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Authors

Zhang, Jian-Ping
Lencz, Todd
Zhang, Ryan X
et al.

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Pharmacogenetic Associations of Antipsychotic Drug-Related Weight Gain: A Systematic Review and Meta-analysis

Jian-Ping Zhang*[,1–3], Todd Lencz[1–3], Ryan X. Zhang[4], Masahiro Nitta[5], Lawrence Maayan[6], Majnu John[1,3,7], Delbert G. Robinson[1–3], W. Wolfgang Fleischhacker[8], Rene S. Kahn[9], Roel A. Ophoff[10], John M. Kane[1–3,11], Anil K. Malhotra[1–3,12], and Christoph U. Correll[1–3,11,12]

[1]Division of Psychiatry Research, The Zucker Hillside Hospital, Northwell Health System, Glen Oaks, NY; [2]Department of Psychiatry, Hofstra Northwell School of Medicine, Hempstead, NY; [3]Center for Psychiatric Neuroscience, The Feinstein Institute for Medical Research, Manhasset, NY; [4]Department of Psychology and Neuroscience, Duke University, Durham, NY; [5]Drug Development Division, Sumitomo Dainippon Pharma Co. Ltd, Tokyo, Japan; [6]Department of Psychiatry, New York University School of Medicine, New York, NY; [7]Department of Mathematics, Hofstra University, Hempstead, NY; [8]Department of Psychiatry and Psychotherapy, Medical University Innsbruck, Innsbruck, Austria; [9]Department of Psychiatry, University Medical Centre Utrecht, Utrecht, The Netherlands; [10]Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA; [11]Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY

[12]Both authors contributed equally to the article.

*To whom correspondence should be addressed; Division of Psychiatry Research, The Zucker Hillside Hospital, Northwell Health System, 75-59 263rd Street, Glen Oaks, NY 11020, US; tel: 718-470-8471, fax: 718-470-1905, e-mail: JZhang1@nshs.edu

Although weight gain is a serious but variable adverse effect of antipsychotics that has genetic underpinnings, a comprehensive meta-analysis of pharmacogenetics of antipsychotic-related weight gain is missing. In this review, random effects meta-analyses were conducted for dominant and recessive models on associations of specific single nucleotide polymorphisms (SNP) with prospectively assessed antipsychotic-related weight or body mass index (BMI) changes (primary outcome), or categorical increases in weight or BMI (≥7%; secondary outcome). Published studies, identified via systematic database search (last search: December 31, 2014), plus 3 additional cohorts, including 222 antipsychotic-naïve youth, and 81 and 141 first-episode schizophrenia adults, each with patient-level data at 3 or 4 months treatment, were meta-analyzed. Altogether, 72 articles reporting on 46 non-duplicated samples (*n* = 6700, mean follow-up = 25.1 wk) with 38 SNPs from 20 genes/genomic regions were meta-analyzed (for each meta-analysis, studies = 2–20, *n* = 81–2082). Eleven SNPs from 8 genes were significantly associated with weight or BMI change, and 4 SNPs from 2 genes were significantly associated with categorical weight or BMI increase. Combined, 13 SNPs from 9 genes (Adrenoceptor Alpha-2A [*ADRA2A*], Adrenoceptor Beta 3 [*ADRB3*], Brain-Derived Neurotrophic Factor [*BDNF*], Dopamine Receptor D2 [*DRD2*], Guanine Nucleotide Binding Protein [*GNB3*], 5-Hydroxytryptamine (Serotonin) Receptor 2C [*HTR2C*], Insulin-induced gene 2 [*INSIG2*], Melanocortin-4 Receptor [*MC4R*], and Synaptosomal-associated protein, 25kDa [*SNAP25*]) were significantly associated with antipsychotic-related weight gain (*P*-values < .05–.001). SNPs in *ADRA2A*, *DRD2*, *HTR2C*, and *MC4R* had the largest effect sizes (Hedges' *g*'s = 0.30–0.80, ORs = 1.47–1.96). Less prior antipsychotic exposure (pediatric or first episode patients) and short follow-up (1–2 mo) were associated with larger effect sizes. Individual antipsychotics did not significantly moderate effect sizes. In conclusion, antipsychotic-related weight gain is polygenic and associated with specific genetic variants, especially in genes coding for antipsychotic pharmacodynamic targets.

Key words: pharmacogenetics/SNP/antipsychotics/weight gain/BMI/meta-analysis

Introduction

Antipsychotics are first-line therapy for schizophrenia-spectrum disorders,[1] and frequently used as monotherapy or combined with mood stabilizers or antidepressants for bipolar disorder[2] and major depression,[3,4] respectively. Despite their efficacy, body weight gain and associated metabolic syndrome are prominent side effects, which increase morbidity and mortality in psychiatric patients.[5–7] Many antipsychotics can cause significant weight gain, especially some second-generation antipsychotics (SGAs), like clozapine, olanzapine, and quetiapine.[5,8] No

consistent clinical predictors of antipsychotic-induced weight gain have been identified, and the pathophysiology of weight gain remains poorly understood.[9] Food intake, energy utilization, metabolism, and body weight are regulated by complex interactions among multiple neurotransmitter systems in multiple brain regions, which are pharmacodynamic targets of antipsychotics to some extent.[5,10] Genetic factors may play an important role because genome-wide association studies found multiple genes associated with obesity in the general population,[11] and functions of proteins that are pharmacodynamic antipsychotic targets may be affected by genetic variants.[12,13]

Since the late 1990s, pharmacogenetic research has attempted to elucidate genetic underpinnings of antipsychotic-related weight gain. The present study aimed to conduct a comprehensive meta-analysis of the associations of genetic variants with antipsychotic-related weight gain. One key methodological issue in the pharmacogenetics of antipsychotic drug response is that most studies used chronic patient samples.[14] Therefore, the present meta-analysis also included data from 3 cohorts of patients with first episode psychosis or minimal prior drug exposure that were largely unpublished, in addition to published studies.

Methods

Literature Search

Two investigators (J-P.Z., R.X.Z., M.N. and/or L.M.) independently conducted an electronic PubMed/Web of Science search (last: December 31, 2014) for pharmacogenetic studies of antipsychotic-related weight change. Combinations of the following key words were used: antipsychotic(s), neuroleptic(s), genetic(s), genomic(s), gene, single nucleotide polymorphism (SNP), polymorphism, weight gain, body mass index (BMI), obesity, and metabolic. We also screened reference lists from identified papers and reviews for additional studies. Inclusion criteria were: (1) humans with mental illness; (2) longitudinal data on body weight or BMI change, or percentage of patients gaining significant weight or BMI within each genotype group after a specified period of antipsychotic treatment; and (3) sufficient data to compute an effect size (ES). Exclusion criteria were: (1) animal or healthy subject studies; (2) cross-sectional studies or longitudinal studies that did not report pre- and post-treatment change in weight or BMI; (3) studies of metabolic syndrome not reporting separate weight or BMI data; (4) studies of SNPs not examined in other studies ("orphan" SNPs); and (5) studies reporting data overlapping with previously published papers (data from the largest report were included). If a SNP was studied in ≥2 independent samples, data from the 3 additional cohorts were added whenever possible so that each SNP was meta-analyzed with ≥5 samples. One study examined candidate genes in association with antipsychotic-related weight gain[15] using data from the CATIE trial (Clinical Antipsychotic Trials of Intervention Effectiveness), but it was excluded from the meta-analysis due to its use of different weight gain phenotype. Weight gain was defined in the study as the maximum percent weight change at any time point during the first 18 months of treatment, which was different from all other studies where weight gain was defined as weight change between 2 time points, eg, from baseline to a follow-up time point.

Data Extraction and Outcome Variables

Data were independently extracted by 2 authors (J-P.Z., M.N. and/or L.M.); disagreements were resolved by consensus. For missing information, first and/or last authors were contacted requesting additional/unpublished data.

Primary outcome was change in weight or BMI from baseline until after a specified period of antipsychotic treatment. Whenever ≥1 assessment time points were reported, we picked the one closest to 2–3 months (preferring 3 mo) to increase homogeneity. Change in kg or kg/m^2 were preferred but pooled with percent change in weight or BMI if only these were reported. Secondary outcome was the percentage of patients within each genotype group gaining significant weight or BMI during antipsychotic treatment. Most studies used ≥7% body weight gain, but some used ≥5% or ≥10%, which were also pooled.

Additional Cohorts

Three additional cohorts that had published data for at least 1 SNP but for which we obtained patient-level data were also included in the meta-analysis.

1. In the Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY sample) study, 222 pediatric patients (age = 13.8 ± 3.6 y; male = 57%) with ≤7 days of antipsychotic lifetime history initiated clinicians' choice antipsychotics (aripiprazole, olanzapine, quetiapine or risperidone) for the first time and were followed for 3 months.[16]
2. In the Zucker Hillside Hospital First Episode Schizophrenia Clinical Trial (ZHH-FE sample), 81 first-episode schizophrenia patients (age = 23.0 ± 4.9 y; male = 75%) were randomized to risperidone or olanzapine and followed for 4 months.[17,18]
3. In the European First Episode Schizophrenia Trial (EUFEST sample), 141 first-episode schizophrenia patients (age = 25.6 ± 5.2 y; male = 60%) were randomized to amisulpride, haloperidol, olanzapine, quetiapine or ziprasidone and had weight change data at 3 months follow-up.[19]

All 3 cohorts were genotyped on approximately 1 million SNPs using the Illumina Omni-1Quad platform, followed by standard quality control procedures (details published previously[20]). For SNPs included in the meta-analysis, but not genotyped, the SNAP online tool from the Broad Institute was accessed to find proxy SNPs using either

the 1000 Genomes Pilot 1 or HapMap 3 CEU population panel, with parameters set as $r^2 \geq .80$ and distance ≤100kb.

