



Association of allelic variation in genes mediating aspects of energy homeostasis with weight gain during administration of antipsychotic drugs (CATIE Study)

Hemant K. Tiwari^{1*}, Amit Patki¹, Jeffrey Lieberman², T. Scott Stroup², David B. Allison^{1,3,4}, Rudolph L. Leibel⁵ and Wendy K. Chung⁵

¹ Section on Statistical Genetics, Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL, USA

² Department of Psychiatry, Columbia University Medical Center, New York State Psychiatric Institute, New York, NY, USA

³ Department of Nutrition Sciences, University of Alabama at Birmingham, Birmingham, AL, USA

⁴ Nutrition Obesity Research Center, University of Alabama at Birmingham, Birmingham, AL, USA

⁵ Department of Pediatrics, Division of Molecular Genetics and the Naomi Berrie Diabetes Center of Columbia University Medical Center, Columbia University, New York, NY, USA

Edited by:

Colin Palmer, University of Dundee, UK

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*Correspondence:

Hemant K. Tiwari, Section on Statistical Genetics, Department of Biostatistics, University of Alabama at Birmingham, Ryals Public Health Building, Suite 327, Birmingham, AL 35294, USA.
e-mail: htiwari@uab.edu

Antipsychotic drugs are widely used in treating schizophrenia, bipolar disorder, and other psychiatric disorders. Many of these drugs, despite their therapeutic advantages, substantially increase body weight. We assessed the association of alleles of 31 genes implicated in body weight regulation with weight gain among patients being treated with specific antipsychotic medications in the clinical antipsychotic trials in intervention effectiveness study, we found that rs2237988 in Potassium Channel Inwardly Rectifying Subfamily J Member 11 (*KCNJ11*), rs13269119 in Solute carrier family 30 member 8 (*SLC30A8*), and rs9922047 in fat mass and obesity associated (*FTO*) were associated with percent weight gain. We also observed the significant interaction of rs11643744 by treatment effect on the weight gain.

Keywords: antipsychotic drugs, weight gain, schizophrenia, CATIE Study, candidate genes, energy homeostasis, *KCNJ11* gene, *FTO* gene

INTRODUCTION

Antipsychotic drugs (APDs) are effective treatments for several common psychiatric conditions, including schizophrenia and bipolar disorder. There has been a dramatic increase in the use of APDs in recent years. Some but not all APDs are associated with weight gain and metabolic dysregulation, a concern because many individuals with psychotic disorders are already metabolically vulnerable (Allison et al., 1999; Allison and Casey, 2001; Cope et al., 2005; Brecher et al., 2007; Strassnig et al., 2007; Correll et al., 2009; Varley and McClellan, 2009). Though possessing many advantages, many APDs have a major liability by virtue of their ability to promote substantiated weight gain and metabolic dysregulation in an already metabolically vulnerable population. During the past decade there have considerable research efforts to quantify, understand, prevent, and alleviate these adverse effects. Also, the marked increase in the use of these drugs, the importance of the mental illnesses they are used to treat, their profound effects on weight and metabolic functioning, and the known harms of obesity, diabetes, and metabolic dysregulation all underscore the importance of continued research in this area.

Even among patients taking any single APD, there is great variability in the amount of weight gained while taking the drug. These inter-individual differences could be due to genetic differences in the genes encoding the molecular targets for the drug in question

and/or the genes encoding molecules affecting the pharmacokinetics of the drug (Cope et al., 2005). Although several investigators have examined genetic predictors of weight gain among persons taking APDs, few have tested for genetic mediators of weight gain response *per se*, or have examined a large number of candidate genes in large number of subjects (Need et al., 2009). In this study, therefore, we aimed to examine in the clinical antipsychotic trials in intervention effectiveness (CATIE) study by testing for genetic association of weight gain with single nucleotide polymorphisms (SNPs) in genes involved in body weight regulation.

MATERIALS AND METHODS

GENE SELECTION AND STUDY DATA

We related 31 obesity-related genes to the effects of five APDs (perphenazine, olanzapine, quetiapine, risperidone, and ziprasidone) on the weight gain in 732 participants with genotypic data (out of 774 participants receiving treatment with at least one of these drugs) of the total 1493 subjects in CATIE study. The baseline antipsychotic medication at the time of randomization and other descriptive analysis such as distribution of age, sex, race, and baseline weight is given in **Table 1**. The CATIE study was conducted between January 2001 and December 2004 at 57 clinical sites in the United States, ascertaining individuals who were 18–65 years of age, had the DSM-IV diagnosis of schizophrenia, and were able to take appropriate oral medications. Patients were randomly

Table 1 | Baseline covariates and antipsychotic drug history of patients with available genotypic data prior to randomization.

