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Pharmacogenetics of leptin in antipsychotic-associated weight gain and obesity-related complications

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Abstract

Second-generation antipsychotics can greatly improve symptoms of psychosis-spectrum disorders. Unfortunately, these drugs are associated with weight gain, which increases a patient's risk for developing chronic diseases including Type 2 diabetes, cardiovascular diseases or other obesity-related complications. There are interindividual differences in weight gain resulting from antipsychotic drug use that may be explained by pharmacodynamic characteristics of these agents as well as clinical factors. In addition, genetic variations in pathways associated with satiety are increasingly recognized as potential contributors to antipsychotic-associated weight gain. Polymorphisms in the leptin gene, as well as the leptin receptor gene, are potential pharmacogenetic markers associated with these outcomes. This article summarizes evidence for the associations of the leptin gene and the leptin receptor gene polymorphisms with antipsychotic-induced weight gain, potential mechanisms underlying these relationships, and discusses areas for future pharmacogenetic investigation.

Keywords

antipsychotic; leptin; leptin receptor; obesity; polymorphism; weight gain

Antipsychotic-associated weight gain and related metabolic complications are major side effects of many second-generation antipsychotics (SGA) [1]. **This phenomenon is especially** concerning in patients with psychosis-spectrum disorders who are nearly twice as likely as the general population to be obese [2]. Although weight gain is a relatively common side effect from many SGAs, the amount of weight gained by patients is highly variable [1,3]. Considering that the pathways responsible for antipsychotic-associated weight gain are not yet fully understood, investigating relationships between this outcome and genetic variants may help to account for some of the variability observed and explain the mechanisms by which it occurs. **Over the past decade, a number** of pharmacogenetic investigations have studied polymorphisms in genes believed to be involved in antipsychotic-associated weight gain [4]. Thus far, candidates such as *HTR2C* have yielded promising results [5,6]. Building upon this foundation, an increasing number of studies also suggest a relationship between drug-associated weight gain and genes related to neuropeptides known to influence appetite and satiety such as leptin. **This article summarizes** the available literature investigating the relationship between *LEP* and *LEPR*

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polymorphisms and antipsychotic-associated weight gain, with a focus on psychosis-spectrum disorders such as schizophrenia.

Obesity is a growing epidemic & patients with schizophrenia are at an increased risk

Obesity is increasing in the general population and places those affected at an increased risk for serious diseases. Data from the 2007–2008 National Health and Nutrition Examination Survey (NHANES) illustrate that 68% of the US population has an overweight BMI (> 25 kg/m²), and 33.8% are considered obese (BMI ≥ 30 kg/m²) [7]. **There are numerous consequences** of obesity which include an increased risk of developing chronic diseases including diabetes, hypertension, stroke and coronary heart disease [8]. **Metabolic syndrome is a related outcome** that is characterized by abdominal obesity, dyslipidemia, hypertension and impaired fasting glucose [8]. People with metabolic syndrome are at a twofold higher risk of cardiovascular disease, stroke and cardiovascular-related mortality [9].

Psychiatric patient populations such as those with schizophrenia are more likely to develop obesity, metabolic dysregulation and cardiovascular disease than the general population [10–12]. This is due in part to the effects of antipsychotic treatment, but evidence also suggests an increased risk independent of drug therapy. Some clinical characteristics associated with risk for obesity in schizophrenia include negative symptoms and poor self-care, which often results in poor diet choices (e.g., high in fat, low in fiber) and inadequate exercise [13]. Moreover, patients with schizophrenia often have less access to and are less likely to seek medical attention [13], making it even more difficult to intervene and prevent complications owing to metabolic disturbances and weight gain.

Weight gain & SGAs

The likelihood of significant weight gain associated with antipsychotic medications varies and appears to reflect differences in the pharmacodynamic properties of these drugs. The degree of weight gained from SGAs is typically greatest early in treatment as meta-analyses have determined mean weight increases from 1.4 to 11 lb (0.6–5 kg) over the initial 4–12 weeks of therapy [3]. Antipsychotic-associated weight gain is believed to reach a plateau by year 1 of treatment [14,15], although there is still controversy regarding the timing of this plateau for each SGA [16]. Antipsychotics with the highest degree of weight gain observed after 10 weeks of exposure in clinical trials include clozapine, olanzapine and risperidone, while ziprasidone is less likely to cause weight gain [1]. While SGAs such as olanzapine and clozapine have the greatest relative risks for weight gain, they are also two of the most effective and efficacious agents [17–19]. This dilemma often forces prescribers to balance the risks of weight gain-associated sequelae versus the potential for improved symptom control and function.

Clinical & genetic factors related to weight gain during antipsychotic treatment

In addition to drug-specific factors, clinical factors – psychiatric and nonpsychiatric – may also influence the likelihood of an individual being overweight. Most studies suggest that a low or normal baseline BMI is predictive of greater weight gain in the context of antipsychotic treatment [16]. Family history may also influence BMI status as illustrated through positive correlations between the BMIs of the parents of study participants and weight gain observed over the course of treatment [20]. Sex [21,22] and age [23–25] may

also be contributing factors since females and younger patients (particularly children and adolescents) appear to be more vulnerable to antipsychotic-induced weight gain.

The relationship between psychiatric history or diagnosis and the magnitude of weight gained is still under investigation. **In studies of olanzapine** and risperidone, weight gain was associated with a diagnosis of undifferentiated schizophrenia [26] and presence of negative symptoms [25]. In addition, some findings suggest that clinical outcomes are positively associated with weight gain over 6 weeks of treatment [22,27], although other literature has not confirmed this relationship in cases of long-term treatment [16].

Genetic factors have also emerged as potential predictors of antipsychotic-associated weight gain. A series of twin and sibling studies suggest that there may be 60–80% heritability of weight gain from clozapine, olanzapine or risperidone [20,28,29]. Several genetic association studies have also linked SGA-associated weight gain to variants in many genes, including *BDNF* [30], *HTR2A* [31], *HTR2C* [32], *DRD2* [33] and *ADRA2A* [34,35]. Therefore it appears likely that some combination of genetic variations may be the key to predicting and understanding antipsychotic-associated weight gain.

Pharmacology of antipsychotic-associated weight gain: the usual suspects

Despite some correlations with clinical factors, it is clear that antipsychotic medication utilization is related to the extent of weight gained from these drugs, although the mechanism(s) by which this occurs is still under exploration. Several studies suggest that selectivity for known pharmacodynamic targets of SGAs such as the serotonin 2C (5-HT_{2C}), histamine 1 (H₁) and dopamine 2 (D₂) receptors are at least partially responsible for weight gain-associated side effects [36,37].