Statistical Analysis

Outcomes were analyzed separately for each SNP using Comprehensive Meta-Analysis software version 2 (Biostat) whenever ≥2 studies contributed data (otherwise data went into the "orphan" SNP category). For continuous and categorical outcomes, Hedges' *g* and OR, ±95% CIs, were calculated as the ES measure. For each SNP with sufficient data, both dominant and recessive genetic models were meta-analyzed in association with weight or BMI changes. For selected SNPs in which results from dominant and recessive models on the primary outcome were suggestive of additive effects of the risk allele, a formal test of additive genetic model was conducted. For each study, a linear regression of BMI change on the number of risk alleles (0, 1, 2) was simulated based on summary statistics (mean, SD, *n*) from each genotype group in R statistical package, and the regression coefficient was converted to Hedges' *g* with corresponding SE (supplementary methods). Pooled ESs were computed with a random effects model to accommodate heterogeneity across included studies.[21] In each meta-analysis, a cohort was included only once. Statistical significance of the pooled ES was set at alpha = .05 without multiple testing correction because each SNP was chosen based on previous research, following a hypothesis-driven approach.

Study heterogeneity was assessed using Q and I^2 statistics, with $I^2 < 25\%$ representing low, ~50% moderate, and >75% representing high heterogeneity.[21] Whenever heterogeneity was present, moderator and meta-regression analyses were conducted to explore moderator effects. Sensitivity analyses were conducted to assess potential influences of any one single study on the pooled ES. Within each meta-analysis, included studies were removed one at a time to check for significant alterations of the pooled ES and associated *P*-values. Publication bias was assessed with the funnel plot, Egger's regression test,[22] and the "Trim and Fill" method.[23]

Based on the Venice guideline of systematically assessing cumulative evidence on genetic association,[24] each SNP was assigned a category based on 3 criteria: (1) amount of evidence (A: large-scale evidence, total sample size $n > 1000$; B: moderate amount of evidence, $n = 500$–1000; C: little evidence, $n < 500$); (2) replication (A: statistically significant overall ES with no/minimal between-study heterogeneity, $I^2 < 25\%$; B: statistically significant overall ES with moderate to large between-study heterogeneity, $I^2 \geq 25\%$; C: insignificant overall ES); and (3) evidence of bias (A: statistically significant overall ES without evidence of bias based on "Trim and Fill" method and Egger's test; B: evidence of bias without significance level change after adjustment, or insignificant overall ES without evidence of bias; C: evidence of bias). To generate an overall index of the strength of evidence, categories of A, B, and C were assigned a score of 3, 2, and 1, respectively, and a total score across the 3 categories was calculated. A total score = 8–9 was considered strong evidence supporting the genotype-phenotype association, a score = 6–7 was considered moderate evidence, and a score ≤5 was considered minimal evidence.

To explore polygenic effects of SNPs, a polygenic risk score was computed in the SATIETY and EUFEST cohorts using an additive genetic model combining top SNPs that were significantly associated with weight gain from the meta-analysis. We also assessed the percent variance explained by the risk score.

Results

Literature Search

The literature search produced 586 unduplicated hits, of which 72 reports (see table 1 for details) met inclusion criteria, entering into the meta-analysis (supplementary figure 1). Sample sizes varied from 32 to 481 and most studies included chronic patients (21 studies included first-episode or antipsychotic-naïve patients). Altogether, the 72 reports referred to 46 independent samples, as several published studies reported on different genes or SNPs from the same cohort. After eliminating redundancy, the total sample size from the 46 samples was 6615. Including the 3 additional cohorts ($n = 444$; 289 of which were already published), the total independent sample size in 46 samples was 6770. Most studies were short-term, ranging from 4 weeks to 4 months, but 16 studies (22%) had follow-up at ≥1 year (mean follow-up= 25.1 ± 42.0 wk, range = 1 mo to 7 y). Most patients were either Caucasian or Asian, including 30 studies (41.7%) with all Asian patients. The most common antipsychotics were olanzapine (52.8%), risperidone (41.7%), and clozapine (40.3%). Thirty-five studies involved monotherapy with a single antipsychotic, including clozapine (studies = 15), olanzapine (studies = 15), risperidone (studies = 4), and iloperidone (studies = 1). Most studies included schizophrenia patients (94.4% of studies), but some also included patients with various psychiatric diagnoses (table 1).

Included Genes and SNPs

Altogether, 38 SNPs from 20 genes/genomic regions on 15 chromosomes were reported in ≥2 independent cohorts, entering into subsequent meta-analyses. Table 2 lists the included SNPs, genes or genomic regions, and other relevant information, as well as proxy SNPs used in the 3 additional cohorts as necessary. The major alleles, minor alleles, and minor allele frequency were based on the 1000 Genome CEU population. Three included SNPs (rs1799732, rs1801028, and rs1051312) did not have proxy SNPs in the 3 additional cohorts, therefore, only

Table 1. Demographic, Illness Treatment and Outcome Information of All 72 Included Studies

Study (First Author, Year)	Genes (SNPs) Included in Meta-Analysis	*n*	Length (wk)	Age	% Male	% Caucasian	Diagnoses	%FE, Drug-Naïve	APs	Outcome Variables
Basile 2001[71]	*HTR2C* (rs6318), *ADRB3* (rs4994), *TNF* (rs1800629), *HTR2A* (rs6313, rs6314)	80	6	33.1 ± 8.4	65	72	SCZ	NR	CLZ	Weight change
Basile 2002[72]	*HTR2C* (rs3813929)	80	6	NR	65	72	SCZ	NR	CLZ	Weight change
Bishop 2006[73]	*GNB3* (rs5443)	42	6	36.0 ± 8.7	81	NR	SCZ	50%	OLZ	% Weight change
Brandl 2012[74]	*LEP* (rs7799039) *LEPR* (rs1137101)	181	6 to 14	35.9 ± 10.9	65	70	SCZ, SZA	NR	Various APs	% Weight change
Calarge 2009[75]	*LEP* (rs7799039)	74	2 y	11.7 ± 2.9	91	84	Various diagnoses	NR	RIS	BMI change
Chowdhury 2012[76]	*MC4R* (rs17782313)	224	6 to 14	35.6 ± 10.5	67	70	SCZ, SZA	NR	Various APs	% Weight change
Czerwensky 2013[77]	*MC4R* (rs17782313)	173	4	39.3 ± 14.7	37	NR	Various diagnoses	28%	Various APs	BMI change Weight change
Czerwensky 2013[78]	*MC4R* (rs489693)	169	4	39.3 ± 14.7	37	NR	Various diagnoses	28%	Various APs	BMI change Weight change
Ellingrod 2005[79]	*HTR2C* (rs3813929)	42	6	NR	81	100	SCZ	NR	OLZ	>10% Weight gain
Ellingrod 2007[80]	*LEP* (rs7799039) *LEPR* (rs1137101)	37	6	37.0 ± 8.4	81	NR	SCZ	NR	OLZ	BMI change
Fernandez 2010[81]	*LEP* (rs7799039) *LEPR* (rs1137101)	56	14	39.1 ± 9.0	79	NR	SCZ	NR	CLZ	Weight change, BMI change
Godlewska 2009[36]	*HTR2C* (rs3813929, rs518147)	107	6	29.3 ± 10.0	50	100	SCZ	34	OLZ	% BMI change, ≥10% BMI gain
Herken 2009[82]	*PPARG* (rs1801282)	95	6	34.4 ± 13.0	52	100	SCZ	NR	OLZ	Weight change BMI change
Hoekstra 2010[83]	*HTR2C* (rs3813929)	32	8	8.7 ± 2.8	88	NR	PDD	NR	RIS	Weight change BMI change
Hong 2001[84]	*HTR2A* (rs6313) *HTR2C* (rs6318) *HTR6* (T267C)	93	17	37.1 ± 8.2	65	0 (100% Asian)	SCZ	0	CLZ	Weight change
Hong 2010[85]	*ANKK1* (rs1800497) *DRD2* (rs1799978, rs7131056, rs6275, rs2242591)	479	4 y	47.2 ± 13.2	61	0 (100% Asian)	SCZ	NR	CLZ, OLZ, RIS	≥7% weight gain
Houston 2012[86]	*ANKK1* (rs1800497) *DRD2* (rs1079598, rs1801028, rs2242591) *HTR2C* (rs3813929, rs518147, rs6318)	205	8	NR	NR	100	Various diagnoses	NR	OLZ	Weight change
Huang 2011[87]	TNF (rs1800629)	500	5 y	43.9 ± 9.1	60	0 (100% Asian)	SCZ	NR	CLZ, OLZ, RIS	% Weight change >7% Weight gain
Kang 2008[88]	*LEP* (rs7799039)	74	>3 mo	47.2 ± 11.6	68	0 (100% Asian)	SCZ	NR	OLZ	Weight change, ≥7% weight gain