	Olanzapine (2nd generation; N = 167)	Perphenazine (1st generation; N = 138)	Quetiapine (2nd generation; N = 164)	Risperidone (2nd generation; N = 169)	Ziprasidone (2nd generation; N = 94)	Total (N = 732)
AGE – YEAR (MEAN ± SD)						
Age	40.94 ± 11.17	40.81 ± 10.61	41.38 ± 11.21	40.99 ± 11.10	40.44 ± 11.16	40.96 ± 11.03
BASELINE WEIGHT – LBS (MEAN ± SD)						
Baseline weight	195.09 ± 46.12	193.87 ± 50.24	197.62 ± 45.51	197.94 ± 51.00	192.44 ± 41.37	195.74 ± 47.30
SEX – NUMBER (%)						
Male	123 (74)	102 (74)	123 (75)	125 (74)	66 (70)	539 (74)
Female	44 (26)	36 (26)	41 (25)	44 (26)	28 (30)	193 (26)
RACE – NUMBER (%)						
White	110 (66)	88 (64)	117 (71)	112 (66)	56 (60)	483 (66)
Black	53 (32)	43 (31)	43 (26)	49 (29)	31 (33)	219 (30)
Other	4 (3)	7 (5)	4 (2)	8 (5)	7 (7)	30 (4)
BASELINE ANTIPSYCHOTIC MEDICATION – NUMBER (%)						
1st Generation	17 (10)	10 (7)	16 (10)	19 (11)	12 (13)	74 (10)
2nd Generation	78 (47)	55 (40)	77 (47)	74 (44)	38 (40)	322 (44)
1st and 2nd Generation	5 (3)	6 (4)	6 (4)	9 (5)	4 (4)	30 (4)
None	67 (40)	67 (49)	65 (40)	67 (40)	40 (43)	306 (42)

assigned to oral olanzapine, perphenazine, quetiapine, risperidone under double-blinded treatment conditions in Phase 1, and followed for up to 18 months or until treatment was discontinued for any reason. Ziprasidone was added to the study in 2002. Information on the prior antipsychotic medications names and their generation are given in **Table S1A** in Supplementary Material and number of individuals randomized to a particular antipsychotic drug at base line is given in **Table S1B** in Supplementary Material. Note that the information provided in **Tables S1A,B** in Supplementary Material is restricted to individuals included for further genetic analysis.

In addition to the primary psychiatric outcomes, patients were also monitored for metabolic effects of the drugs, including pulse, blood pressure, and body weight to evaluate the effect of antipsychotic treatments on weight gain, glucose and lipid metabolism, waist-hip ratio (WHR), and body mass index (BMI; Stroup et al., 2003 and Lieberman et al., 2005).

We investigated total weight gain in *lbs* within the duration of the study, weight gain per month of treatment, and weight gain > 7% in 732 individuals. The results are shown in the **Table 2A** (without any covariate adjustment) and **Table 2B** with covariates such as age, age squared, sex, race, baseline weight (only included for weight gain outcome variable), and treatment (olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine). Our results given in **Table 2A** were similar to the results given in **Table 3** of original study by Lieberman et al. (2005). Note that Lieberman et al. (2005) did not adjust for covariates in their analysis of weight measures.

Genome-wide association analysis (GWAS) of the CATIE data was conducted by Perlegen Sciences by using the Affymetrix 500 K gene chip on 774 cases. Only 732 individuals had both clinical and genetic data available. The 1084 SNPs spanning the 31 selected candidate genes were used to perform the *post hoc* association analysis for effects of gene-by-drug interactions on weight gain during

the course of treatment. Genes related to body weight regulation were selected, in part, because of their roles in the neural systems affected by psychotropic agents and included (Chung and Leibel, 2008; Lindgren and McCarthy, 2008; van Vliet-Ostapchouk et al., 2009; Walley et al., 2009). These included the dopamine receptors *DRD2* and *DRD4*; Serotonin Transporter (*SLC6A4*), 5-Hydroxytryptamine Receptors (*HTR1A*, *HTR2A*, *HTR2C*, *HTR1F*, and *HTR6*); adrenergic receptors (*ADRA1A*, *ADRA2A*, *ADRB3*); Histamine receptors 1 and 2 (*HRH1*, *HRH2*); Cholinergic receptor, muscarinic 3 (*CHRM3*); synaptosomal associated protein *SNAP25*; genes associated with obesity including Leptin (*LEP*), Leptin receptor (*LEPR*), and fat mass and obesity associated (*FTO*); and genes associated with type 2 diabetes including peroxisome proliferator activated receptor gamma (*PPARG*); Transcription Factor 7 Like 2 (*TCF7L2*), Potassium Channel Inwardly Rectifying Subfamily J Member 11 (*KCNJ11*), hematopoietically expressed homeobox (*HHEX*), Insulin like Growth Factor Binding Protein 2 (*IGF2BP2*), CDK5 Regulator Subunit-Associated Protein 1-Like (*CDKAL1*), Solute carrier family 30 member 8 (*SLC30A8*), Cyclin Dependent Kinase Inhibitors 2A and 2B (*CDKN2A* and *CDKN2B*), and Insulin degrading enzyme (*IDE*). We included intragenic SNPs and SNPs within or 50 kb 5' or 3' of these candidate genes. The list of all genes included in the study and number of SNPs within and flanking the genes are provided in **Table S2** in Supplementary Material.

Body weight was measured at baseline and then repeatedly at the post-randomization visits. The timing of the visits varied by patient; hence, we did not have gain-in-weight measurements for all individuals at specific intervals following the start of treatment. With antipsychotics, the majority of weight gain (but by no means all) generally occurs by 120 days (Wetterling, 2001; Gentile, 2006; Gebhardt et al., 2009). This observation, coupled with the fact that we had considerable data around that time point, led to our choice of 120 days in the model. Hence, we predicted

Table 2A | Weight measures without adjusting for covariates.

