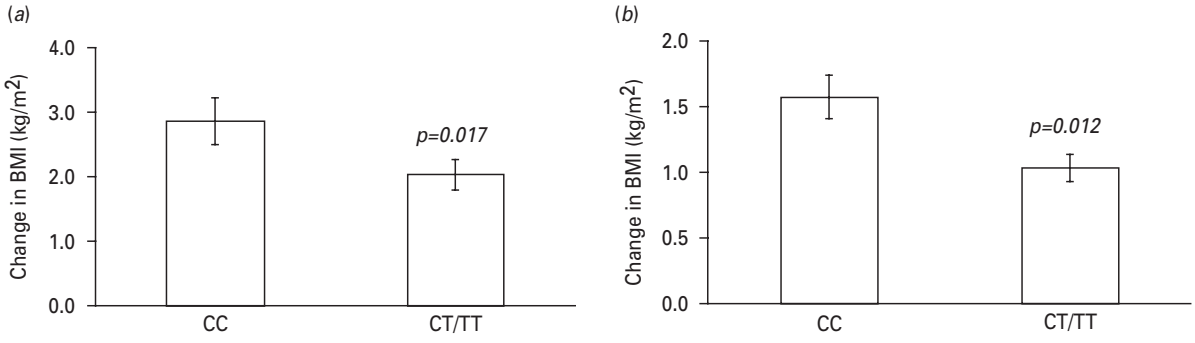

Fig. 1. The association between methylenetetrahydrofolate reductase (MTHFR) 677C/T genotype and weight gain for Spanish (*a*) and Chinese Han (*b*) schizophrenia patients. Data are expressed as mean±S.E.M. BMI: body mass index.

The two polymorphisms were found to be in strong linkage disequilibrium (D'=0.866 and 1.00, r^2=0.127 and 0.198 in Chinese and Spanish groups respectively) in which the 677T allele was almost exclusively carried with the 1298A allele.

Association of MTHFR 677C/T and 1298A/C polymorphisms with weight gain

As shown in Table 1, the baseline BMI, age, and gender distribution of both samples were not significantly different between genotypes of the 677C/T MTHFR polymorphism. The CC genotype had greater changes in BMI than T allele carriers: 1.58±1.25 *vs.* 1.04±1.16 kg/m^2 in Chinese (p=0.012) and 2.86±1.53 *vs.* 2.02±1.54 kg/m^2 in the Spanish sample (p=0.017) (Fig. 1).

Dividing the Spanish cohort into patients who received or did not receive olanzapine, and the Chinese cohort into those receiving either risperidone or chlorpromazine, resulted in the absence of a significant drug×MTHFR genotype interaction.

The baseline BMI, age, and gender distribution of both study populations were not significantly associated with the 1298A/C MTHFR polymorphism. Nor were the changes in BMI of either study population significantly different between 1298A/C AA genotype and C carriers: 1.27±1.24 *vs.* 1.08±1.17 kg/m^2 in Chinese Han samples (p=0.242) and 2.18±1.66 *vs.* 2.40±1.45 kg/m^2 in Spanish samples (p=0.621) respectively.

Gene–gene interaction

Previous findings in these two cohorts (Reynolds et al., 2002; Templeman et al., 2005) showed that the T allele of the 5-HT2C receptor gene (HTR2C) -759C/T polymorphism had a protective effect against antipsychotic-induced weight gain. Association of this polymorphism with changes in BMI were as follows: in the Chinese cohort T carriers 0.71±1.11 kg/m^2 (n=38), C/CC genotype 1.33±1.21 kg/m^2 (n=141) p=0.004; in the Spanish cohort T carriers 1.24±1.46 kg/m^2 (n=16), C/CC genotype 2.48±1.54 kg/m^2 (n=50) p=0.012. The relationship between the effects of the HTR2C -759C/T and the MTHFR 677C/T polymorphisms was investigated. Analysing the association of weight gain with both polymorphisms together in each cohort, no significant interaction between the

polymorphisms was detected but a significant overall effect was observed (p=0.001 in the Chinese sample; p=0.019 in the Spanish sample), indicating an additive effect of the two polymorphisms. Thus carriage of two risk factors (HTR2C C/CC genotype and MTHFR 677 CC genotype) was associated with mean gains of 3.23 and 1.81 kg/m^2 in Spanish (n=14) and Chinese (n=41) cohorts respectively; equivalent values for subjects carrying neither risk factor were 1.35 (n=10) and 0.63 (n=25) kg/m^2.

Discussion

This study indicated that MTHFR 677C/T polymorphism is associated with antipsychotic-induced weight gain in first-episode patients with schizophrenia. Individuals carrying the T allele showed less weight gain compared to the common CC genotype after 8–10 wk or 3 months' treatment with antipsychotic drugs. This finding, observed in two patient cohorts of different ethnicity, indicates the effect to be a robust and reproducible one. The study had 90% power to identify a medium (0.50) effect size in the main cohort; previous studies of association of the well-replicated -759C/T polymorphism of HTR2C with antipsychotic drug-induced weight gain in a subgroup of the Chinese sample and in the Spanish sample have demonstrated substantially larger effect sizes of 0.90 and 0.86 respectively (Reynolds et al., 2002; Templeman et al., 2005). In order for pharmacogenetic risk factors to explain a good proportion of the variance and thereby to have substantial predictive value, strong effects are needed. In this we are aided substantially by the cohorts studied here; each only included first-episode patients who had never previously received antipsychotic drug treatment. This eliminates much of the variance associated with prior drug treatment, which can induce significant weight gain within a few weeks of initial treatment (Zhang et al., 2004).