Table 1. *Continued*

Study (First Author, Year)	Genes (SNPs) Included in Meta-Analysis	*n*	Length (wk)	Age	% Male	% Caucasian	Diagnoses	%FE, Drug-Naïve	APs	Outcome Variables
Kuzman 2008[89]	*HTR2C* (rs3813929) *MDR1* (rs2032582, rs1045642)	108	4 mo	30.6 ± 11.5	0	100	SCZ	64	OLZ, RIS	≥7% Weight gain
Kuzman 2011[90]	*HTR2C* (rs3813929) *MDR1* (rs2032582, rs1045642)	101	3 mo	33.5 ± 10.6	0	100	SCZ, SZA, delusional disorder	100	OLZ, RIS	BMI change
Laika 2010[91]	*HTR2C* (rs3813929)	56	4	41.6 ± 15.9	50	100	Various diagnoses	NR	OLZ	Weight change, BMI change
Lane 2006[92]	*HTR2A* (rs6313, rs6314) *HTR2C* (rs3813929) *HTR6* (rs1805054) *DRD2* (rs1799732, rs1801028) *ANKK1* (rs1800497) BDNF (rs6265)	123	6	34.0 ± 9.7	55	0 (100% Asian)	SCZ	NR	RIS	Weight change >7% weight gain
Le Hellard 2009[93]	*INSIG2* (rs10490624, rs17047764, rs17587100, rs7566605)	160	3 mo	21.9 ± 8.9	61	100	SCZ spectrum disorders	0	Various APs	BMI change
Lencz 2010[94]	*DRD2* (rs1799732)	58	16	23.5 ± 4.9	76	28	SCZ, SZA, SZP	100	RIS, OLZ	Weight change
Lin 2006[95]	*MDR1* (rs1045642)	41	6 wk	35.7 ± 8.8	80	90	SCZ	NR	OLZ	Weight change
Malhotra 2012[20]	*MC4R* (rs489693)	139	12	13.4 ± 3.8	58	55.4	Various diagnoses	100	RIS, APZ, QTP	BMI change Weight change
		73	6	33.5 ± 8.3	62	70	SCZ	0	CLZ	BMI change Weight change
		40	6	35.2 ± 11.	55	100	SCZ, SZA	0	RIS, APZ, QTP	BMI change Weight change
		92	12	26.0 ± 5.2	58	100	SCZ, SZA, SZP	100	Various APs	BMI change Weight change
Miller 2005[96]	*HTR2C* (rs3813929)	41	6 mo	35.6 ± 9.7	63	85	SCZ	0	CLZ	Weight change % BMI change >7% BMI gain
Monteleone 2010[97]	*CNR1* (rs1049353)	83	26.1	44 ± 10.5	60	100	Various diagnoses	NR	Various APs	≥7% weight gain
Mou 2008[98]	*LEP* (rs7799039)	84	10	24 ± 6.0	65	0 (100% Asian)	SCZ	100	RIS, CPZ	≥7% weight gain
Mueller 2005[99]	*SNAP25* (rs1051312, rs3746544, rs8636)	59	14	40.1 ± 9.5	78	25	SCZ, SZA	0	Various Aps	Weight change BMI change
Mueller 2012[100]	*ANKK1* (rs1800497) *DRD2* (rs1799732, rs1799978, rs1079598, rs6275, rs7131056)	206	6 or 14	35.7 ± 10.4	68	72> >62	SCZ, SZA	0	Various APs	% Weight change >7% Weight gain
Musil 2008[101]	*SNAP25* (rs1051312, rs3746544, rs8636)	162	5	34.2 ± 12.3	57	100	SCZ, SZA	NR	Various APs	BMI change
Opgen-Rhein 2010[102]	*HTR2C* (rs3813929, rs6318) *INSIG2* (rs17587100, rs10490624, rs17047764, 7566605) *LEP* (rs7799039)	128	6	38.6 ± 12.0	63	100	SCZ, SZA	17	Various AP	>7% Weight gain

Table 1. *Continued*

Study (First Author, Year)	Genes (SNPs) Included in Meta-Analysis	*n*	Length (wk)	Age	% Male	% Caucasian	Diagnoses	%FE, Drug-Naïve	APs	Outcome Variables
Park 2006[103]	*ADRA2A* (rs1800544)	62	Over 1 y	46.5 ± 11.1	71	0 (100% Asian)	SCZ	NR	OLZ	Weight change % Weight change >10% Weight gain
Park 2008[104]	*HTR2C* (rs3813929)	79	Over 1 y	46.1 ± 12.1	67	0 (100% Asian)	SCZ	NR	OLZ	Weight change BMI change >7% Weight gain
Park 2009[105]	*GNB3* (rs5443)	79	Over 1 y	46.6 ± 11.6	67	0 (100% Asian)	SCZ	NR	OLZ	Weight change % Weight change BMI change >10% Weight gain
Park 2011[106]	*CNR1* (rs1049353, rs806368)	78	Over 1 y	46.4 ± 11.6	67	0 (100% Asian)	SCZ	NR	OLZ	>7% Weight gain
Perez-Iglesias 2010[107]	*LEP* (rs7799039) *LEPR* (rs1137101) *FTO* (rs9939609)	194	1 y	28.4 ± 8.3	58	94	SCZ spectrum disorders	100	Various APs	Weight change BMI change
Popp 2009[108]	*HTR2C* (rs6318)	102	4	37.5 ± 13.7	45	100	SCZ, SZA	NR	Various APs	BMI change
Reynolds 2002[68]	*HTR2C* (rs3813929)	123	6 and 10	26.6 ± 7.7	52	0 (100% Asian)	SCZ	100	Various APs	BMI change >7% Weight gain
Reynolds 2003[109]	*HTR2C* (rs3813929)	32	6	NR	66	0 (100% Asian)	SCZ	100	CLZ	BMI change
Reynolds 2012[110]	*FTO* (rs9939609)	93	1 y	25.5 ± 6.7	74	100	Psychosis	100	Various APs	Weight change BMI change
Ryu 2006[111]	*LEP* (rs7799039)	71	4	30.5 ± 7.6	45	0 (100% Asian)	SCZ	NR	Various APs	BMI change
Ryu 2007[112]	*HTR2C* (rs3813929)	84	4	30.1 ± 7.5	46	0 (100% Asian)	SCZ	69	Various APs	BMI change >7% BMI change
Shao 2008[113]	*HTR2C* (rs3813929, rs518147)	170	1 y	23.1 ± 5.1	35	0 (100% Asian)	SCZ	100	NR	>7% Weight gain
Shing 2014[114]	*FTO* (rs9939609)	218	6–14 wk	NR	66	69	SCZ or SZA	0	Various APs	% Weight change
Sicard 2010[115]	*HTR2C* (rs518147, rs3813929, rs6318)	205	Average 10 wk	35.9 ± 10.1	69	68	SCZ or SZA	0	Various APs	% Weight change >7% Weight gain
Sickert 2009[116]	*ADRA2A* (rs1800544)	129	10	36.5 ± 9.0	74	50	SCZ or SZA	0	Various Aps	Weight change
Song 2014[117]	*FTO* (rs9939609)	237	6 mo	27.5 ± 7.6	54	0 (100% Asian)	SCZ	100	RIS	Weight change BMI change
Souza 2008[118]	*GNB3* (rs5443)	208	6 wk, 14 wk	35.9 ± 10.3	68	68	SCZ or SZA	0	Various APs	Weight change

Table 1. *Continued*

Study (First Author, Year)	Genes (SNPs) Included in Meta-Analysis	*n*	Length (wk)	Age	% Male	% Caucasian	Diagnoses	%FE, Drug-Naïve	APs	Outcome Variables
Srisawat 2014[119]	*MTHFR* (rs1801131, rs1801133)	182	8 wk	26.2 ± 7.4	46	0 (100% Asian)	SCZ	100	Various Aps	BMI change
		72	3 mo	25.4 ± 6.8	74	100	SCZ	100	Various APs	BMI change
Steaker 2012[120]	*PPARG* (rs1801282)	138	4 wk	Range[17–88]	46	NR	Various diagnoses	NR	OLZ	Weight change BMI change
Templeman 2005[121]	*HTR2C* (rs3813929) *LEP* (rs7799039)	73	6 wk, 3 mo	25.2 ± 0.8	75	100	Psychosis	100	Various APs	BMI change >7% BMI change
Theisen 2004[122]	*HTR2C* (rs3813929)	97	12	22.1 ± 7.7	59	100	SCZ spectrum disorders	0	CLZ	BMI change >7% BMI change
Thompson 2010[123]	*HTR2C* (rs3813929)	216	4	NR	NR	NR	SCZ	NR	Iloperidone	Weight change
Tiwari 2010[124]	*INSIG2* (rs17587100, rs7566605, rs10490624, rs17047764)	154	Average 10 wk	35.8 ± 9.8	71	58	SCZ, SZA	0	CLZ, OLZ, RIS, HAL	% Weight change
Tiwari 2010[125]	*CNR1* (rs1049353, rs806368)	183	Average 10 wk	36.1 ± 10.2	68	64	SCZ, SZA	0	Various APs	% Weight change
Tsai 2002[126]	*HTR2C* (rs3813929)	80	4 mo	36.7 ± 8.4	65	0 (100% Asian)	SCZ SZA	0	CLZ	BMI change >7% BMI change
Tsai 2003[127]	TNF (rs1800629)	99	4 mo	36.0 ± 8.0	66	0 (100% Asian)	SCZ	0	CLZ	Weight change
Tsai 2004[128]	*GNB3* (rs5443) *ADRB3* (rs4994)	87	4 mo	37.0 ± 8.2	64	0 (100% Asian)	SCZ or SZA	0	CLZ	Weight change % Weight change
Tsai 2011[129]	BDNF (rs6265)	481	>2 y	43.9 ± 8.9	60	0 (100% Asian)	SCZ	0	CLZ, OLZ, RIS	% Weight change
Ujike 2008[130]	*HTR2C* (rs3813929, rs6318) *HTR2A* (rs6213) *ADRB3* (rs4994) *GNB3* (rs5443)	164	4 mo	51.8 ± 10.9	62	0 (100% Asian)	SCZ	0	OLZ	% BMI change
Van Winkel 2010[131]	*MTHFR* (rs1801131, rs1801133)	104	3 mo	31.3 ± 11.7	68	NR	SCZ or SZA	NR	Various APs	Weight change
Wang 2005[132]	*ADRA2A* (rs1800544)	93	1 y	38.4 ± 8.1	53	0 (100% Asian)	SCZ	0	CLZ	Weight change >7% Weight gain
Wang 2005[133]	*GNB3* (rs5443)	134	1 y	38.5 ± 8.0	60	0 (100% Asian)	SCZ	0	CLZ	Weight change % Weight change
Wang 2010[134]	TNF (rs1800629)	55	8 y	37.2 ± 7.7	49	0 (100 Asian)	SCZ	0	CLZ	Weight change BMI change
Zai 2012[135]	BDNF (rs6265)	257	6 wk	31.8 ± 7.9	76	100	SCZ SZA	0	Various APs	Weight Δ >7% Weight gain
Zhang 2003[136]	*ANKK1* (rs1800497)	117	10 wk	26.0 ± 8.0	50	0 (100% Asian)	SCZ	100%	Various APs	BMI change Weight change >7% Weight gain