	Olanzapine	Quetiapine	Risperidone	Perphenazine	Ziprasidone
Total weight gain (SE)	9.90 (1.31)	2.01 (1.32)	1.08 (1.53)	-1.57 (1.55)	-2.05 (1.80)
Weight gain/month (SE)	1.82 (0.33)	0.73 (0.35)	0.47 (0.26)	0.02 (0.26)	-0.55 (0.54)
Percent weight gain (SE)	4.64 (0.62)	0.68 (0.67)	0.30 (0.72)	-0.69 (0.79)	-1.97 (0.79)
Weight gain > 7% – no./total no. (%)	45/167 (27)	23/164 (14)	25/169 (15)	16/138 (12)	6/94 (6)

Table 2B | Weight measures after adjusting for covariates.

	Olanzapine	Quetiapine	Risperidone	Perphenazine	Ziprasidone
Total weight gain (SE)	9.76 (1.27)	2.24 (1.30)	1.07 (1.52)	-1.41 (1.55)	-2.43 (1.78)
Weight gain/month (SE)	1.70 (0.32)	0.96 (0.37)	0.41 (0.24)	0.05 (0.27)	-0.97 (0.52)
Percent weight gain (SE)	5.56 (0.69)	1.61 (0.73)	1.12 (0.68)	0.23 (0.79)	-1.51 (0.86)
Weight gain > 7% – no./total no. (%)	49/167 (29)	29/164 (18)	28/169 (17)	19/138 (14)	7/94 (7)

Table 3A | Weight measures without adjusting for covariates (Model 1: weight gain was estimated using combined data for all treatments).

	Olanzapine	Quetiapine	Risperidone	Perphenazine	Ziprasidone
Weight gain at 120th day (SE)	5.05 (0.60)	2.55 (0.60)	2.81 (0.52)	1.05 (0.68)	0.84 (0.80)
Percent weight gain at 120th day (SE)	2.75 (0.31)	1.46 (0.30)	1.58 (0.27)	0.77 (0.34)	0.47 (0.41)
Weight gain > 7% — no./total no. (%)	22/167 (13)	13/164 (8)	11/169 (7)	11/138 (8)	3/94 (3)

Table 3B | Weight measures after adjusting for covariates (Model 1: weight gain was estimated using combined data for all treatments).

	Olanzapine	Quetiapine	Risperidone	Perphenazine	Ziprasidone
Weight gain at 120th day (SE)	4.98 (0.58)	2.60 (0.59)	2.82 (0.51)	1.07 (0.68)	0.80 (0.79)
Percent weight gain at 120th day (SE)	2.73 (0.31)	1.48 (0.30)	1.58 (0.27)	0.79 (0.34)	0.46 (0.40)
Weight gain > 7% – no./total no. (%)	22/167 (13)	13/164 (8)	8/169 (5)	11/138 (8)	3/94 (3)

weight gain for each subject at the 120th day with a mixed model using weights measured at given time points as outcome, and both drug treatment duration and the square-root of drug treatment duration after randomization as predictors. We derived the prediction equation for weight gain at the 120th day by two ways, namely, Model 1 predicted weight gain estimated using combined data with all treatments as a non-linear function of time points only as described above; and Model 2 predicted weight gain estimated separately for each treatment as a non-linear function of time points and randomized treatment (i.e., we derived the five prediction equations for weight gain for each treatment by stratified sample with respect to treatments olanzapine, quetiapine, risperidone, perphenazine, and ziprasidone). Model 1 results are depicted in **Tables 3A,B** with and without covariate adjustments, respectively. Similarly, we estimated weight gain, percent weight gain, and weight gain > 7% at 120th day, using model 2 and the results are depicted in **Tables 4A,B** without adjustment of covariates and with adjustment of covariates, respectively. Note that model 1 weight gain predictions were underestimating compared to other studies (Allison et al., 1999; Wirshing et al., 1999; Sicard et al., 2010; Cuerda et al., 2011; and Citrome et al.,

2011), specifically for olanzapine-induced weight gain in schizophrenic patients. However, model 2 weight gain predictions were consistent with other studies. Both outcome variables, namely, weight gain and percent weight gain were checked for normality, and observations beyond four SD were considered to be outliers and were omitted from further analysis in the generalized linear model (GLM). However, we observed that both the analyses including outliers and the analyses excluding outliers gave similar results.

We tested Hardy–Weinberg equilibrium (HWE) at each locus by using the chi-square with 1 degree of freedom (*df*) test (Weir, 1996). SNPs on the X chromosome were tested for HWE test by using data from females only. We also computed linkage disequilibrium (LD) among markers in the same gene by using r^2 values. We tested the effect of each of 1084 SNPs on weight gain and percent weight gain at the 120th day by using a GLM framework.

We modeled age, age squared, sex, race, baseline weight (only included for weight gain outcome variable), and treatment (olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine) as covariates in the linear model in addition to additive

Table 4A | Weight measures without adjusting for covariates (Model 2: weight gain was estimated separately for each treatment).