Transgenic research in rodents has helped to clarify the role of the 5-HT_{2C} receptor as a vital component in the regulation of food intake, adiposity and levels of blood-based biomarkers of metabolic function (e.g., glucose, insulin and leptin) [38,39]. 5-HT_{2C} receptors are believed to influence metabolic function by regulating transmission of melanocortin and its precursor pro-opiomelanocortin (POMC), which are two neuropeptides with anorexigenic effects (i.e., decrease feeding and increase energy expenditure) [36,37]. Olanzapine and clozapine both have strong affinity for, and antagonize the 5-HT_{2C} receptors, which may explain their associations with greater weight gain. Ziprasidone, which is less likely to induce weight gain, also has moderate affinity for 5-HT_{2C} receptors [36]. This suggests that the involvement of additional pharmacodynamic factors is important.

Antipsychotic drugs also block D₂ receptors, which are part of another pharmacologic pathway that may regulate appetite and satiety. All first- and second-generation antipsychotics have some degree of activity at D₂ receptors [40,41]. Thus far, D₂ receptors have been implicated in addictive and impulsive behaviors like pathological eating, obesity and gambling [42,43]. Consequently, dopamine signaling, particularly in the mesocorticolimbic system, is believed to be involved in hyperphagia and reward-seeking behaviors [44,45].

Finally, there is strong evidence of an association between H₁ receptor antagonism by antipsychotics and weight gain [36,37]. Animal studies have established histamine as an anorexigenic factor [46,47], while antagonism of H₁ receptors has been demonstrated to cause increased food intake [48]. Chronic olanzapine exposure can downregulate H₁ receptor expression in the arcuate nucleus and ventromedial hypothalamus [49], which can subsequently impair appetite suppression.

Leptin physiology & signaling

Recently, the search for a comprehensive mechanistic explanation for antipsychotic-associated weight gain has expanded to include the roles of other hormones involved in appetite and satiety. One such hormone is leptin, an anorexigenic factor that was discovered in the mid-1990s when knockout mice for the *ob* gene encoding leptin were created [50]. These *ob/ob* mice became hyperphagic, extremely obese, diabetic and completely leptin deficient.

The leptin neuropeptide in humans is encoded by *LEP*, which maps to chromosome 7q31.3 and consists of three exons separated by two introns [51] (see Figure 1). An N-terminus signaling sequence is cleaved from the 167 amino acid-long product to form the leptin peptide [50]. In humans, leptin circulates in two forms: as an unbound peptide or; bound to a soluble leptin receptor (sOB-R) [52]. Leptin is primarily secreted by white adipose tissue in a pulsatile fashion [53], such that leptin levels are elevated in the evening and early morning [54].

Leptin signaling is mediated through the leptin receptor, which belongs to the class I family of cytokine receptors [55]. In humans, *LEPR* maps to chromosome 1p31 and contains 20 exons, two of which are noncoding (see Figure 2) [56]. The *LEPR* transcript is alternatively spliced to several different isoforms that all share the same extracellular and transmembrane domains [57]. The only known long isoform (also known as LEPRb or OB-RL) is primarily involved in hypothalamic signaling, whereas the short isoforms (OB-Rs also known as LEPRa, LEPRc and LEPRd) are thought to mediate leptin transport [58]. The soluble leptin receptor (sOB-R or LEPRE) only has the extracellular domain [59] and circulates throughout the periphery [60].

Leptin exerts its action via its receptors throughout the human body. In particular, LEPRb is highly expressed in the hypothalamus and, unlike short LEPR isoforms, possesses docking sites responsible for intracellular signal transduction [61]. After the leptin peptide binds to this receptor, signal transduction at LEPRb occurs by autophosphorylation of a tyrosine kinase, Janus-kinase2 (Jak2), leading to the phosphorylation of several tyrosine residues that activate signal transducers and activators of transcription isoforms (STAT3 and STAT5) [62,63]. Other downstream signals of LEPRb that have yet to be fully characterized include phosphoinositide 3-kinase, mammalian target of rapamycin and AMP-activated protein kinase [64].

Much of what is understood about the effects of leptin on energy regulation comes from understanding its actions at the arcuate nucleus. There, leptin acts on receptors in the POMC/melanocortin neuropathway, which suppresses appetite and increases energy expenditure. Furthermore, leptin inhibits production of two orexigenic (appetite stimulating) peptides: neuropeptide Y and agouti-related peptides [65]. In addition to hypothalamic targets, leptin is also believed to act alongside gut peptides (e.g., glucagon-like peptide 1 and cholecystokinin) at the nucleus of the solitary tract to signal for satiety [64,65].

Role of leptin in obesity & antipsychotic-associated weight dysregulation

Leptin is produced by adipose tissue, and circulating leptin levels are positively correlated with BMI [52]. Thus, increased adipose tissue is generally associated with greater leptin levels [66]. The relationship between leptin levels and adipose tissue may explain why in cross-sectional studies, women (who have a larger percentage of adipose mass than men) tend to have higher leptin levels than men [67,68]. Another hypothesis is that the discrepancy in leptin levels is owing to the effect of sex steroids on leptin production. Estrogen, progesterone and androgen receptors are found in adipose tissue [69–71], and

there is evidence that estrogen stimulates leptin expression in women, whereas in men, testosterone levels are negatively correlated with leptin levels [72,73].

Some studies indicate that obese individuals have higher serum leptin levels than nonobese populations [52,74]. Therefore, many investigators hypothesize that obese people may actually be resistant to the effects of leptin, which include inducing the sensation of satiety and increasing energy expenditure. The hypotheses that antipsychotics may somehow contribute to leptin dysregulation or that a genetic predisposition to leptin resistance may influence the degree of weight gain experienced by a patient have recently been tested.

Several studies have attempted to determine what effect(s) antipsychotics have on leptin. It is generally understood that the use of antipsychotics (especially SGAs), and not the diagnosis of a psychosis-spectrum disorder, is associated with both an increase in weight and an increase in serum leptin levels [14,75]. However, after controlling for BMI, there does not appear to be a strong correlation between antipsychotic use and changes in leptin levels [14]. In addition, the effect of treatment on leptin levels is evident regardless of the dose of SGA used [75]. These observations suggest that increases in serum leptin are most likely owing to weight gained during treatment rather than a direct effect of antipsychotics on leptin production. The increase in leptin serves as the body's attempt to curb the increased food intake. **Still, as previously** mentioned, there is a great deal of interindividual variance in the amount of weight gain experienced while taking antipsychotic drugs. One interesting hypothesis is that genetic variation in leptin system genes influences the body's ability to effectively modify appetite and energy expenditure in the context of increased food consumption and resulting weight gain.

Function of *LEP* & *LEPR* genetic polymorphisms

There is evidently a relationship between antipsychotic use, weight gain or metabolic disturbances and leptin; however, what exactly links these variables is still under investigation. Studies of genetic variability in leptin system genes might provide answers and help us account for some of the interindividual differences observed in patients who develop metabolic disturbances while on antipsychotics.