Table 1. *Continued*

Study (First Author, Year)	Genes (SNPs) Included in Meta-Analysis	*n*	Length (wk)	Age	% Male	% Caucasian	Diagnoses	%FE, Drug-Naïve	APs	Outcome Variables
Zhang 2003[137]	*LEP* (rs7799039)	128	10 wk	26.0 ± 7.0	48	0 (100% Asian)	SCZ	100%	RIS, CPZ	BMI change Weight change >7% Weight gain
Zhang 2007[138]	*LEP* (rs7799039)	102	Average 7 y	47.2 ± 6.3	66	0 (100% Asian)	SCZ	0	CLZ	BMI change
Zhang 2008[139]	BDNF (rs6265)	196	At least 2 y	NR	66	0 (100% Asian)	SCZ	100%	Various APs	BMI change

Notes: AMI, amisulpride; AP, antipsychotic; APZ, aripiprazole; BMI, body mass index; CLZ, clozapine; CPZ, chlorpromazine; FE, first episode; FLU, fluphenazine; HAL, haloperidol; OLZ, olanzapine; QTP, quetiapine; RIS, risperidone; SCZ, schizophrenia; SNP, single nucleotide polymorphism; SULP, sulpiride; SZA, schizoaffective disorder; SZP, schizophreniform disorder; ZIP, ziprasidone; *LEP*, Leptin; *LEPR*, Leptin receptor; *ADRA2A*: Adrenoceptor alpha 2A; *ADRB3*: Adrenoceptor beta 3; *ANKK1*: Ankyrin repeat and kinase domain containing 1; BDNF, Brain-derived neurotrophic factor; *CNR1*, Cannabinoid receptor 1; *DRD2*, Dopamine receptor D2; *FTO*, Fat mass and obesity associated; *GNB3*, Guanine nucleotide binding protein (G protein), beta polypeptide 3; HTR2A, 5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled; *HTR2C*, 5-hydroxytryptamine (serotonin) receptor 2C, G protein-coupled; HTR6, 5-hydroxytryptamine (serotonin) receptor 6, G protein-coupled; *INSIG2*, Insulin-induced gene 2; *MC4R*, Melanocortin 4 receptor; *MDR1* (*ABCB1*), ATP-binding cassette, sub-family B (MDR/TAP), member 1; *MTHFR*, Methylenetetrahydrofolate reductase; *PPARG*, Peroxisome proliferator-activated receptor gamma; *SNAP25*, Synaptosomal-associated protein, 25kDa; TNF, Tumor necrosis factor.

published studies were meta-analyzed for these 3 SNPs. The 5-Hydroxytryptamine (Serotonin) Receptor 2C (*HTR2C*) polymorphism, rs3813929 (−759C/T) was the most studied SNP (published studies = 22). Seven SNPs from Dopamine Receptor D2 (*DRD2*) were included in the meta-analysis, the most in a single gene.

Overview of the Meta-analytic Results

Altogether, 11 SNPs from 8 genes were significantly associated with weight or BMI change, and 4 SNPs from 2 genes were significantly associated with study-defined significant weight gain (table 3). Combined together, 13 SNPs from 9 genes (Adrenoceptor Alpha-2A [*ADRA2A*], Adrenoceptor Beta 3 [*ADRB3*], Brain-Derived Neurotrophic Factor [*BDNF*], *DRD2*, Guanine Nucleotide Binding Protein [*GNB3*], *HTR2C*, Insulin-induced gene 2 [*INSIG2*], Melanocortin-4 Receptor [*MC4R*], and Synaptosomal-associated protein, 25kDa [*SNAP25*]) were significantly associated with antipsychotic-related weight gain (*P*-values: ≤.05–.001). SNPs in *ADRA2A*, *DRD2*, *HTR2C*, and *MC4R* had the largest ES (Hedges' *g*s = 0.30–0.80, ORs = 1.47–1.96). Forest plots for the significant results are included in supplementary figures 1–5. Heterogeneity across studies was not large for most significant SNPs, except for rs489693 (AA vs C carriers, I^2 = 80%), rs1799732 (Ins/Ins vs Del carriers, I^2 = 62.6%), rs3813929 (CC vs T carriers, I^2 = 65.9%), and rs518147 (GG vs C carrier, I^2 = 57.6%). Publication biases existed for several SNPs. However, the direction of publication bias actually underestimated the ES for rs6275, rs7131056, and rs17047764 (ie, the corrected ESs became larger). In contrast, adjusting publication bias eliminated the significance for rs3813929 (secondary outcome, adjusted OR = 1.51, 95% CI = 0.91–2.49). Even after adjusting for potential publication bias, the ES was still significant for rs489693 (AA vs C, adjusted Hedges' *g* = 0.66, 95% CI = 0.09–1.23). Using the modified Venice guideline, 2 *HTR2C* SNPs, rs3813929 and rs518147, achieved a score of 8, 3 SNPs from *ADRA2A*, *DRD2* (rs1799732), and *GNB3* had a score of 7, and 4 SNPs from *DRD2* (rs6275, rs7131056), *INSIG2* (rs17047764), and *MC4R* (rs489693) obtained a score of 6.

Specific Meta-analytic Results

5-Hydroxytryptamine (Serotonin) Receptor 2C Gene. *HTR2C* was the most studied gene, and 3 SNPs were included in the meta-analysis. The most studied SNP, rs3813929, was reported in 22 studies with additional information from the SATIETY and EUFEST sample, totaling 24 studies. The ZHH FE sample did not have any T-allele carrier genotype, and was not included in the analysis. Among these studies, 20 studies reported continuous weight or BMI change data and 18 reported categorical weight gain data. Study duration ranged from 4 weeks to 1 year. The C allele was associated with significantly more weight gain than the T allele. Because