	Olanzapine	Quetiapine	Risperidone	Perphenazine	Ziprasidone
Weight gain at 120th day (SE)	6.96 (0.61)	2.43 (0.59)	2.83 (0.50)	−0.10 (0.68)	−1.05 (0.80)
Percent weight gain at 120th day (SE)	3.71 (0.32)	1.38 (0.30)	1.59 (0.26)	0.39 (0.37)	−0.57 (0.41)
Weight gain > 7% – no./total no. (%)	30/167 (18)	13/164 (8)	11/169 (7)	9/138 (7)	3/94 (3)

Table 4B | Weight measures after adjusting for covariates (Model 2: weight gain was estimated separately for each treatment).

	Olanzapine	Quetiapine	Risperidone	Perphenazine	Ziprasidone
Weight gain at 120th day (SE)	6.83 (0.59)	2.47 (0.58)	2.85 (0.49)	−0.05 (0.68)	−1.02 (0.78)
Percent weight gain at 120th day (SE)	3.66 (0.31)	1.40 (0.30)	1.59 (0.26)	0.40 (0.36)	−0.55 (0.40)
Weight gain > 7% – no./total no. (%)	32/167 (19)	11/164 (7)	8/169 (5)	8/138 (6)	3/94 (3)

and dominance effects of the SNP. However, almost all of the individuals were off the prior drugs within 3 months after randomization. To control for extraneous variance due to antipsychotic drug history before randomization, and continual use of drugs (a cross-titration period) in addition to treatment drugs after randomization, we created a variable called “highest generation drug.” The highest generation drug was defined as the maximum of first and/or second generation drugs used before randomization to treatment drugs. We included two interaction terms in the linear model to control for extraneous variance due to prior drug use and are described as follows. The first interaction term in the linear model included highest generation drug used before randomization by its duration (i.e., how long the individual was on the highest generation drug before randomization). In cases in which the participant was taking multiple drugs of the same generation, we chose the drug with the longest duration of administration. Similarly, to control for extraneous variance due to some participants’ continual use of prior drugs in addition to randomized treatment drug in the titration period, we included the second interaction term in the model involving highest generation drug among prior drugs by its duration. Similar models were used for quantile regression (Redden et al., 2004) by using data at the 10th and 90th quantiles of the respective variables. Note that using these covariates will control for extraneous variance and will have very little effect on our association testing of primary outcome and SNPs. Multiple test correction for association testing was performed using a method proposed by Gao et al. (2008) for correlated SNPs within genes.

RESULTS

Five treatment drugs were randomly assigned to the patients in the study: olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine. After adjustment for covariates, treatment drug had a significant effect on percent weight gain (p -values < 0.0001). In a pair-wise comparison of each treatment drug, ziprasidone was used as a reference because it has been found to produce the lowest weight gain compared with the other drugs in this study (Allison et al., 1999; Brecher et al., 2007; Strassnig et al., 2007). Olanzapine had a significant effect on both weight gain and percent weight gain after Scheffe correction for multiple

pair-wise comparisons (p -values < 0.0001). Means and SEs are in **Tables 2–4**. **Tables 5A,B** contain the significant p -values for main effects of SNPs and also SNP x Treatment interaction effects in genes *FTO*, *KCNJ11*, *CDKL1*, and *SLC30A*, using a GLM and a quantile regression method corresponding to phenotypes estimated using combined treatment groups (Model 1) and separately within each treatment group (Model 2), respectively. We included only *FTO*, *KCNJ11*, *CDKL1*, and *SLC30A* in **Tables 5A,B** because the five SNPs (rs11643744 in *FTO* (model 1 p -value = 0.024 and model 2 p -value = 0.02), rs9922047 in *FTO* (model 1 p -value = 0.002 and model 2 p -value = 0.05), and rs2237988 in *KCNJ11* (model 1 p -value = 0.013), rs4712595 in *CDKL1* (model 2 p -value = 0.03 and marginally significant (p = 0.051) for model 1, and rs13269119 in *SLC30A8* (model 2 p -value = 0.04)) in these genes were found to be significant after a multiple tests correction. HWE test results and association results for all 1084 SNPs are provided in **Tables S3A,B** in Supplementary Material for weight gain when weight gain was estimated using all treatment groups together (model 1) and in **Tables S4A,B** in Supplementary Material for percent weight gain when weight gain was estimated separately within each treatment group (model 2). In the SNP association analysis using quantile regression at the 10th percentile, SNP rs2237988 5' of *KCNJ11* in an intron of *ABCC8* (which encodes the Sulfonylurea Receptor) showed a significant association with percent weight gain even after multiple tests correction for multiple testing (Multiple tests corrected p -value 0.013, **Table 5A** for model 1). However, the significant association was not observed with percent weight gain when similar analysis was performed using estimated percent weight gain separately within each treatment group (p = 3.78×10^{-4} and multiple tests corrected p -value 0.30 in **Table 5B**). We further analyzed rs2237988 with adjustments for diabetes status since *KCNJ11* and *ABCC8* have been causally implicated in diabetes mellitus (Florez et al., 2003). Results are shown in **Tables 6A,B** for model 1 (phenotype estimated using combined treatment groups) and model 2 (phenotype estimated using separately within each treatment group), respectively. We found that rs2237988 showed significant associations with percent weight gain when these parameters were adjusted for serum glucose concentration [p = 2.6×10^{-6} (multiple test corrected p -value = 0.003) in **Table 6A**] using model 1.