Many SNPs have been discovered in *LEP* and *LEPR*. In *LEP*, -2548G/A (rs7799039) and A19G (rs2167270) are candidate SNPs studied for associations with obesity in addition to cancer [76] and hypertension [77]. In humans, the *LEP*-2548G/A polymorphism appears to influence leptin transcription, expression and secretion such that AA genotype carriers have twice the rate of leptin secretion and 60% more leptin mRNA transcription than G allele carriers [78]. In an obese population, those homozygous for G alleles of the *LEPA19G* polymorphism had lower leptin concentrations [79]. The functional consequences of the A19G SNP have not been described, but its close chromosomal proximity to the -2548 promoter variant indicates that linkage disequilibrium between the markers could mean that they are markers for the same causal variation. Other genetic variations in the 5'- and 3'-UTRs have also been linked with obesity and BMI status [80]; however their biological functions have not yet been elucidated.

A number of variants within *LEPR* have been studied for relationships with obesity or weight status [81]. These include Gln223Arg or 668G/A (rs1137101), Lys656Asn (rs8179183), Ser343Ser (rs1805134) and Lys109Arg (rs1137100). At this point, the biological functions of these polymorphisms have not been well studied in humans. *In vitro* experiments suggest that the *LEPR* Q223R polymorphism has no effect on leptin signaling [82]. **Nonetheless, candidate gene association** studies have found that the Q223R polymorphism is a marker for fat mass, obesity and increased BMI [83–85]. **The functional**

characterization of other *LEPR* polymorphisms is still limited, although the *LEPR* Ser343Ser polymorphism was also associated with overweight status in a female French population [86]. Despite these positive association reports, meta-analyses of studies on the *LEPR* Q223R SNP [87] and other commonly studied *LEPR* SNPs (e.g., *LEPR* Q223R, K109R and N656K [88]) have not found significant evidence for associations with obesity. Interestingly, a recent genome-wide association study of sOB-R in women of European ancestry identified a number of polymorphisms associated with the sOB-R serum level phenotype – all of which were located in *LEPR* [89]. It is plausible that the *LEPR* variants selected for candidate gene association studies do not represent the causal variants, but rather are linked to the causal variant(s). Alternatively, known differences in allele frequencies across racial and ethnic groups, or the use of less specific phenotypes (e.g., weight or BMI instead of sOB-R levels) may have contributed to the inconsistent associations and mechanistic information regarding these variants.

Pharmacogenetics of *LEP* & *LEPR*

Many studies have examined the relationships between *LEP* and *LEPR* polymorphisms and metabolic dysfunction. However, only 14 have been conducted in the context of antipsychotic use. Six of the reviewed studies were cross-sectional (see Table 1) and seven were prospective (see Tables 2 & 3). One study is only available in Chinese and is not reviewed extensively herein [90]. **The available studies all represent candidate** gene association investigations, where variants were selected based on *a priori* knowledge of associations with being overweight, obesity outcomes or by virtue of being located in known coding regions of *LEP* or *LEPR*. Many focused on the *LEP*-2548G/A (rs7799039) polymorphism, while others also examined polymorphisms within *LEP* (rs4731426 C/G) and several in the leptin receptor: *LEPR* Q223R (rs1137101), *LEPR* N656K (rs8179183), rs7602 and rs1171276.

Leptin system genes & antipsychotic-associated weight gain: cross-sectional studies

Four of the seven available cross-sectional studies reported at least one significant association between a *LEP* or *LEPR* polymorphism and BMI or weight with details summarized in Table 1. Highlights of these investigations are reviewed here in chronological order. The first study reviewed was an investigation of 168 predominantly Caucasian subjects who had a severe and persisting mental illness requiring treatment with either risperidone or olanzapine [91]. No data on drug dose or duration of exposure was reported. **The primary goal of this investigation** was to perform a ‘physiogenomic’ study comparing weight profiles between patients on risperidone and olanzapine and to determine whether selected candidate SNPs were associated with any of the study end points. **Upon relating** polymorphisms in *LEPR* to patient weight, there was a significant association between participants carrying the minor allele (G) coding for K at *LEPR* N656K and ‘protection’ against higher weight while on risperidone; in fact, the K allele frequency was 0% in weights over 100 kg.

A second cross-sectional study published in 2008 included 134 participants with a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis of schizophrenia or schizoaffective disorder [92]. The primary goal of this study was to characterize associations between *LEP*-2548G/A and *HTR2C*-759C/T genotypes and several metabolic parameters (e.g., weight, BMI and waist circumference) in these individuals. **The participants were prescribed** olanzapine, clozapine or risperidone for any duration prior to evaluation. Associations between *LEP* or *HTR2C* genotype groups and BMI did not reach statistical significance; **however**, within subjects of the *HTR2C*-759 C/

CC genotype group, there was a significant association between *LEP*-2548 G allele carriers and BMI. Those participants with the -759 C/CC and -2548G combination had an approximately 2 kg/m² higher BMI, approximately a 10 cm greater waist circumference and were significantly more likely to have metabolic syndrome than those without this genotype combination. This effect remained statistically significant when the results were stratified by medication prescribed (e.g., either olanzapine/clozapine use vs risperidone).

Gregoor *et al.* conducted an investigation of the *LEP*-2548G/A SNP in conjunction with the *LEPR* Q223R SNP in 200 subjects with schizophrenia or schizoaffective disorder [93]. These participants were primarily taking clozapine, olanzapine or risperidone and had been treated with one of these agents for at least 3 months. In this investigation there was no evidence for association between genotype and obesity (BMI >30 kg/m²). However, the authors did report evidence of a potential sex difference in associations with *LEPR* variants. Women with the *LEPR* 223QQ genotype (i.e., homozygous for AA) were approximately twice as likely to be obese than R allele carriers (i.e., G allele carriers).

In a follow-up study using the same subject population, Gregoor *et al.* further investigated interactions between *LEP*, *LEPR* and *HTR2C* polymorphisms and weight-related outcomes [94]. The primary objective of this study was to characterize associations between obesity and two *HTR2C* SNPs (rs3813929/759C/T and rs1414334), and two leptin polymorphisms (*LEP*rs7799039/-2548G/A and *LEPR* rs1137101/Q223R). In this analysis, the authors identified a significant association between obesity and the absence of the *HTR2C*-759 T allele and the presence of the *LEP*-2548 G allele. This association is consistent with results from the study by Yevtushenko *et al.* [92]. **No other significant** associations were identified, although the authors reported a trend towards significance among subjects with the *HTR2C* rs1414334 C allele in combination with either *LEP*-2548 G allele or the *LEPR* 223 R allele.

A case-control retrospective study of subjects diagnosed with schizophrenia or schizoaffective disorder also examined weight gain in the context of *LEP* and *HTR2C* SNPs, as well as insulin-induced gene 2 (*INSIG2*) variants [95]. The study population (n = 128) was predominantly male and of European or Turkish descent. A total of 54% of participants were prescribed monotherapy with an SGA (primarily clozapine or olanzapine), and 46% were on two or more antipsychotics. A total of 43% of participants were also taking other psychotropics associated with weight gain (e.g., mood stabilizers or antidepressants). The primary end point was to characterize the relationship between clinically significant weight gain after being treated with an antipsychotic for at least 6 weeks and *LEP*-2548G/A, *INSIG2* and *HTR2C* variants (including the -759C/T variant). No association was found between clinically significant weight gain and the *LEP*-2548G/A polymorphism.