The absence of an effect in the 1298A/C polymorphism, despite it being in strong linkage disequilibrium (high D' values) with the significantly associated 677 genotype, presumably relates to the large differences in allele frequency between the two polymorphisms, as reflected by low r^2 values.

In two previous cross-sectional studies the 677C/T polymorphism is associated with metabolic syndrome following antipsychotic drug treatment (Ellingrod et al., 2008, 2012), although these authors find the 677T allele to be a risk factor, whereas we find a consistent effect of the 677T allele in protecting against antipsychotic drug-induced weight gain. This may well indicate the difference between effects on initial weight gain and its long-term consequences, in which differing pharmacogenetic influences are apparent (Reynolds et al., 2013). In another study the 1298A/C but not 677C/T polymorphism was associated with metabolic syndrome in schizophrenia (van Winkel et al., 2010a). The one previous longitudinal study of changes in weight and metabolic parameters following 3 months' treatment with second-generation antipsychotics also found an association with the 1298A/C but not 677C/T polymorphism (van Winkel et al., 2010b). This study differed from the present investigation of first-episode drug-naive patients in that weight but not BMI was measured, and the 104 patients were older (mean 31.3 yr) with first admission on average over 6yr previously; thus prior treatment may well have confounded subsequent weight gain. However, their finding that the 1298A allele is associated with less weight gain is not inconsistent with our finding given the close linkage disequilibrium between the two polymorphisms studied. As discussed by van Winkel et al. (2010b), there are no clinical or ethnic factors identified that may be responsible for the discrepancies between these findings, although it is notable that most studies were not powered to identify significant differences between the effects of the two closely linked polymorphisms. Nevertheless these various reports all indicate that functional genetic variation in MTHFR can influence antipsychotic drug-induced weight gain.

It is conceivable that pharmacogenetic associations such as that identified here may vary depending on the treatment regime. Different drugs may have differing mechanisms underlying their effect on body weight – certainly the greater effect of olanzapine over risperidone and several other antipsychotics supports this – and these pharmacological mechanisms may be differentially influenced by genetic polymorphisms. Our study was not powered to subdivide samples into treatment subgroups; however, further work needs to address the possible drug specificity of such pharmacogenetic findings.

There was no significant interaction between -759C/T of HTR2C and 677C/T of MTHFR on antipsychotic-induced weight gain, indicating that both polymorphisms exert independent influences on this side effect. However, the gene–gene analysis resulted in substantial increases in statistical significance, demonstrating an additive effect of the two polymorphisms. Clearly there are other genetic influences that are likely to contribute to determining initial weight gain associated with antipsychotic drug treatment, including polymorphisms for genes for leptin, melanocortin receptor 4, adrenoreceptor alpha2A and g-protein beta3 among probably many others (Reynolds, 2012).

The exact mechanism by which MTHFR polymorphisms might contribute to determining antipsychotic drug-induced weight gain is unclear. Both variant alleles of 677C/T and 1298A/C MTHFR polymorphisms cause decreased enzyme activity (Weisberg et al., 1998), although it is not easy to distinguish effects of two closely linked polymorphisms *in vivo*. MTHFR is an important enzyme in one-carbon metabolism and, via its role in DNA synthesis and methylation (Sugden, 2006), may influence gene expression (Jirtle and Skinner, 2007); such epigenetic effects could be involved in antipsychotic

drug-induced weight gain. Diminished levels of genomic DNA methylation (Stern et al., 2000) and gene-specific DNA methylation (Burghardt et al., 2012) have been reported to be associated with the 677TT genotype. It is therefore possible that decreased MTHFR enzyme activity in 677TT genotype results in decreased DNA methylation of genes involved in body weight regulation.

DNA methylation status is influenced by gene–nutrient interaction. It has been suggested that the MTHFR 677TT genotype affects DNA methylation status through an interaction with folate status (Friso and Choi, 2002). These authors found that genomic DNA methylation in peripheral blood mononuclear cells was directly correlated with folate status, inversely correlated with homocysteine levels, and only 677TT subjects with low folate accounted for decreased DNA methylation (Friso et al., 2002). Thus folate status in addition to the 677C/T MTHFR polymorphism might modulate DNA methylation of genes relating to the regulation of food intake, energy expenditure or body weight regulation, and thus could be an unexplored factor contributing to the variance in this and previous studies.

In conclusion, this present study indicates the association of the MTHFR 677C/T single polymorphism with weight gain following initial antipsychotic drug treatment in first-episode psychotic patients. Furthermore, the effect of the 677T allele appears to have a protective effect additional to that of the well-established HTR2C -759T allele against antipsychotic-induced weight gain. These two polymorphisms, in addition to several other possible genetic factors, might be valuable as pharmacogenetic markers of this important and limiting side effect.

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Statement of Interest

G.P. Reynolds has received honoraria for educational lectures, advisory panel membership and/or travel support from the following pharmaceutical companies: Lundbeck, Janssen-Cilag, Otsuka and Sunovion.

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