Table 5A | The p-values corresponding to the association results for significant markers with p-values corrected for multiple testing in parenthesis, using prediction model 1 (i.e., weight gain and percent weight gain at 120th day estimated with combined treatment groups).

Phenotype	Gene	SNP	Generalized linear model			Quantile regression (90th quantile)			Quantile regression (10th quantile)		
			p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	
Weight gain	FTO	rs11643744	0.57 (1.00)	0.08 (1.00)	0.58 (1.00)	0.99 (1.00)	0.48 (1.00)	3.0 × 10⁻⁵ (0.024)			
	FTO	rs9922047	0.17 (1.00)	0.77 (1.00)	0.96 (1.00)	0.48 (1.00)	0.004 (1.00)	0.27 (1.00)			
	KCNJ11	rs2237988	0.007 (1.00)	0.75 (1.00)	0.72 (1.00)	1.0 (1.00)	0.003 (1.00)	0.82 (1.00)			
	CDKAL1	rs4712595	0.06 (1.00)	0.36 (1.00)	0.53 (1.00)	0.29 (1.00)	3.1 × 10 ⁻⁴ (0.25)	0.81 (1.00)			
	SLC30A8	rs13269119	4.3 × 10 ⁻⁴ (0.34)	0.07 (1.00)	0.21 (1.00)	0.63 (1.00)	3.3 × 10 ⁻⁴ (0.26)	0.89 (1.00)			
Percent weight gain	FTO	rs11643744	0.78 (1.00)	0.19 (1.00)	0.65 (1.00)	0.63 (1.00)	0.36 (1.00)	0.003 (1.00)			
	FTO	rs9922047	0.15 (1.00)	0.30 (1.00)	0.58 (1.00)	0.27 (1.00)	2.2 × 10⁻⁶ (0.002)	0.49 (1.00)			
	KCNJ11	rs2237988	0.010 (1.00)	0.76 (1.00)	0.70 (1.00)	0.79 (1.00)	1.68 × 10⁻⁵ (0.013)	0.92 (1.00)			
	CDKAL1	rs4712595	0.04 (1.00)	0.41 (1.00)	0.20 (1.00)	0.88 (1.00)	6.43 × 10 ⁻⁵ (0.051)	0.56 (1.00)			
	SLC30A8	rs13269119	1.1 × 10 ⁻³ (0.87)	0.16 (1.00)	0.26 (1.00)	0.38 (1.00)	8.6 × 10 ⁻⁵ (0.068)	0.90 (1.00)			

The p-values in bold are significant after multiple test correction at the significance level of 0.05.

Table 5B | The p-values corresponding to the association results for significant markers with p-values corrected for multiple testing in parenthesis, using prediction model 2 (i.e., weight gain and percent weight gain at 120th day estimated separately within each treatment group).

Phenotype	Gene	SNP	Generalized linear model			Quantile regression (90th quantile)			Quantile regression (10th quantile)		
			p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	
Weight gain	FTO	rs11643744	0.51 (1.00)	0.06 (1.00)	0.41 (1.00)	0.50 (1.00)	0.61 (1.00)	2.49 × 10⁻⁵ (0.02)			
	FTO	rs9922047	0.33 (1.00)	0.96 (1.00)	0.85 (1.00)	0.38 (1.00)	0.05 (1.00)	0.33 (1.00)			
	KCNJ11	rs2237988	0.02 (1.00)	0.75 (1.00)	0.77 (1.00)	0.64 (1.00)	0.01 (1.00)	0.77 (1.00)			
	CDKAL1	rs4712595	0.07 (1.00)	0.68 (1.00)	0.15 (1.00)	0.44 (1.00)	0.01 (1.00)	0.98 (1.00)			
	SLC30A8	rs13269119	6.90 × 10 ⁻⁴ (1.00)	0.14 (1.00)	0.19 (1.00)	0.60 (1.00)	4.91 × 10 ⁻³ (1.00)	0.88 (1.00)			
Percent weight gain	FTO	rs11643744	0.97 (1.00)	0.42 (1.00)	0.63 (1.00)	0.79 (1.00)	0.22 (1.00)	7.31 × 10 ⁻³ (1.00)			
	FTO	rs9922047	0.21 (1.00)	0.62 (1.00)	0.66 (1.00)	0.40 (1.00)	5.93 × 10⁻⁵ (0.05)	0.71 (1.00)			
	KCNJ11	rs2237988	0.04 (1.00)	0.89 (1.00)	0.99 (1.00)	0.29 (1.00)	3.78 × 10 ⁻⁴ (0.30)	0.95 (1.00)			
	CDKAL1	rs4712595	0.04 (1.00)	0.75 (1.00)	0.29 (1.00)	0.78 (1.00)	3.70 × 10⁻⁵ (0.03)	0.63 (1.00)			
	SLC30A8	rs13269119	4.52 × 10 ⁻³ (1.00)	0.38 (1.00)	0.28 (1.00)	0.81 (1.00)	5.29 × 10⁻⁵ (0.04)	0.89 (1.00)			

The p-values in bold are significant after multiple test correction at the significance level of 0.05.

Table 6A | The p-values corresponding to the association results for rs2237988 marker in KCNJ11 after adjusting for diabetes status/glucose level with p-values corrected for multiple testing in parenthesis.