A two-part candidate gene association study in Venezuela examined *LEP*-2548G/A and *LEPR* Q223R variants in conjunction with baseline physical characteristics and metabolic response to metformin during chronic clozapine use [96]. Participants with schizophrenia were included if they had been prescribed clozapine for at least 3 months. The primary end point of the first phase of this study was to characterize the relationships between *LEP*-2548G/A and *LEPR* Q223R variants and differences in the frequency of metabolic syndrome, obesity and other metabolic variables (e.g., waist circumference, blood glucose, hemoglobin A1c, lipids, leptin and cortisol). Among the 56 participants, there was no significant association between either *LEP* or *LEPR* SNP and the frequency of metabolic syndrome or obesity. **However, there was an association** between observable *LEPR* 223QQ and lower baseline triglyceride levels, only in males after controlling for clozapine dose.

The *LEPR* N665K polymorphism was examined in a Belgium-based study that also investigated ‘clock genes’ (e.g., *MC3R*, *PER2*, *SDC3* and *NR3C1*) and their relationships with weight and other anthropometric parameters [97]. This was a candidate gene association study of 261 subjects with schizophrenia who were on a stable dose of antipsychotic (risperidone, olanzapine, clozapine, quetiapine, amisulpride, aripiprazole or a first-generation antipsychotic) for at least 3 months. Subjects were allowed to take concomitant medications (including benzodiazepines, anticholinergic agents, mood stabilizers and antidepressants). No significant associations were observed between the *LEPR* N665K polymorphism and weight, BMI, waist circumference, hip circumference or waist:hip circumference ratio.

To date, cross-sectional studies have identified some associations between *LEP* and *LEPR* SNPs and weight gain, particularly when *LEP* –2548G/A variants were examined in the context of *HTR2C* variants [92,94] or when *LEPR* Q223R variants were studied for sex differences [93]. However, some of these studies did not find leptin genotypes to be significant on their own. This could be owing in part to the nature of cross-sectional studies and the recruitment of participants with varying histories of antipsychotic use. While these associations were not consistent across studies, there is enough evidence to suggest a pharmacogenetic relationship between *LEP* polymorphisms and obesity-associated outcomes in patients on chronic antipsychotic therapy for 3 months or longer.

Leptin system genes & antipsychotic-associated weight gain: short-term prospective studies

Ellingrod *et al.* conducted a small candidate gene association study of 37 Caucasian schizophrenia subjects taking olanzapine for 6 weeks which investigated the relationships between *LEP* and *LEPR* genotypes with weight gain early on in treatment [98]. In this study, subjects underwent a 4–7 day washout prior to olanzapine treatment whereby participants were titrated to a fixed dose for the duration of the study. Subjects who were carriers of the G allele for both the *LEP* –2548G/A and *LEPR* Q223R SNPs and had high olanzapine serum levels (defined as plasma olanzapine >20.6 ng/ml) had a greater increase in BMI after 6 weeks versus AA homozygotes. Interestingly, the high proportion of males (81%) in this population combined with the association of G allele presence in *LEPR* Q223R and a greater change in BMI mimics a similar trend, albeit not statistically significant, found by Gregoor *et al.* [93] which associated the G allele with obesity in Caucasian males.

Srivastava *et al.* recruited 130 North Indian subjects with schizophrenia or schizoaffective disorder taking olanzapine for 6 weeks with the goal of studying polymorphisms in genes involved in appetite regulation – *LPL*, *TAG*, *CL* and *LEP* – and olanzapine-associated weight gain [99]. Participants already taking an antipsychotic prior to the study underwent a 3 day washout period. Subjects with the G allele for the *LEP* rs4731426 C/G polymorphism and one *LEP* haplotype (see Table 2) were associated with greater than average weight gain relative to the rest of the sample population. There was no evidence for association when a commonly used definition of ‘clinically significant’ weight gain (>7% from baseline) was used to define this outcome.

Leptin system genes & antipsychotic-associated weight gain: longer-term prospective studies

Additional prospective studies have also examined relationships between *LEP* or *LEPR* genotypes and weight gain during chronic treatment, defined here as investigations with greater than 6 weeks of antipsychotic exposure. Templeman *et al.* studied 73 drug-naïve Caucasian subjects experiencing their first significant episode of psychosis [100]. Study

participants were enrolled in this 9-month prospective study of flexibly-dosed SGA agents (including risperidone, olanzapine, quetiapine, ziprasidone and amisulpride). The investigators selected one candidate SNP (*LEP*-2548G/A) for analysis with weight gain after 6 weeks, 3 months and 9 months of treatment. There was no evidence for an association between the *LEP*-2548G/A genotype early in treatment, but at 9 months, *LEP*-2548GG homozygous subjects had approximately 2 kg/m² greater change in BMI in comparison to A allele carriers.

Zhang *et al.* investigated Han Chinese inpatients diagnosed with chronic schizophrenia who were prescribed a stable dose of clozapine for at least 2 years [101]. The primary goal of this investigation was to examine the relationship between the *LEP*-2548G/A genotype and clozapine-induced weight gain over this time period. **Similar to the aforementioned findings** in Caucasian populations by Templeman *et al.* [100], subjects carrying the G allele for *LEP*-2548G/A had an approximately 2 kg/m² greater increase in BMI than AA homozygotes. When stratifying the results by sex, the G allele effect on BMI was observed in men but not in women.

In a similar study, Korean inpatients with schizophrenia were recruited with the primary goal of characterizing the relationship between the *LEP*-2548G/A SNP and weight gain during olanzapine treatment. Participants had no prior use of olanzapine or clozapine and were administered olanzapine for a minimum of 3 months [102]. Consistent with previously reviewed studies, subjects carrying the G allele for *LEP*-2548 had greater weight gain than AA homozygous patients after 3 months of treatment. None of the 74 patients carried the GG genotype. Though not statistically significant, the authors noted a trend towards the AG genotype being associated with clinically significant weight gain (77% with AG genotype vs 48% with AA genotype; $p = 0.054$).

The most recent prospective study investigated the *LEP*-2548G/A and *LEPR* Q223R SNPs as well as *FTO* and *SH2B1* variants in association with BMI and weight before and after 12 months of exposure to antipsychotics [103]. This study included predominantly Caucasian subjects experiencing their first episode of schizophrenia or schizophreniform disorder. The study population was predominantly drug naive, and participants were prescribed a variety of first- and second-generation antipsychotics over the course of the study. In this study, 71% of subjects experienced clinically significant weight gain but no significant associations with either *LEP* or *LEPR* variants were observed.