Table 2. List of Genes and SNPs Included in the Meta-analysis

rs#	# Studies	Gene	SNP	Chr	Position	Region	Major Allele	Minor Allele	MAF	Proxy SNP	R^2	D′	Major Allele	Minor Allele	MAF
rs1800544	3	*ADRA2A*	−1291C/G	10	111076745		C	G	0.48	rs521674	0.92	1	A	T	0.26
rs4994	3	*ADRB3*	Trp64Arg	8	37823798	(Missense)	T (Trp)	C (Arg)	0.10						
rs1800497	5	ANKK1	Taq1A (Glu713Lys)	11	112776038	Exon 8	G	A	0.30	rs7118900	0.90	1	G	A	0.18
rs6265	4	*BDNF*	Val66Met	11	27658369	(Missense)	G	A	0.23						
rs1049353	3	CNR1	1359G/A	6	88143916		G	A	0.14						
rs806368	2	CNR1		6	88140381	3′ UTR	T	C	0.28						
rs1799732	3	*DRD2*	−141C Ins/Del	11	113475529: 113475530	Intron	C	—	0.24	NA					
rs1079598	2	*DRD2*		11	112801484	Intron 1	T	C	0.21	rs1079594	1	1	A	C	0.13
rs1799978	2	*DRD2*		11	113475629	Intron	A	G	0.11						
rs1801028	2	*DRD2*	Ser311Cys	11	112788694	Exon 7	C	G	0.02	NA					
rs2242591	2	*DRD2*		11	112785131	Downstream	G	A	0.20	rs6278	1	1	C	A	0.13
rs6275	2	*DRD2*	C939T	11	113412755	Exon (synon)	C	T	0.47						
rs7131056	2	*DRD2*		11	113459052		C	A	0.48						
rs9939609	3	*FTO*		16	53820527	Intron	T	A	0.36	rs3751812	1	1	G	T	0.45
rs5443	6	*GNB3*	C825T	12	6954875	Exon (synon)	C	T	0.48						
rs6313	4	HTR2A	102T/C	13	46895805	Intron	C	T	0.43						
rs6314	2	HTR2A	His452Tyr	13	47409034	Exon	C	T	0.07						
rs3813929	22	*HTR2C*	−759C/T	X	113818520	Upstream, promoter	C	T	0.12						
rs6318	7	*HTR2C*	Cys23Ser	X	113871991	Exon 5	G	C	0.17						
rs518147	4	*HTR2C*	−697G/C	X	113818582	5′UTR	G	C	0.29						
rs1805054	2	HTR6	267T/C	1	19666020		C	T	0.17	rs1977101	1	1	A	G	0.13
rs10490624	3	*INSIG2*		2	118104916	Intron	A	G	0.09						
rs17047764	3	*INSIG2*		2	118868582		G	C	0.19	rs3849327	0.94	1	T	C	0.16
rs17587100	3	*INSIG2*		2	118838410		A	C	0.06	rs17526937	1	1	A	G	0.04
rs7566605	3	*INSIG2*		2	118078449		G	C	0.30						
rs7799039	12	*LEP*	−2548A/G	7	128238730		G	A	0.43	rs10487506	1	1	G	A	0.47
rs1137101	4	*LEPR*	Q223R	1	65592830	(Missense)	A	G	0.41						
rs489693	5	*MC4R*		18	60215554		C	A	0.33						
rs17782313	2	*MC4R*		18	60183864		T	C	0.22	rs476828			A	G	0.27
rs1045642	3	MDR1	3435C/T	7	87509329		T, C	A	0.40						
rs2032582	2	MDR1	2677G/T(A)	7	87531302	(Missense)	G	A	0.34						
rs1801131	3	MTHFR	1298A/C	1	11794419	(Missense)	A	C	0.23						
rs1801133	3	MTHFR	677C/T	1	11796321	(Missense)	C	T	0.33						
rs1801282	2	PPARG	Pro12Ala	3	12351626	Intron (Missense)	C	G	0.07						
rs1051312	2	*SNAP25*	DdeII(T/C)	20	10306440	3′ UTR	T	C	0.15	NA					
rs3746544	2	*SNAP25*	MnlI(T/G)	20	10306436	3′ UTR	T	G	0.29						
rs8636	2	*SNAP25*	TaiI(T/C)	20	10307094	3′ UTR	C	T	0.27						
rs1800629	4	TNF	G-308A	6	31575254		G	A	0.10						

Note: MAF, minor allele frequency.

Table 3. Meta-analytic Results of Associations Between Antipsychotic Drug-Related Weight Gain and Genotype

Gene	rs#	SNP	Genotype Comparison	BMI or Weight Change					BMI or Weight Change >7% or 10%					Category & Score
				Hedges' *g* (95% CI)	*P*	# Study (Total *n*)	I^2	"T&F"	OR (95% CI)	*P*	# Study (Total *n*)	I^2	"T&F"	
ADRA2A	rs1800544	−1291C/G	CC vs G	**−0.22 (−0.39, −0.05)**	**.01**	6 (645)	0%	0	0.50 (0.24, 1.05)	.07	5 (516)	61%	+2	B,B,A
			GG vs C	**0.30 (0.09, 0.51)**	**.01**	6 (645)	24%	0	1.74 (0.79, 3.85)	.17	5 (516)	58%	0	7
			Additive (G)	**0.20 (0.06, 0.33)**	**.004**	6 (645)	30%	0						
ADRB3	rs4994	Trp64Arg	Trp/Trp vs Arg	−0.20 (−0.48, 0.09)	.18	6 (680)	54%	+1	1.10 (0.44, 2.77)	.83	3 (358)	47%	0	B,B,C
			Arg/Arg vs Trp	**0.84 (0.20, 1.47)**	**.01**	2 (235)	0%	NA						5
ANKK1	rs1800497	Taq1A (Glu713Lys)	CC vs T	0.05 (−0.09, 0.19)	.51	7 (842)	0%	0	0.97 (0.75, 1.25)	.80	7 (1181)	0%	+3	B,C,C
			TT vs C	−0.09 (−0.44, 0.26)	.61	7 (842)	35%	+2	0.93 (0.64, 1.35)	.70	7 (1179)	0%	−3	4
			Additive (C)	0.05 (−0.09, 0.19)	.46	7 (842)	9%	−2						
BDNF	rs6265	Val66Met (G/A)	AA vs G	0.06 (−0.41, 0.53)	.81	7 (1393)	82%	+2	0.79 (0.37, 1.68)	.53	5 (609)	0%	−1	A,C,C
			GG vs A	0.13 (−0.07, 0.32)	.21	7 (1393)	61%	0	**1.49 (1.02, 2.18)**	**.04**	5 (609)	0%	0	5
CNR1	rs1049353	1359 G/A	AA vs G	−0.08 (−0.51, 0.36)	.74	4 (534)	0%	0	1.31 (0.51, 3.39)	.57	5 (522)	0%	−3	B,C,C
			GG vs A	0.04 (−0.14, 0.23)	.64	4 (534)	0%	+1	1.04 (0.69, 1.58)	.84	5 (522)	0%	+3	4
	rs806368		AA vs G						0.84 (0.53, 1.35)	.47	2 (251)	0%	NA	C,C,B
			GG vs A						0.92 (0.50, 1.71)	.80	2 (251)	0%	NA	4
DRD2	rs1799732	−141C Ins/Del	Del/Del vs Ins	0.36 (−0.07, 0.79)	.10	3 (305)	0%	0	1.94 (0.65, 5.76)	.23	2 (247)	0%	NA	C,A,A
			Ins/Ins vs Del	**−0.44 (−0.86, −0.02)**	**.04**	3 (305)	63%	0	0.63 (0.27, 1.46)	.28	2 (247)	46%	NA	7
			Additive (Del)	**0.31 (0.07, 0.54)**	**.01**	3 (305)	0%	0						
	rs1079598		CC vs T	−0.07 (−0.75, 0.61)	.85	5 (595)	55%	0	2.28 (0.74, 7.07)	.15	4 (485)	0%	−1	B,C,C
			TT vs C	0.06 (−0.13, 0.24)	.53	5 (595)	0%	+1	0.72 (0.45, 1.13)	.15	4 (485)	0%	+2	4
	rs1799978		AA vs G	−0.19 (−0.43, 0.06)	.13	4 (486)	0%	+1	0.88 (0.62, 1.26)	.49	5 (940)	7%	+3	C,C,C 3
	rs1801028	Ser311Cys	CC vs T	0.17 (−0.33, 0.66)	.50	2 (241)	0%	NA						C,C,C 3
	rs2242591		AA vs G	−0.17 (−0.91, 0.58)	.66	4 (480)	51%	+1	0.84 (0.54, 1.31)	.44	4 (814)	0%	−1	C,C,C
			GG vs A	0.10 (−0.11, 0.31)	.34	4 (480)	0%	0	1.07 (0.77, 1.48)	.71	4 (814)	0%	+1	3
			Additive (G)	0.09 (−0.13, 0.32)	.42	4 (480)	17%	0						
	rs6275	C939T	CC vs T	**−0.35 (−0.54, −0.16)**	**<.001**	4 (482)	0%	−1	0.79 (0.59, 1.07)	.13	5 (942)	0%	−1	C,A,B
			TT vs C	**0.29 (0.04, 0.53)**	**.02**	4 (482)	5%	−1	1.39 (0.86, 2.22)	.18	5 (942)	32%	0	6
			Additive (T)	**0.25 (0.09, 0.41)**	**.002**	4 (482)	0%	−1						
	rs7131056		AA vs C	0.14 (−0.14, 0.43)	.32	4 (480)	47%	−1	1.15 (0.62, 2.14)	.66	5 (939)	68%	0	C,A,B
			CC vs A	**−0.31 (−0.51, −0.12)**	**.002**	4 (480)	0%	−1	0.78 (0.52, 1.15)	.20	5 (939)	31%	0	6
			Additive (A)	**0.19 (0.03, 0.34)**	**.02**	4 (480)	0%	0						
FTO	rs9939609		AA vs T	0.03 (−0.25, 0.31)	.85	6 (790)	49%	−1	0.72 (0.18, 2.92)	.65	3 (364)	66%	−1	A,C,C
			TT vs A	−0.01 (−0.15, 0.12)	.85	7 (1027)	0%	0	1.52 (0.96, 2.42)	.08	3 (364)	0%	+2	5
GNB3	rs5443	C825T	CC vs T	−0.18 (−0.38, 0.02)	.08	10 (1004)	44%	0	0.74 (0.49, 1.13)	.16	4 (443)	0%	−2	A,B,B
			TT vs C	**0.28 (0.08, 0.48)**	**.006**	8 (865)	32%	0	1.20 (0.71, 2.03)	.49	4 (443)	2%	+2	7
			Additive (T)	**0.18 (0.04, 0.32)**	**.01**	8 (865)	30%	0						