Phenotype	Adjusting for	Generalized linear model			Quantile regression (90th quantile)			Quantile regression (10th quantile)		
		p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	
Percent weight gain	Diabetes	0.028 (1.00)	0.78 (1.00)	0.93 (1.00)	0.40 (1.00)	4.3 × 10 ⁻⁴ (0.47)	0.95 (1.00)			
	Glucose	0.025 (1.00)	0.78 (1.00)	0.88 (1.00)	0.55 (1.00)	2.6 × 10⁻⁶ (0.003)	0.81 (1.00)			
Weight gain	Diabetes	0.020 (1.00)	0.75 (1.00)	0.75 (1.00)	0.56 (1.00)	0.004 (1.00)	0.69 (1.00)			
	Glucose	0.021 (1.00)	0.70 (1.00)	0.72 (1.00)	0.60 (1.00)	2.6 × 10 ⁻⁴ (0.28)	0.68 (1.00)			

The p-values in bold are significant after multiple test correction at the significance level of 0.05.

The analyses were performed for both weight gain and percent weight gain at 120th day estimated with combined treatment groups.

Table 6B | The p-values corresponding to the association results for rs2237988 marker on KCNJ11 after adjusting for diabetes status/glucose level with p-values corrected for multiple testing in parenthesis.

Phenotype	Adjusting for	Generalized linear model			Quantile regression (90th quantile)			Quantile regression (10th quantile)		
		p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	
Percent weight gain	Diabetes	0.03 (1.00)	0.78 (1.00)	0.92 (1.00)	0.31 (1.00)	1.19 × 10 ⁻³ (0.94)	0.95 (1.00)			
	Glucose	0.03 (1.00)	0.78 (1.00)	0.84 (1.00)	0.54 (1.00)	4.67 × 10⁻⁵ (0.04)	0.84 (1.00)			
Weight gain	Diabetes	0.02 (1.00)	0.75 (1.00)	0.78 (1.00)	0.51 (1.00)	7.95 × 10 ⁻⁴ (0.63)	0.70 (1.00)			
	Glucose	0.02 (1.00)	0.70 (1.00)	0.65 (1.00)	0.65 (1.00)	4.78 × 10 ⁻³ (1.00)	0.67 (1.00)			

The p-values in bold are significant after multiple test correction at the significance level of 0.05.

The analyses were performed for both weight gain and percent weight gain at 120th day estimated separately within each treatment group.

Also, percent weight gain association with rs2237988 was significant after adjusting for serum glucose concentration in model 2 ($p = 4.67 \times 10^{-5}$ and multiple tests corrected p -value 0.04 in **Table 6B**). The SNPs rs4712595 of *CDKL1* and rs13269119 of *SLC30A8* showed significant associations with percent weight gain even after stringent multiple tests correction for multiple testing in the analysis of 10th percentile, when percent weight was analyzed using estimated percent weight gain separately within each treatment group (multiple tests corrected p -value 0.03 and 0.04, respectively, see **Table 5B**). Since both genes *CDKL1* and *SLC30A8* have been implicated in diabetes mellitus, we further analyzed rs4712595 and rs13269119 adjusting for diabetes status (see Results in **Tables 6C,D**). Only association between rs13269119 of *SLC30A8* and percent weight gain remain significant after adjusting of glucose ($p = 5.08 \times 10^{-5}$, and $p = 0.04$ with multiple tests correction).

The SNP rs9922047 in *FTO* (a non-coding SNP in intron 1) was significantly associated with percent weight gain in the quantile regression at the 10th percentile using model 1 (multiple tests corrected p -value = 0.002) and also in model 2 (multiple tests corrected p -value = 0.05). An interaction between rs11643744 (another non-coding SNP in intron 1) in the *FTO* and treatment drug for weight gain was found to be significant after multiple tests correction in both models 1 (multiple tests corrected p -value = 0.024) and 2 (multiple tests corrected p -value = 0.02).

The adjusted mean values and SEs of weight gain for each genotype at rs2237988 (*KCNJ11*), rs4712595 (*CDKAL1*), rs13269119 (*SLC30A8*), rs9922047 (*FTO*) are shown in **Tables 7A–D**, respectively. The adjusted mean values and SEs from the quantile regression model for the treatment drug-by-genotype interaction effect at rs11643744 in *FTO* gene are shown in **Table 8**. We also investigated whether significant associations of *KCNJ11*, *CDKAL1*, *SLC30A8*, *FTO* SNPs with drug-related weight gain might be due to antecedent predisposition to adiposity, as reflected in baseline body weight. The association p -values of SNPs with baseline weight and BMI in all candidate genes are given in **Tables S5A,B** in Supplementary Material. There was no significant association detected for any candidate gene – including *KCNJ11*, *CDKAL1*, *SLC30A8*, *FTO* – with the baseline weight or BMI.