All of the aforementioned investigations studied antipsychotic use, leptin genotypes and weight implications in adult populations. To the best of our knowledge, only one published study to date has examined this phenomenon in a pediatric population. **This was a candidate gene association** study of children aged 7–17 years old with the primary objective of investigating associations between risperidone-induced weight gain, plasma leptin concentration and *LEP*-2548G/A genotype [104]. Interestingly, the findings of this pediatric study are in contrast to what many of the other studies in this article have found. A total of 74 participants, who were primarily male Caucasians were prescribed risperidone for at least 6 months. The authors observed that *LEP*-2548 A carriers had greater increases in weight and BMI z-score than GG homozygotes after 1 year and 2 years of treatment. The same relationship held true even after controlling for concomitant use of selective serotonin-reuptake inhibitors and α_2 -agonists, which have also been associated with weight gain in this population.

These prospective studies provide clearer support for a significant relationship between the *LEP*-2548G/A variant and weight gain or increased BMI. **Of note is that two studies** [100,103] utilized antipsychotic-naive first-episode subjects, which are ideal for studies of

weight gain and treatment response. Only one [98] of two studies found an association between the *LEPR* Q223R variant and weight gain; however, this was in the context of high drug concentration and a *LEP* -2548G/A genotype interaction.

Discussion

Studies investigating the relationship of *LEP* and *LEPR* polymorphisms and metabolic outcomes in psychiatric populations prescribed antipsychotic drugs have yielded somewhat conflicting results. However, a careful look at these investigations reveals a few notable trends. A total of six of the 13 reviewed studies identified associations between the *LEP* -2548 G allele and weight gain or increased BMI [92,98,100–102,105]. Subjects in these investigations were predominantly prescribed olanzapine or clozapine, which are the SGAs most associated with treatment-associated weight gain [2] and have high 5-HT_{2C} affinity [36]. Conversely, the observation by Calarge *et al.* [104] that the *LEP* -2548 A allele is associated with increased BMI, is in agreement with findings from an earlier study conducted in a Han Chinese population that also found the *LEP* -2548 AA genotype to be associated with weight gain after 10 weeks [90]. Participants in these two studies were primarily treated with risperidone or antipsychotics other than olanzapine or clozapine. These findings suggest that the relationship between *LEP* -2548G/A genotype and weight gain may be dependent upon the type of antipsychotic a patient is currently or has previously taken (particularly clozapine and olanzapine vs others). If *LEP* genotype associations indeed differ across medication groups, this is consistent with a unique or additional mechanism by which clozapine and olanzapine influence weight or obesity outcomes relative to other antipsychotics studied. While this is not a new concept, the growing body of literature supporting the role of leptin gene variants in weight gain from clozapine or olanzapine use is a step forward in clarifying the mechanisms by which this occurs. Some studies have proposed that this unique mechanism may be in part related to the immunological effects of olanzapine and clozapine. **Specifically, alterations in the levels of cytokines** (including leptin, TNF- α and sTNFR-1 and 2) have been linked to weight gain by these two SGAs [106]. In addition, variations in H1 and muscarinic 3 (M3) receptors, for which olanzapine and clozapine have a stronger affinity than other SGAs, may also provide an explanation for these high effects on weight [107], although M3 affinity has only been linked with a risk of developing Type 2 diabetes thus far [37].

The *LEPR* polymorphism at codon 223 (rs1137101) was also associated with weight gain or increased BMI, but only in the context of analyses stratified by sex [93] or interactions with *LEP* variants [98]. Two studies did not observe *LEPR* Q223R associations with weight gain [96,103]. However, neither of these two studies specifically tested for sex differences, and the use of several different SGAs with varying weight gain liabilities may have limited the ability of the investigators to detect potential associations. Findings regarding the *LEPR* N656K (rs8179183) polymorphism are less conclusive [91,97], although it appears that this variant may be associated with weight gain in the context of risperidone use [91]. These data should be interpreted with caution owing to the limitations of the cross-sectional design employed by both studies as well as the use of concomitant medications [97]. Additional studies of the N656K polymorphism as well as another reported as significant by Srivastava *et al.* [99] (*LEP*rs4731426) are needed before any conclusions can be drawn. Other genetic markers within *LEP* and *LEPR*, such as the polymorphisms identified in a genome-wide association study on plasma sOB-R levels [89], have yet to be further studied in the context of antipsychotic-associated weight gain and may prove to be causal variants.

Only two studies published to date have examined serum leptin levels during antipsychotic exposure [100,104]. Templeman *et al.* observed a trend towards an association between *LEP* -2548 A allele carriers and higher baseline plasma leptin levels in comparison to GG

homozygotes, and further noted that plasma leptin levels increased for almost all patients during treatment [100]. Calarge *et al.* also determined that *LEP*-2548 A allele carriers (who had lower BMI z-scores) had significantly higher leptin concentrations than did GG participants ($p < 0.04$) [104]. These findings are consistent with *in vitro* data identifying greater leptin secretion and leptin mRNA transcription in *LEP*-2548 AA homozygotes compared with G allele carriers [78]. This suggests that individuals with the *LEP*-2548 A allele may have higher leptin levels during antipsychotic treatment which are consistent with normal, anorexigenic signaling. However, it is unclear why associations between the *LEP*-2548 A allele and increased weight gain were observed in two studies [90,104]. As previously mentioned, these studies did not involve treatment with clozapine or olanzapine and therefore suggest that alternative mechanisms of weight gain need to be explored in treatments with other medications like risperidone. In addition, the effects observed in younger patients [104] underscore the importance of examining these phenomena early on in treatment.

Some limitations of the reviewed studies include the aforementioned use of data from patients on a variety of different antipsychotic medications [93,95,97,100,103,105]. In studies with heterogeneous drug treatment, pooling data across many SGA treatment groups may have limited the ability of investigators to detect significant associations between genotype(s) and weight gain or obesity if results from weight-neutral SGAs counterbalanced the effects of weight gain from olanzapine or clozapine within a given genotype or allele group. Although stratification of data by antipsychotic used may have lessened the significance of this issue, the subsequent sample sizes were likely to be too small to detect any true associations of moderate or small effect sizes. Nonetheless, these study samples represent patient populations observed in clinical practice and illustrate that the findings observed may prove to be clinically important and applicable.

Studies of chronic schizophrenia patients [101,102] are generally complicated by an extensive and variable history of antipsychotic use. A history of prior antipsychotic treatment may minimize the magnitude of metabolic effects observed during subsequent treatments. Investigations of weight gain in patients with minimal to no prior antipsychotic use are ideal to avoid this confounder. Opgen-Rhein *et al.* [95] recruited subjects who had not been on antipsychotics 2 months prior to administering study medications, and both Templeman *et al.* [100] and Perez-Iglesias *et al.* [103] studied first-episode populations with limited to no prior antipsychotic history. Larger sample sizes, which could allow for data stratification by drug, may be needed to detect additional associations by specific drugs or groups of drugs.