Table 3. *Continued*

Gene	rs#	SNP	Genotype Comparison	BMI or Weight Change					BMI or Weight Change >7% or 10%					Category & Score
				Hedges' *g* (95% CI)	*P*	# Study (Total *n*)	I^2	"T&F"	OR (95% CI)	*P*	# Study (Total *n*)	I^2	"T&F"	
HTR2A	rs6313	102T/C	CC vs T	−0.12 (−0.28, 0.04)	.16	7 (814)	0%	+1	0.79 (0.48, 1.29)	.34	4 (481)	10%	+1	B,C,C 4
			TT vs C	0.11 (−0.05, 0.27)	.19	7 (814)	0%	0	1.17 (0.71, 1.92)	.54	4 (481)	6%	0	
			Additive (T)	0.08 (−0.04, 0.20)	.17	7 (814)	0%	−2						
	rs6314	His452Tyr	His/His vs Tyr	−0.05 (−0.42, 0.33)	.81	5 (563)	69%	0	0.91 (0.48, 1.71)	.76	4 (485)	41%	0	B,C,B 5
			Tyr/Tyr vs His	0.48 (−0.69, 1.64)	.42	3 (324)	68%	0	1.62 (0.23, 11.38)	.63	2 (246)	32%	NA	
HTR2C	rs3813929	−759C/T	CC vs T	**0.23 (0.04, 0.42)**	**.02**	20 (2082)	66%	0	**1.96 (1.19, 3.22)**	**.009**	18 (1738)	67%	−4	A,B,A 8
	rs6318	Cys23Ser	GG vs C	0.10 (−0.10, 0.29)	.34	9 (1111)	35%	+2	**1.47 (1.03, 2.11)**	**.04**	5 (687)	0%	−1	A,C,C 5
	rs518147	−697G/C	GG vs C	**0.18 (0.02, 0.34)**	**.03**	5 (671)	0%	0	**1.86 (1.03, 3.35)**	**.04**	5 (659)	58%	0	B,A,A 8
HTR6	rs1805054	267T/C	CC vs T	−0.03 (−0.33, 0.28)	.87	5 (576)	48%	+2	0.92 (0.47, 1.80)	.82	3 (361)	30%	0	B,C,C 4
			TT vs C	−0.11 (−0.41, 0.20)	.50	3 (338)	0%	+2	0.33 (0.04, 3.03)	.33	1 (123)	NA	NA	
INSIG2	rs10490624		TT vs C	0.07 (−0.19, 0.33)	.61	5 (666)	44%	+1	0.96 (0.54, 1.71)	.89	4 (485)	24%	+2	B,C,C 4
	rs17047764		CC vs G	**0.31 (0.00, 0.61)**	**.05**	5 (665)	23%	+2	1.55 (0.55, 4.39)	.41	3 (360)	0%	−2	B,A,C 6
			GG vs C	−0.17 (−0.36, 0.02)	.08	5 (665)	10%	0	1.20 (0.81, 1.78)	.37	4 (485)	0%	+1	
			Additive (C)	**0.19 (0.03, 0.35)**	**.02**	5 (665)	10%	0						
	rs17587100		AA vs C	0.05 (−0.22, 0.32)	.73	5 (665)	23%	0	0.65 (0.26, 1.60)	.34	4 (489)	43%	+2	B,C,B 5
	rs7566605		CC vs G	0.06 (−0.19, 0.31)	.64	5 (655)	0%	+2	0.86 (0.36, 2.05)	.74	4 (481)	34%	−1	B,C,C 4
			GG vs C	0.10 (−0.06, 0.27)	.22	5 (655)	11%	0	0.87 (0.59, 1.27)	.46	4 (481)	0%	+1	
LEP	rs7799039	−2548A/G	AA vs G	−0.08 (−0.30, 0.13)	.45	11 (1138)	51%	0	1.24 (0.50, 3.05)	.64	4 (414)	74%	+2	A,C,C 5
			GG vs A	0.16 (−0.01, 0.32)	.06	10 (967)	25%	0	0.73 (0.33, 1.60)	.43	3 (340)	5%	+2	
			Additive (G)	0.07 (−0.06, 0.19)	.27	7 (763)	0%	0						
LEPR	rs1137101	Q223R	AA vs G	0.03 (−0.14, 0.19)	.74	7 (682)	0%	+3						B,C,C 4
			GG vs A	0.09 (−0.11, 0.30)	.38	6 (653)	0%	+1						
MC4R	rs489693		AA vs C	**0.80 (0.20, 1.41)**	**.009**	6 (583)	80%	−1						B,B,B 6
			CC vs A	**−.28 (−0.53, −0.03)**	**.03**	6 (583)	52%	+1						
			Additive (A)	**0.30 (0.04, 0.57)**	**.03**	6 (583)	67%	−1						
	rs17782313		CC vs T	0.14 (−0.29, 0.56)	.53	5 (735)	49%	+1						B,B,C 5
			TT vs C	−0.25 (−0.52, 0.02)	.07	5 (735)	68%	0						
			Additive (C)	0.19 (−0.05, 0.42)	.12	5 (735)	64%	0						
MDR1	rs1045642	3435C/T	CC vs T	−0.02 (−0.22, 0.17)	.81	5 (499)	0%	0	0.87 (0.55, 1.36)	.53	4 (467)	0%	+1	C,C,C 3
			TT vs C	−0.04 (−0.26, 0.18)	.71	5 (499)	0%	+2	0.83 (0.36, 1.89)	.65	4 (467)	61%	0	
	rs2032582	2677G/T(A)	GG vs T	0.06 (−0.13, 0.25)	.54	4 (462)	0%	+1	1.01 (0.53, 1.91)	.98	4 (469)	58%	0	C,C,C 3
			TT vs G	−0.06 (−0.32, 0.20)	.68	4 (462)	0%	+1	0.79 (0.44, 1.39)	.41	4 (469)	2%	0	
MTHFR	rs1801131	1298A/C	AA vs C	0.07 (−0.08, 0.22)	.36	6 (707)	0%	0	1.36 (0.86, 2.15)	.19	3 (359)	0%	+2	B,C,C 4
			CC vs A	−0.16 (−0.57, 0.24)	.43	6 (707)	43%	−2	0.57 (0.09, 3.77)	.56	3 (359)	77%	0	
	rs1801133	677C/T	CC vs T	0.17 (−0.08, 0.41)	.19	6 (705)	58%	0	0.99 (0.49, 1.99)	.98	3 (357)	49%	+1	B,C,B 5
			TT vs C	−0.01 (−0.24, 0.22)	.92	6 (705)	0%	0	1.16 (0.50, 2.70)	.74	3 (357)	0%	−2	
PPARG	rs1801282	Pro12Ala	Pro/Pro vs Ala	0.09 (−0.15, 0.33)	.47	5 (622)	23%	0	0.79 (0.49, 1.30)	.35	4 (529)	0%	+1	B,C,B 5

Table 3. *Continued*

Gene	rs#	SNP	Genotype Comparison	BMI or Weight Change					BMI or Weight Change >7% or 10%					Category & Score
				Hedges' *g* (95% CI)	*P*	# Study (Total *n*)	I^2	"T&F"	OR (95% CI)	*P*	# Study (Total *n*)	I^2	"T&F"	
SNAP25	rs1051312	DdeII(T/C)	TT vs C	**−0.58 (−0.87, −0.29)**	**<.001**	2 (218)	0%	NA						C,A,C 5
	rs3746544	MnlI(T/G)	GG vs T	0.03 (−0.27, 0.33)	.86	4 (416)	0%	+1	1.40 (0.66, 2.99)	.38	3 (361)	9%	0	C,C,C
			TT vs G	0.09 (−0.24, 0.43)	.59	4 (416)	63%	+1	0.73 (0.46, 1.15)	.17	3 (361)	0%	0	3
	rs8636	TaiI(T/C)	CC vs T	0.19 (−0.10, 0.47)	.20	4 (418)	48%	0	0.88 (0.56, 1.38)	.57	3 (364)	0%	0	C,C,C
			TT vs C	−0.09 (−0.41, 0.23)	.58	4 (418)	0%	+2	1.40 (0.67, 2.93)	.38	3 (364)	0%	0	3
TNF-alpha	rs1800629	G-308A	AA vs G	0.21 (−0.49, 0.90)	.56	4 (796)	18%	0	0.23 (0.01, 4.53)	.34	1 (500)	NA	NA	B,C,B
			GG vs A	0.15 (−0.08, 0.37)	.20	7 (1090)	44%	0	1.10 (0.65, 1.87)	.73	4 (862)	43%	0	5

Note: "T&F": "Trim and Fill" method to assess potential publication bias. 0 = no missing study (no evidence of publication bias); negative value = # missing studies favoring the major or minor allele carriers in the comparison; positive value = # missing studies favoring the homozygotes in the comparison. Bolded results: $P \leq .05$. "Additive": additive genetic model with the risk allele in the parenthesis. "Category & Score": categories and scores of the strength of evidence based on the modified Venice guideline.[24]

the gene is located in the X chromosome, C hemizygosity in males is equivalent to the CC genotype in females. Because the T allele is relatively rare (frequency = 12%), it was not possible to meta-analyze TT vs C carriers. The pooled ES from 20 studies was small (Hedges' $g = 0.23$, $P = .017$, with significant heterogeneity; table 3; supplementary figure 1). Although meta-regression analysis showed that studies with larger sample sizes had smaller ES ($P = .003$), this finding might be confounded by the fact that larger studies tended to be in chronic patients. Therefore, a series of subgroup analyses was conducted to further dissect the heterogeneity.

When studies were divided into subgroups based on treatment duration, the short-term studies (4–8 wk) produced larger ESs, (Hedges' $g = 0.44$, $P = .004$, studies=12, $n = 1209$). Although there was no evidence of publication bias, the heterogeneity across studies was still high ($I^2 = 76.1\%$). When further classifying samples into chronic vs first-episode patients, the first-episode samples with short-term follow-up produced the largest ES (Hedge's $g = 0.67$, $P = .002$, studies = 6, $n = 589$) compared to chronic samples (Hedge's $g = 0.21$, $P = .27$, studies = 6, $n = 620$), with a significant between-group difference ($Q = 9.74$, $df = 1$, $P = .002$; supplementary figure 2). In contrast, the studies with longer-term duration (3–4 mo, and 6 mo to 1 y) did not produce significant pooled ESs, and there was no difference between first-episode and chronic samples, although the overall trend favored the CC genotype. When mixing studies with different treatment lengths, the pooled ES in first-episode studies (Hedges' $g = 0.47$, $P = .02$, studies = 8, $n = 810$) was significantly higher than in chronic samples (Hedges' $g = 0.14$, $P = .18$, studies=12, $n = 1280$), $Q = 4.75$, $df = 1$, $P = .03$). Results for the categorical outcome variable were similar, but to some extent, less significant. Moderator analyses of race, sex, and specific antipsychotic were not significant.