DISCUSSION

We performed genetic analysis on predicted induced weight gain and percent weight gain at the 120th day in schizophrenic patients from CATIE study. The analyses were performed on outcome variable estimated using two ways, namely, predicted weight gain estimated using combined data with all treatments (model 1); and predicted weight gain estimated separately for each treatment (model 2). We found a significant association of rs2237988 in the *KCNJ11* gene with percent weight gain estimated using combined data with all treatments. *KCNJ11* encodes an ATP-sensitive potassium channel, Kir6.2, – that interacts with the SUR1 (*ABCC8*) subunit to determine insulin release (Inagaki et al., 1995). Both *ABCC8* and *KCNJ11* have been causally implicated in rare forms of diabetes, and ATP-sensitive potassium channels mediate some aspects of hypothalamic function related to food intake (Spanswick et al., 1997). In several studies type 2 diabetes

prevalence among persons with schizophrenia has been found to be higher than in the general population (Lean and Pajonk, 2003; Gough and O'Donovan, 2005; Holt and Peveler, 2006; Allison et al., 2009). Also, the risk of diabetes in schizophrenia is increased by use of atypical APDs (Lean and Pajonk, 2003). The Consensus Statement, issued in 2004, indicated that drug-induced insulin resistance may occur because of weight gain or change in body fat distribution, or by direct effects on insulin-sensitivity target tissues (American Diabetes Association et al., 2004). We therefore further analyzed the genotypic data in *KCNJ11* for association with percent weight gain with adjustment for baseline diabetes status (presence or absence), and serum glucose concentration at the 120th day after randomization. The serum glucose concentration was estimated for each subject at the 120th day with a mixed model by using the serum glucose concentration measured at given time points as the outcome. The association of rs2237988 in *KCNJ11* with percent weight gain remained significant after multiple tests correction and with adjustment for the serum glucose concentration ($p = 0.003$). However, the significant association between rs2237988 and percent weight gain was not significant when using estimated percent weight gain separately within each treatment group. We also observed significant associations of rs4712595 of *CDKL1* gene and rs13269119 of *SLC30A8* with percent weight gain estimated at 120th day separately within each treatment. Both *CDKL1* gene and *SLC30A8* have been implicated for Type 2 diabetes. Thus, we further analyzed the genotypic data with percent weight gain with adjustment for baseline diabetes status (presence or absence), and serum glucose concentration at the 120th day after randomization. The association of rs13269119 in *SLC30A8* with percent weight gain remained significant after multiple tests correction and with adjustment for the serum glucose concentration ($p = 0.04$). We found that rs4712595 of *CDKAL1* association disappeared after correction for diabetes status; implying weight gain may be mediated by type 2 diabetes in the presence of rs4712595 in Schizophrenic patients. Genetic intervals containing *SLC30A8* (8q24.11) and *CDKL1* (6p22.3) have both been repeatedly implicated in type 2 diabetes (T2D) by association analyses (Lyssenko et al., 2008; McCarthy, 2010). *SLC30A8* (solute carrier family 30 (zinc transporter), member 8) mediates zinc transport, specifically in beta cells. The gene is co-expressed in insulin-producing cells (Chimienti et al., 2004) where zinc participates in the processing of proinsulin to insulin and the release of insulin in response to glucose (Kirchhoff et al., 2008). *CDKL1* (cdk5 regulatory subunit-associated protein 1-like 1) is associated with T2D and low birthweight, the latter possibly contributing to the risk of diabetes. In individuals in whom T2D is associated with allelic variation in *CDKL1*, T2D is not contingent upon obesity, as it is for many other diabetes-associated genes. The molecular physiology of this protein is not well understood, but it may play a role in proinsulin processing and/or mitochondrial oxidative metabolism related to beta cell release of insulin in response to glucose (Steinthorsdottir et al., 2007; Kirchhoff et al., 2008; Ohara-Imaizumi et al., 2010). Atypical antipsychotic medications may adversely affect beta cell function directly (Ader et al., 2005) – rendering allelic variation in genes such as *SLC30A8* and *CDKL1* possible mediators of individual susceptibility to T2D as a consequence of exposure to these drugs. Increased circulating

Table 6C | The p-values corresponding to the association results for rs4712595 marker on CDKAL1 after adjusting for diabetes status/glucose level with p-values corrected for multiple testing in parenthesis.

Phenotype	Adjusting for	Generalized linear model			Quantile regression (90th quantile)			Quantile regression (10th quantile)		
		p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect
Percent weight gain	Diabetes	0.04 (1.00)	0.62 (1.00)	0.23 (1.00)	0.74 (1.00)	2.81 × 10 ⁻³ (1.00)	0.43 (1.00)			
	Glucose	0.04 (1.00)	0.59 (1.00)	0.15 (1.00)	0.78 (1.00)	0.01 (1.00)	0.33 (1.00)			
Weight gain	Diabetes	0.07 (1.00)	0.70 (1.00)	0.22 (1.00)	0.31 (1.00)	5.62 × 10 ⁻³ (1.00)	0.94 (1.00)			
	Glucose	0.07 (1.00)	0.70 (1.00)	0.07 (1.00)	0.43 (1.00)	1.31 × 10 ⁻³ (1.00)	0.97 (1.00)			

The analyses were performed for both weight gain and percent weight gain at 120th day estimated separately within each treatment group.

Table 6D | The p-values corresponding to the association results for rs13269119 marker on SLC30A8 after adjusting for diabetes status/glucose level with p-values corrected for multiple testing in parenthesis.