Trends based on sex [93,101] or those conducted in study samples heavily weighted towards males [96–98,100,104], provide mechanistic insights as well as important information regarding differences between males and females. Of note, previous studies of antipsychotic-associated weight gain and the X-linked *HTR2C* have identified some trends suggestive of sex effects, although these studies were also limited by treatment heterogeneity and smaller sample sizes [5]. In the context of studies reviewed here, two have identified significant interactions or differential associations when *HTR2C* and *LEP/LEPR* variants were analyzed together [92,105]. It is plausible that the satiety-regulating activities of 5-HT_{2C} and leptin signaling work in concert or in parallel. Furthermore, differences in weight-related outcomes may exist in males and females in the context of exposure to agents with differential 5-HT_{2C} affinity owing to inherent differences in gene expression and leptin signaling. Superimposing *LEP/LEPR* variability on this complex association is likely to be a source for some of the inconsistencies observed across studies of leptin and antipsychotic-associated weight gain. In the context of high 5-HT_{2C} affinity (e.g., with clozapine or olanzapine treatment), increased appetite resulting from reduced 5-HT_{2C} expression

conferred by the $-759C$ polymorphism could result in a pharmacologically and genetically influenced state of hyperphagia in which the body's ability to compensate for increased food intake and adipose accumulation may be further impaired in those with lower baseline leptin production owing to the *LEP*-2548G allele.

While it has been established that leptin levels may increase as a result of antipsychotic use, surprisingly, no studies have objectively examined whether these leptin levels or leptin polymorphisms affect feeding behavior or appetite while on antipsychotics. Such an investigation may provide additional information characterizing whether antipsychotic-associated increases in leptin are indeed a reflection of increased feeding and development of adipose tissue or if leptin production or leptin receptor sensitivity is compromised during drug exposure.

Additional value may be derived from further characterization of the relationships between leptin polymorphisms and abnormalities in other metabolic markers such as insulin, blood glucose, cholesterol, low-density lipoproteins and triglycerides. These may serve as more specific phenotypes that may help researchers focus on multiple mechanistic pathways that converge to result in obesity outcomes following antipsychotic treatment. Of the studies reviewed here, two revealed an association between leptin polymorphisms, antipsychotic use and metabolic markers. Yevtushenko *et al.* [92] determined that in the context of the *HTR2C* $-759C/CC$ genotype, the *LEP*-2548 G allele was associated with metabolic syndrome. Fernandez *et al.* [96] reported that after controlling for clozapine dose, *LEPR* 223QQ males had significantly lower triglyceride levels. Identifying other genetic markers relating to specific metabolic components associated with obesity might further clarify why patients on olanzapine and clozapine are at a higher risk of developing rapid-onset diabetes compared with people on risperidone or quetiapine [108].

Future perspective

Weight gain and obesity-related sequelae are serious complications of SGAs that affect some patients more than others. Although lifestyle and clinical factors may partly contribute, the studies reviewed here suggest that some individuals taking antipsychotics may be genetically predisposed to gain more weight than other antipsychotic users and that variability in *LEP* and *LEPR* are important in this regard. Differential relationships observed in studies of olanzapine and clozapine when compared with other drugs suggest that genetic influences are likely to differ for all antipsychotics. More specifically, the influence of specific polymorphisms may differ depending on the drug(s) being studied. Complicating the picture more is a hypothesis that these relationships may be different in males and females. The studies reviewed in this article suggest the involvement of more than one genetic factor as some determined significant associations in change in BMI when linking *LEP*-2548G/A genotype with *LEPR* Q223R [98] or *HTR2C* $-759C/T$ genotype [92]. The idea that obesity is a multifactorial process should come as no surprise since there are a multitude of biological factors involved in energy intake, thermogenesis and energy metabolism.

Accordingly, future investigations should continue to examine the interaction between *LEP* and *LEPR* polymorphisms along with other genes involved in metabolic regulation in the context of antipsychotic-associated weight gain. **Examining these relationships in medications** other than clozapine and olanzapine will be particularly informative. It is generally accepted that agents such as aripiprazole, ziprasidone and iloperidone are less likely to induce significant weight gain than olanzapine or clozapine. However, weight gain is still observed in some individuals taking these drugs [109]. Thus, identifying genetic

signatures that better characterize risk for weight- and obesity-related outcomes across all available antipsychotic drugs will be clinically important.

The candidate genes discussed herein focused on leptin signaling as well as 5-HT_{2C}. This is obviously one small piece of a multifactorial network of pathways which influence metabolic outcomes in antipsychotic-treated patients. Other metabolic pathway genes may also be associated with antipsychotic-associated weight gain (e.g., *MC3R* [97], *INSIG2* [95], *FTO* and *SH2B1* [103]). A comprehensive, multifactorial approach is now needed to move the field forward. Further research in this area will hopefully generate consensus data that are mechanistically and therapeutically informative. If genetic markers can reliably predict a patient's risk for significant weight gain from these drugs, metabolic-related morbidity and mortality may be reduced and patient adherence and treatment outcomes will likely improve.

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Executive summary

Antipsychotic-associated weight gain

Second-generation antipsychotics (SGA) are effective in the treatment of psychosis-spectrum disorders. However, certain SGAs (especially clozapine and olanzapine) are known to cause weight gain and related sequelae (e.g., diabetes, dyslipidemia and cardiovascular disease).

Interindividual variations in SGA-associated weight gain may be explained by variations in genes that regulate appetite and metabolism.

Impact of *LEP/LEPR* variants on weight gain in the context of antipsychotic use

Many studies identified associations between the *LEP*-2548 G allele and weight gain, particularly in studies of olanzapine or clozapine. Associations between *LEPR* Q223R variants and weight gain are unclear; however, there is preliminary evidence that suggests that sex and *LEP* genotype may influence these relationships.

Future areas for investigation

Additional studies are needed to clarify the effects of sex and *HTR2C* variants in combination with leptin variants in SGA-associated weight gain.

Prospective studies with larger, drug-naive populations are needed. Controlling for specific SGAs used (particularly for those with greater weight-gain liability) may help to differentiate drug-specific mechanisms of weight gain.

Future pharmacogenetic studies should also examine SGA-associated alterations in metabolic biomarkers (e.g., blood glucose, insulin and cholesterol), with the goal of better predicting risk of diabetes or heart disease.