The above-mentioned results were similar for rs518147 (table 3), but overall ES's were smaller. Due to the small number of included studies, no meta-regression or moderator analysis was conducted. The meta-analytic findings for rs6318 were inconsistent, in that the primary outcome was not significant, but the secondary outcome was significant with evidence of publication bias (table 3).

Dopamine Receptor D2 Gene. Three of seven SNPs in *DRD2* included in the analysis showed significant associations with weight gain (table 3). For rs1799732, an additive model of the risk allele (deletion of C) was identified, ie, each additional risk allele was associated with a 0.31 SD of extra weight gain, $P = .01$. For rs6275, the T-allele was the risk allele because TT homozygotes gained more weight than C carriers (Hedges' $g = 0.29$, $P = .02$) and CC homozygotes gained less weight than T carriers (Hedges' $g = -0.35$, $P < .01$). Both heterogeneity and publication bias were minimal. Similar findings were observed for

rs7131056 (table 3). Due to the small number of studies, moderator analyses were not performed.

ADRA2A Gene and GNB3 Gene. One SNP in *ADRA2A*, rs1800544, was significantly associated with weight gain across 6 studies, with the G allele increasing the risk. Both heterogeneity and publication bias were minimal (table 3; supplementary figure 4). Similarly, 1 SNP in *GNB3*, rs5443, was associated with weight gain across 10 studies. TT homozygotes of this SNP gained significantly more weight than the C carriers (Hedges' $g = 0.26$, $P = .01$; table 3; supplementary figure 5). Heterogeneity was small, and there was no evidence of publication bias. When analyzing 5 short-term studies only (treatment durations ≤3 mo), the pooled ES became even larger (Hedges' $g = 0.39$, $P < .001$, studies = 5, $n = 486$).

MC4R Gene and INSIG2 Gene. Two SNPs near *MC4R* were included in the meta-analysis, and one of them (rs489693) was significantly associated with weight gain in 6 studies. AA homozygotes of this SNP gained more weight than the C allele carriers (Hedges' $g = 0.80$, $P = .009$; table 3; supplementary figure 3). Heterogeneity across studies was high, and there was publication bias. However, even after adjusting for potentially missing studies, the association remained significant (Hedges' $g = 0.66$, $P < .05$). The ZHH FE cohort was an extreme outlier. The pooled ES became more significant after dropping this sample (Hedges' $g = 1.05$, $P = 1.9 \times 10^{-7}$). There was no significant moderator variable. Similarly, only 1 of 4 SNPs in *INSIG2*, rs17047764, was significantly associated with weight gain ($P = .048$, table 3). After adjusting for potential publication bias, the pooled ES remained significant.

Polygenic risk scores (PRS) were computed combining 6 top SNPs from *HTR2C*, *DRD2*, *ADRA2A*, *GNB3*, *MC4R*, and *INSIG2*. Number of risk alleles in each SNP (ie, 0, 1, or 2) was multiplied by its pooled ES from the additive model (table 3), and the sum of the 6 products was the PRS. This PRS explained 5.6% of the total variance in weight gain in each of the SATIETY and EUFEST cohorts, Ps < .01 (supplementary figure 6).

ADRB3, BDNF, and SNAP25. One SNP from each of these 3 genes was significantly associated with weight gain, but either the sample size was small (studies = 2 for rs4994 in *ADRB3* and rs1051312 in *SNAP25*), or the primary outcome was not significant (rs6265 in *BDNF*; table 3).

Discussion

To our best knowledge, this is the first comprehensive meta-analytic review of pharmacogenetics of antipsychotic-related weight gain that examined quantitatively multiple genetic variants. We investigated 38 SNPs in 20 genes or genetic regions distributed in 15 chromosomes in association with antipsychotic-related weight gain in 6770 patients from 46 non-overlapping samples published in 72 reports and including patient-level data from 3 cohorts providing unpublished data on 33 SNPs that were added to the meta-analysis. We found that 13 SNPs from 9 genes (*ADRA2A*, *ADRB3*, *BDNF*, *DRD2*, *GNB3*, *HTR2C*, *INSIG2*, *MC4R*, and *SNAP25*) were significantly associated with antipsychotic-related weight gain. Among these genes, *HTR2C* was most consistently associated with antipsychotic-related weight gain, and there was moderate evidence supporting the association of *ADRA2A*, *DRD2*, *GNB3, MC4R*, and *INSIG2*, based on the modified Venice guidelines. Relationships of other genes (*ADRB3, BDNF* and *SNAP25*) with antipsychotic-related weight gain were less consistent. Finally, polygenic scores using 6 SNPs seemed to explain a small proportion of weight gain.

With the widespread use of SGAs, weight gain and related metabolic syndrome have become a significant public health issue.[25] Weight gain is especially prominent in young and antipsychotic-naïve patients.[5,16,26] Extensive effort has been made to understand the pathophysiological mechanisms of drug-related weight gain, and genetic variations seem to play a significant role.[10,13] The present study aimed at providing a comprehensive and quantitative review of the literature on pharmacogenetics of antipsychotic drug-related weight gain. Previously, meta-analyses of pharmacogenetic association of single genes with antipsychotic-related weight gain have been published, but methodological issues limited their conclusions. First, many previous meta-analyses included cross-sectional studies where obesity or 1-time assessments of weight were correlated with a genetic variant. Body weight is determined by multiple factors including genetic, behavioral and medication effects.[9] Without longitudinal assessments of weight change during antipsychotic treatment, the alleged genotype-phenotype association may be confounded by other, unmeasured variables. For example, it has been shown in multiple GWAS that *FTO* is associated with obesity in the general populations,[27] and most of these studies had 1-time measurements of obesity. However, in longitudinal studies of weight gain, *FTO* was not associated with antipsychotic-related weight gain in 7 studies (table 3). In the present meta-analysis, we included only longitudinal studies. Second, previous meta-analyses tended to pool studies of different treatment durations. ESs of a particular genetic variant on weight gain may be different at different time points. Moreover, antipsychotic-related weight gain is asymptotic and it is unclear when the weight gain begins to plateau, which also depends on the degree of prior antipsychotic-related weight gain. Mixing studies of different treatment durations may bias assessments of the true effect size. In the present review, we preferred time points closest to 2–3 months and we analyzed specific time

points whenever enough studies were available. In addition, previous meta-analyses tended to mix studies with chronic and antipsychotic-naïve or first-episode samples with minimal prior antipsychotic exposure. Studying patients with minimal drug exposure in pharmacogenetics minimizes order effects and increases the signal-to-noise ratio.[14] In the present review, we added unpublished data from 3 first-episode/drug-naïve cohorts, and separated chronic samples from first-episode/antipsychotic-naïve samples whenever possible.

Results for Pharmacodynamic Targets of Antipsychotic Drugs

HTR2C showed the most consistent association with antipsychotic-related weight gain, with multiple SNPs showing this association and in a large number of studies, including both primary (continuous variable) and secondary (categorical) outcomes. Not only is it one of the first studied genes in antipsychotic-related weight gain, it is also one of the most studied genes. The *HTR2C* gene encodes the 2C subtype of serotonin receptor (5-HT2C) and is located on the Chromosome Xq24. Experimental studies demonstrated the relevance of 5-HT2C receptors in regulating appetite and food intake,[28] and 5-HT2C agonists, such as dexfenfluramine and lorcaserin, can decrease food intake, resulting in significant weight loss.[29] 5-*HTR2C* antagonists, including many antipsychotics, may increase food intake, despite satiety, causing weight gain in animal models.[30,31] Mice deficient in 5-HT2C develop hyperphagia leading to obesity.[32,33] The most studied SNP in *HTR2C*, rs3813929, is located in the promoter region of the gene and may play a role in regulating gene expression. Several studies found that the T-allele is associated with increased transcriptional activity of the gene, compared to the C allele.[34,35] Although the C-allele is the major allele in the population, the T-allele seems to be protective against antipsychotic-related weight gain in the meta-analysis, perhaps by enhancing gene expression of *HTR2C*, which partially counterbalances the 5-HT2C antagonistic antipsychotic effect. This SNP is located in the beginning of a CpG island (83 CpG count, chromosome X:113818520-113819453, UCSC Genome Browser) in the promoter region of *HTR2C*, suggesting that DNA methylation pattern variation may play a role in the SNP effect. Another SNP, rs518147, is only 62bp away from rs3813929. These 2 SNPs may be in high linkage disequilibrium,[36] representing probably the same signal. The third SNP in the *HTR2C* gene, rs6318, is located in an exon about 150 kb from the first 2 SNPs. It is a missense SNP resulting in cysteine to serine substitution in position 23 of the protein sequence, which may disrupt a disulfide bridge affecting the receptor function.[37]