Phenotype	Adjusting for	Generalized linear model			Quantile regression (90th quantile)			Quantile regression (10th quantile)		
		p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect	p-Value for main effect of SNP	p-Value of SNP x treatment interaction effect
Percent weight gain	Diabetes	1.96 × 10 ⁻³ (1.00)	0.30 (1.00)	0.38 (1.00)	0.78 (1.00)	5.75 × 10 ⁻⁴ (0.46)	0.91 (1.00)			
	Glucose	1.98 × 10 ⁻³ (1.00)	0.28 (1.00)	0.33 (1.00)	0.77 (1.00)	5.08 × 10⁻⁵ (0.04)	0.95 (1.00)			
Weight gain	Diabetes	6.79 × 10 ⁻⁴ (0.54)	0.14 (1.00)	0.33 (1.00)	0.67 (1.00)	8.78 × 10 ⁻⁴ (0.70)	0.80 (1.00)			
	Glucose	6.54 × 10 ⁻⁴ (0.52)	0.16 (1.00)	0.38 (1.00)	0.74 (1.00)	2.30 × 10 ⁻⁴ (0.18)	0.78 (1.00)			

The p-values in bold are significant after multiple test correction at the significance level of 0.05.

The analyses were performed for both weight gain and percent weight gain at 120th day estimated separately within each treatment group.

insulin, or alterations of the timing and magnitude of endogenous release, may cause of increased body weight by effects on food intake (Mäkimattila et al., 1999), and might account for the association with weight gain detected here.

Fat mass and obesity associated has been associated with adiposity in several large genome-wide association studies (Dina et al., 2007; Frayling et al., 2007; Scuteri et al., 2007). The *FTO* SNP, rs9939609, which was previously associated with obesity, was not

associated with weight gain in our study. Recently, Perez-Iglesias et al. (2010) investigated the association of *FTO* rs9939609 with weight gain in the context of treatment with haloperidol, Olanzapine, risperidone, ziprasidone, aripiprazole, or quetiapine. After 1 year of treatment with APDs, there was no significant effect on weight gain of the 3 genotypes defined by the rs9939609 variant. However, the two SNPs associated with weight gain in CATIE, rs9922047, and rs11643744 are within 10 kb, and 20 kb respectively, of rs9939609 and are in LD with rs9939609. Note that LD varies among populations and estimation of LD depends on the sample size. Therefore, it is possible that Perez-Iglesias et al. (2010) did not observed any association with rs9939609 due to difference between genetic make-up of the studies (Spanish sample in Perez-Iglesias and European American sample in our study) and small sample size ($n = 143$ in Perez-Iglesias and $n = 732$ in our study). *FTO* encodes a putative non-heme dioxygenase, but it is unclear how genetic variation at the *FTO* locus leads to increased adiposity (Han et al., 2010). The association may be conveyed – in part – by effects related to a nearby gene, *RPGRPIL*, that is a component of the ciliary basal body, an organelle implicated in the obesity of individuals with Bardet–Biedl syndrome (Stratigopoulos et al., 2008, 2011).

The genes implicated in this analysis play a role in energy homeostasis, presumably by hypothalamic mechanisms. These genes have also been implicated in aspects of glucose/insulin homeostasis. We endeavored to control for the latter because we were focused more on body weight effects, and the subjects were not fully phenotyped regarding diabetes. However, some antipsychotics have been implicated having direct adverse consequences for beta cell function (Best et al., 2005). The genes that we identified here may mediate effects on both body weight and diabetes susceptibility.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/pharmacogenetics_and_pharmacogenomics/10.3389/fgene.2011.00056/abstract

Table 7A | Adjusted mean percent weight gain corresponding to genotypes at rs2237988 (*KCNJ11*), using model 2.

Genotype	Mean	SE	N
C/C	1.479	0.189	490
C/T	1.801	0.291	205
T/T	3.017	0.405	36

Table 7B | Adjusted mean percent weight gain corresponding to genotypes at rs4712595 (*CDKAL1*), using model 2.

Genotype	Mean	SE	N
C/C	1.66	0.28	201
C/T	1.80	0.24	328
T/T	1.26	0.28	194

Table 7C | Adjusted mean percent weight gain corresponding to genotypes at rs13269119 (*SLC30A8*), using model 2.

Genotype	Mean	SE	N
C/C	1.40	0.17	586
C/G	2.48	0.37	130
G/G	4.09	1.33	15

Table 7D | Adjusted mean percent weight gain corresponding to genotypes at rs9922047 (*FTO*), using model 2.

Genotype	Mean	SE	N
C/C	1.56	0.34	133
C/G	1.81	0.21	357
G/G	1.45	0.29	237

Table 8 | Adjusted mean weight gain in lbs for treatment and genotypes at rs11643744 (*FTO* gene) in the interaction analyses.

Treatment drug	A/A			A/G			G/G		
	Mean	SE	N	Mean	SE	N	Mean	SE	N
Olanzapine	4.44	0.77	94	-0.53	1.01	56	2.00	1.63	17
Perphenazine*	2.20	0.84	86	2.70	0.87	43	2.86	3.26	9
Quetiapine	4.14	0.94	80	1.48	0.83	74	4.57	1.56	10
Risperidone	2.71	0.84	85	3.16	0.83	63	1.24	1.52	20
Ziprasidone	3.11	1.17	52	2.31	1.41	35	3.23	1.58	6

*Except Perphenazine, which is first generation antipsychotic drug, all treatment drugs in table are second generation antipsychotic drug.

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