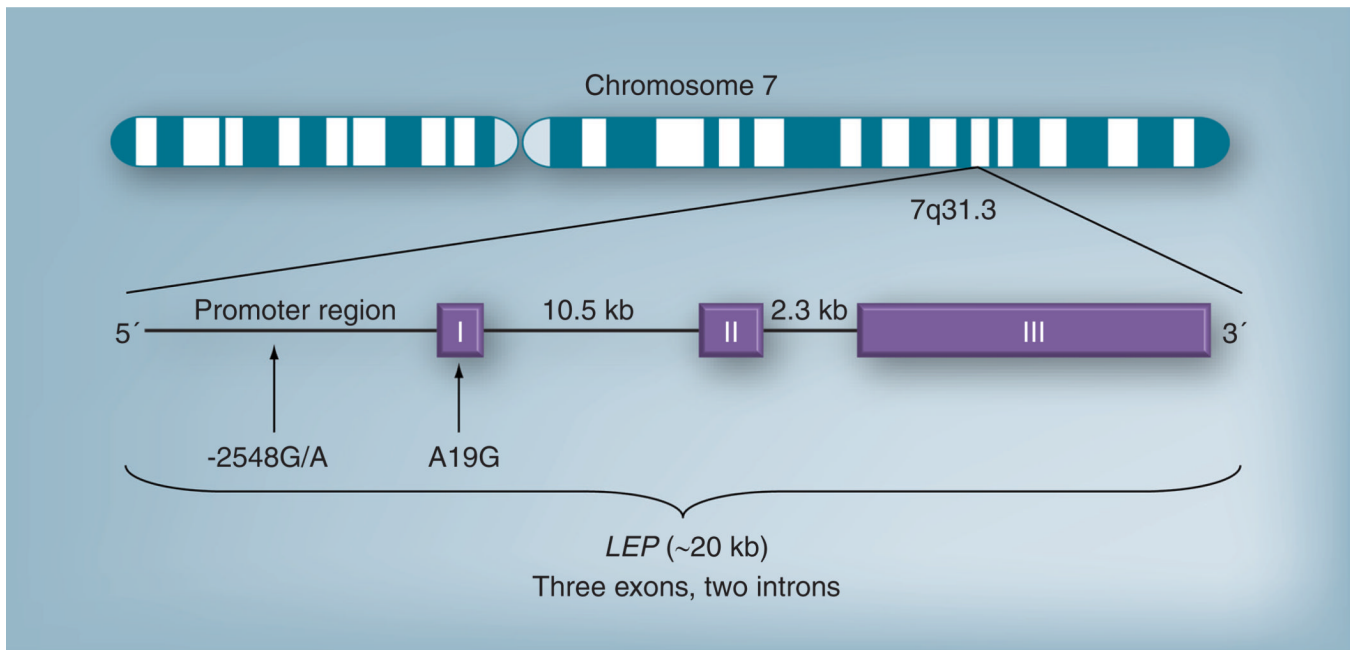


Figure 1. Proposed structure and organization of the leptin gene

Exon 1 is thought to be an untranslated 29 bp sequence. The 5' flanking region in intron 1 contains a TATA box-like sequence at -87 to -81; and three GC boxes at -79 to -74, -155 to -150, and -160 to -155. Exon 2 is 172 bp long. Exon 3 is 1039 bp long. *LEP*. Leptin.

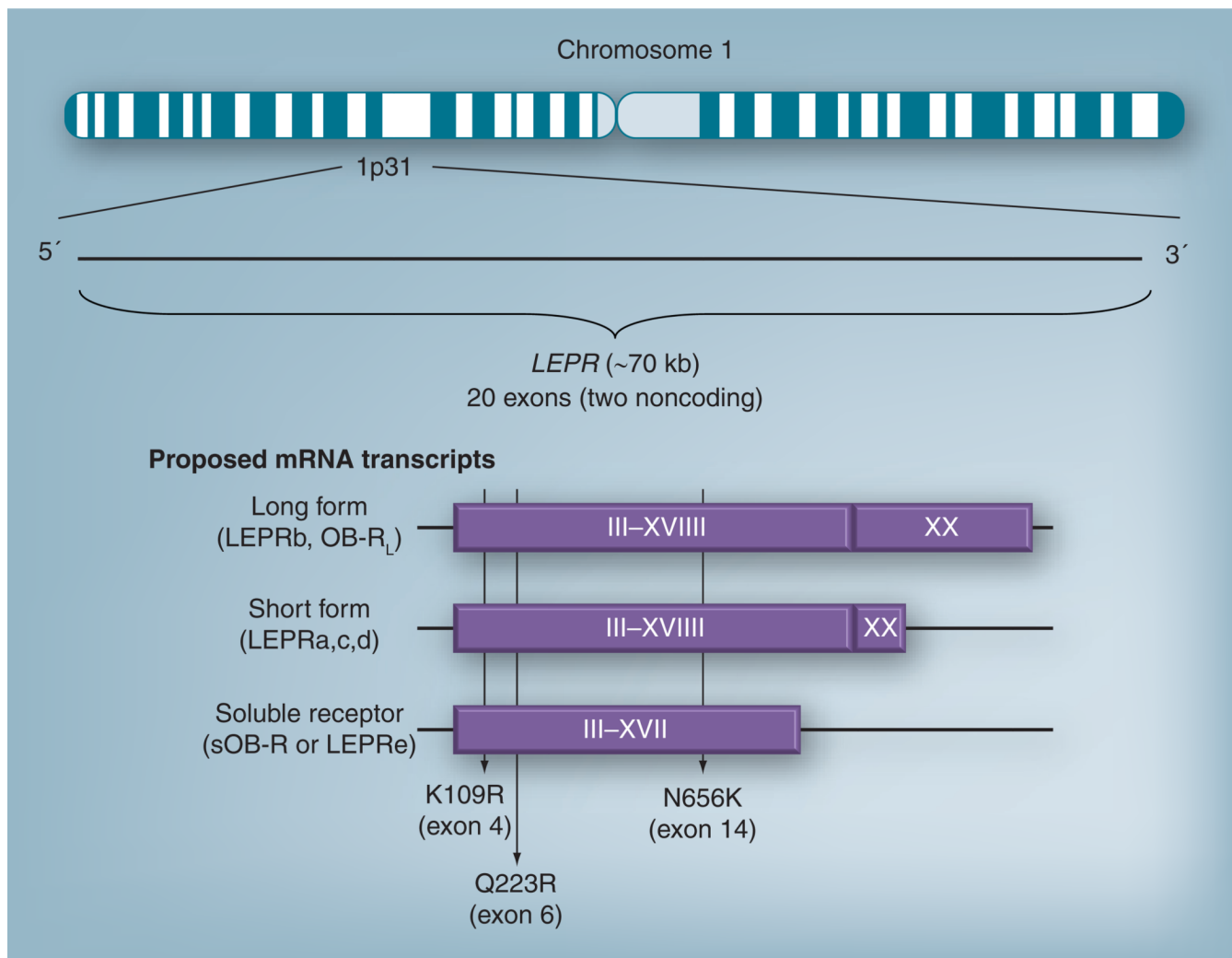


Figure 2. Proposed structure and organization of the leptin receptor gene

Exons 1 and 2 are noncoding, but have the potential to form secondary structures [56]. Exon 3 contains the initiation codon [56]. Exons 3–17 code for the extracellular domain that all isoforms possess [58]; this extracellular domain is approximately 816 amino acids long [110]. Exon 18 codes for the transmembrane domain, which comprises approximately 23 amino acids [110]. Exons 19 and 20 code for the intracellular domain. Exon 20 codes for the last 274 amino acid residues of LEPR_b [56]. The proposed splice site is located between exon 19 and intron 19 [56]. The location of SNPs K109R, Q223R and N656K are indicated. The silent P1019 polymorphism is at nucleotide position 3037 [56]. Structure and function of leptin receptor isoforms: LEPR_a: no intracellular domain; facilitates leptin transport across the blood–brain barrier [58]. LEPR_b: full intracellular domain necessary for cell signaling via JAK2/STAT3 and phosphoinositide-3 kinase pathways; contains 203 [59] or 303 [110] intracellular amino acid residues. LEPR_b is primarily found in the hypothalamus, but is also present in adipocytes, pancreatic islet cells, skeletal muscle, heart, kidneys, adrenals, immune cells and liver [59]. LEPR_e is the soluble form of leptin thought to inhibit transporter action of LEPR_a [58] and circulate throughout the body [59]. The isoforms are formed either by splicing or post-translational editing [59].