DRD2 had a robust association with antipsychotic-related weight gain. Three of seven SNPs included in the meta-analysis showed a significant relationship, although the number of studies and total sample sizes were not large. Being the main pharmacodynamic target of antipsychotics,[38] variations in *DRD2* function are plausible in explaining antipsychotic-related adverse events. At least 2 of the 3 SNPs in *DRD2*, located in Chromosome 11q23.2, rs1799732 (−141C Ins/Del) and rs6275, may be functional polymorphisms. rs1799732 represents a deletion (vs insertion) of cytosine at position −141, located in the 5′ promoter region of *DRD2*. In vitro data showed that cell lines transfected with the Del allele were less active in a luciferase reporter assay than cell lines transfected with the Ins allele.[39] In vivo data with PET imaging also suggested that this polymorphism may influence D2 receptor density in the striatum of healthy volunteers unexposed to antipsychotics.[40] A previous meta-analysis demonstrated that rs1799732 is associated with antipsychotic efficacy.[41] rs6275 (C939T) is a synonymous polymorphism and is in close proximity and high linkage disequilibrium with rs6277 (C957T). Although not resulting in an amino acid sequence change of the D2 receptor protein, the T-allele of rs6277 is associated with down-regulated D2 receptors in the striatum[42] and decreased *DRD2* mRNA stability and half-life.[43] Dopaminergic pathways are involved in the brain reward circuitry and modulate motivation, sense of well-being, and feeding behavior.[44] Many *DRD2* polymorphisms are associated with drug addiction, nicotine consumption, and eating disorders.[45] In animal studies, D2 receptor availability in the striatum was significantly lower in obese than lean rats. In human studies, the availability of the striatal dopamine transporter was negatively correlated with BMI in healthy volunteers.[46] These results led researchers to hypothesize that a hypodopaminergic reward circuitry, which may be caused by the D2 antagonism from antipsychotic treatment, results in abnormal over-eating and obesity.[44] It is possible that certain variants of *DRD2*, such as the Del allele of rs1799732 or the T-allele of rs6275 and rs6277, may already produce fewer D2 receptors, and the subsequent over-eating behavior and weight gain are exacerbated by the use of antipsychotics.

One SNP in *ADRA2A*, rs1800544, was consistently associated with antipsychotic-related weight gain. It is located in the upstream of *ADRA2A*, and may be a binding site for transcription factors (ENCODE, UCSC Genome Browser). Just like 5-HT2C and D2, the alpha-2A receptor is a pharmacodynamic target of many antipsychotics, especially SGAs, including risperidone, olanzapine, and clozapine.[47] Interestingly, the adrenergic system also innervates adipose tissue.[48] Beta-3 adrenergic receptors in the brown adipose tissue are involved in production of heat (thermogenesis or fat burning),[49] whereas alpha-receptors have an inhibitory effect on lipolysis in the adipose tissue.[50] The SNP of interest, rs1800544, was associated with body fat accumulation[51] in a large epidemiological study and affected plasma concentrations of glucose, insulin and cortisol in a human experimental

study.[52] However, it is not clear how the different alleles affect receptor density. Notably, the allele frequency is different between racial groups in that G is the minor allele in CEU (minor allele frequency [MAF] = 27.5%) but the C-allele is the minor allele in Asians (MAF = 27.5%) and Africans (23.7%). To add to the complexity, some of the included studies did not specify whether genotyping was done along the positive or negative DNA strand. In the present meta-analysis, an effort was made to align the correct allele across studies. Nevertheless, caution is warranted when interpreting these findings.

Results for Genes Implicated in Obesity in the General Population

GNB3 also seems be consistently associated with antipsychotic-related weight gain. In 10 studies (n = 1004), the TT homozygotes of rs5443 gained more weight than the C-allele carriers, with minimal heterogeneity across studies and no evidence of publication bias. Heterotrimeric G-proteins are important regulators of intracellular signaling pathways[53] and the beta-3 subunit is encoded by the *GNB3* gene. The SNP, rs5443 (C825T), is located on exon 10 of the *GNB3* gene. The T-allele is associated with alternative splicing of *GNB3* transcription, which results in enhanced signal transduction,[54] and the T-allele carries a higher risk of cardiovascular disease[55] and obesity[56] in the general population. Increased signaling by G-proteins stimulates adipogenesis and may lead to obesity.[56] This SNP seems to be associated with antidepressant efficacy,[57] but it is unclear whether antipsychotics interact with the G-protein subunit directly. It is possible that the SNP moderates the effect of antipsychotics on weight gain. Further studies are warranted to elucidate underlying mechanisms.

Another gene that has moderate evidence for its association with antipsychotic-related weight gain is *MC4R*, located in Chromosome 18q21. In several genome-wide association studies,[58–60] a genomic locus near *MC4R* was associated with obesity in the general population. *MC4R* mutations have been linked to extreme early-onset obesity,[61] and *MC4R* knockout mice develop obesity.[62] The SNP, rs489693, was approaching genome-wide significance in association with antipsychotic-related weight gain in a pediatric antipsychotic-naïve cohort, and this effect was replicated in 3 independent samples.[20] The present meta-analysis added 1 unpublished cohort and 1 published study to the 4 samples. Despite heterogeneity and potential publication bias, AA homozygotes gained significantly more weight than C carriers, with a moderate effect size. *MC4R* neurons in the hypothalamic paraventricular nucleus, activated by α-melanocyte stimulating hormone (α-MSH) produced by the pro-opiomelanocortin (POMC)-expressing neurons, can induce decreased food intake and increased energy expenditure.[63] POMC neurons are partly controlled by serontonergic signals via the 2-HT2C receptors.[64] Studies have shown that deficits in either *MC4R*,[61] POMC,[65] prohormone convertase 1/3 (one of the key enzymes that converts POMC to α-MSH, encoded by the *PCSK1* gene),[66,67] or 5-HT2C[68] resulted in obesity or drug-induced weight gain. Therefore, the POMC pathway may be an important mechanism. In addition, *MC4R* seems to interact with multiple other neurotransmitter pathways, including dopamine, leptin, and BDNF, in regulating appetite, eating, and energy homeostasis.[69]

In contrast to *MC4R*, other genes that have been significantly associated with obesity in the general population or that are involved in appetite regulation and energy homeostasis, including *FTO*, *LEP* (Leptin), *LEPR* (Leptin receptor), *BDNF* and *INSIG2*, were not consistently associated with antipsychotic-related weight gain. In the present meta-analysis, genes that are direct pharmacodynamic targets of antipsychotics were more likely significantly associated with weight gain, except for *MC4R* and *GNB3*. Perhaps, genes that are involved in metabolic regulation, energy homeostasis, and appetite control may impact upon the downstream effects of antipsychotic actions, therefore, it may be more difficult to find significant associations with antipsychotic-induced adverse events.

Several limitations of this meta-analysis must be considered. First, many results were heterogeneous across studies, but for most SNPs the number of studies was not large enough to perform moderator or meta-regression analyses. However, we were able to conduct these analyses for a few SNPs with ≥8 studies. The most significant finding is that pooled ESs tended to be larger in studies with short-term follow-up and those including patients with minimal prior antipsychotic exposure. This finding was true for both *HTR2C* and *GNB3*. The diminishing gene effects during longer-term antipsychotic treatment and follow-up could be explained by a diminishing weight gain signal overall and/or greater contributions of behavioral and environmental factors, including changes in diet and exercise or antipsychotic adherence. Thus, although we attempted to examine more homogeneous samples in terms of patient populations, prior antipsychotic exposure and follow-up duration, the analyzed studies remained heterogeneous. One source of heterogeneity may come from variability in ancestry background, which may present different allele structures and was not well accounted for in meta-analysis. We have attempted to run subgroup analysis in different racial groups whenever possible, but no significant difference was found. Future studies should always include a 2- to 3-month time point, and a greater focus on antipsychotic-naïve and first episode patients would be helpful. Interestingly, the pooled effect size for rs7700039 (−2548A/G) in *LEP* was only marginally significant in 10 studies, and examining the studies with short-term durations and first-episode patients failed to improve the overall ES, suggesting that perhaps

LEP does not play an important role in antipsychotic-related weight gain. Additionally, we detected a significant publication bias for several results, as is expected in mostly single-gene studies. However, the overall bias seemed conservative, as generally the ES increased when potentially missing studies were imputed. Another issue is that although we attempted to evaluate the strength of evidence on the phenotype-genotype association based on the modified Venice criteria, it needs to be acknowledged that the Venice criteria was not designed for pharmacogenetic studies. Therefore, interpretation of these findings should be cautious. Finally, the antipsychotics used in each study were heterogeneous, which may limit the detection of pharmacogenetic signals. Many studies examined clozapine and olanzapine, which confer the highest weigh gain liability and are pharmacologically different from other antipsychotics. The power of detecting a signal may be increased by studying a single agent or agents with similar weight gain properties.[20]

In summary, the present meta-analysis attempted to overcome the limitations of previous reviews and comprehensively examined all genetic variants deemed relevant in association with antipsychotic-related weight gain. Several genes, including *HTR2C*, *DRD2*, *ADRA2A*, *MC4R* and *GNB3* seem to be consistently associated with antipsychotic-related weight gain. ES were larger in patients with minimal prior antipsychotic exposure and in short-term studies. Despite promising findings, the ES of individual SNPs and genes are too small to fulfill the promise of personalized medicine. Because antipsychotic-related weight gain is likely polygenic and affected by environmental factors,[9] future studies should carefully consider study design issues[14,70] and explore combining multiple genetic markers and relevant clinical factors to improve clinical prediction.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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