LEPR: Leptin receptor.

Table 1

Summary of cross-sectional studies examining the association of leptin polymorphisms and metabolic disturbances in antipsychotic use.

Author (year)	n (% male)	Population/ diagnosis	Medications	Dose	Treatment duration	SNP(s) studied	Summary of results	Ref.
Ruano <i>et al.</i> (2007)	168(66)	Caucasian (84%) African- American (14%) Diagnoses not reported [†]	Olanzapine Risperidone	Not available	Patients already on AP; duration unknown	<i>LEPR</i> rs7602 rs1171276 <i>N656K</i> [‡] rs8179183	Significant association between <i>LEPR</i> N656K (rsS179183) and weight in risperidone-treated patients only; G allele carriers were protected against higher weight	[91]
Yevtushenko <i>et al.</i> (2008)	134(65)	Schizophrenia and schizoaffective disorder	Olanzapine Clozapine Risperidone	Not available	Unknown duration of AP exposure	<i>LEP</i> -2548G/A (rs7799039) <i>HTR2C</i> -759C/T (rs3813929)	Among subjects with the <i>HTR2C</i> -759C/CC genotype, those with <i>LEP</i> -2548 G allele versus AA homozygotes had higher BMI, larger waist circumference and presence of metabolic syndrome (BMI 29.89 ± 6.66 kg/m ² vs 26.09 ± 5.53 kg/m ² ; p = 0.021 waist circumference: 103.86 ± 15.61 cm vs 93.78 ± 16.00 cm; p = 0.012; metabolic syndrome 33 patients vs two patients; p = 0.003)	[92]
Gregoor <i>et al.</i> (2009) [§]	200 (67)	Caucasian Schizophrenia, schizoaffective and other psychotic disorders	Clozapine Olanzapine Risperidone Other unspecified	Not available	At least 3 months	<i>LEP</i> -2548G/A (rs7799039) <i>LEPR</i> Q223 ^{8†} (rs1137101)	No significant association with obesity Female QQ homozygotes had higher rate of obesity (defined as BMI >30 kg/m ²) versus R carriers (70.6% obese in QQ vs 38.5% in QR; p = 0.007; vs 40% in RR; p = 0.018)	[93]
Gregoor <i>et al.</i> (2010) [§]	200 (67)	Caucasian Schizophrenia, schizoaffective and other psychotic disorders	Clozapine Olanzapine Risperidone Other unspecified	Not available	At least 3 months	<i>LEP</i> -2548G/A (rs7799039) <i>HTR2C</i> -759C/T (rs3813929)	Combined absence of <i>HTR2C</i> T allele and presence of <i>LEP</i> -2548G allele associated with obesity in persons without an <i>HTR2C</i> T allele (33.9% of subjects vs 22.2% in other genotype groups; OR: 2.88; 95% CI: 1.05-7.95)	[94]
Opgen-Rhein <i>et al.</i> (2010) [¶]	128(62.5)	European (92%) Turkish (8%) Schizophrenia	Olanzapine Clozapine Risperidone Amisulpride Quetiapine Clozapine Some FGAs	Not available	At least 6 weeks	<i>LEPR</i> Q223R (rs1137101) <i>HTR2C</i> -759C/T (rs3813929)	No significant association with obesity	[95]

Author (year)	n (% male)	Population/ diagnosis and	Medications	Dose	Treatment duration	SNP(s) studied	Summary of results	Ref.
Fernandez <i>et al</i> (2010)	56(78.6)	Schizophrenia and schizoaffective disorder	Clozapine	Not available	At least 3 months	<i>LEP</i> -2S48G/A (rs7799039) <i>LEPR</i> Q223R [‡] (rs1137101)	gain (>7% initial bodyweight) after 6 weeks No association between <i>LEP</i> and <i>LEPR</i> variants and frequency of metabolic syndrome or obesity when comparing homozygotes for <i>LEP</i> -2548 GG versus A allele carriers and <i>LEPR</i> 223 QQ vs R allele carriers in all subjects. <i>LEPR</i> 223 QQ genotype was associated with lower triglyceride levels in males after controlling for dose	[96]
Moons <i>et al</i> (2011)	261 (68.6)	Schizophrenia and schizoaffective disorder	Risperidone Olanzapine Clozapine Quetiapine Amisulpride Aripiprazole	Not available	At least 3 months	<i>LEPR</i> N656K [‡] (rs8179183)	No association found with <i>LEPR</i> N656K genotype and weight, BMI, waist circumference, hip circumference or waist:hip ratio	[97]

[‡] Participants recruited from hospitals treating severe, persistent mental illness.

[‡] *LEPR* Q223R (rs1137101) polymorphism: G allele codes for R (arginine), A allele codes for Q (glutamine); *LEPR* N656K (rs8179183) polymorphism: C allele codes for N (asparagine), G allele codes for K (lysine).

[§] Both studies by Gregoor *et al.* utilized the same subject population.

[¶] Case-control, retrospective study.

AP: Antipsychotic; FGA: First-generation antipsychotic; OR: Odds ratio.

Table 2

Summary of short-term (6 weeks exposure) prospective studies examining the association of leptin polymorphisms and metabolic disturbances in antipsychotic use.

Author (year)	n (% male)	Population/ diagnosis	Medication	Dose	Treatment duration	SNPs studied	Summary of results	Ref.
Ellingrod <i>et al</i> (2007)	37(81)	Caucasian, schizophrenia	Olanzapine	12.43 ± 3.04 mg/ day	6 weeks (min. 4 weeks)	<i>LEP</i> -2548G/A (rs7799039) <i>LEPR</i> Q223R [†] (rs1137101)	Significant interaction between the G allele of both <i>LEPR</i> and <i>LEP</i> variants and greater weight gain at higher serum concentrations (3.82 ± 3.31 kg/m ² vs 1.27 ± 1.74 kg/m ² ; p = 0.049)	[98]
Shrivastava <i>et al</i> (2008)	130(41)	North Indian, schizophrenia and schizoaffective disorder	Olanzapine	16.5 ± 3.0 mg/ day	6 weeks (3-day washout if prior AP exposure)	<i>LEP</i> (rs4731426) C/G Leptin haplotype A-C-A-A-G [‡]	G allele was associated with above average (>2.17 kg) weight gain from baseline after 6 weeks (OR: 11.43; 95% CI: 1.49–87.55; p = 0.019) This haplotype associated with above average weight gain (>2.17 kg)	[99]

[†] For *LEPR* Q223R polymorphism, G allele codes for R (arginine), A allele codes for Q (glutamine).

[‡] Haplotype A-C-A-A-G: rs10487506 A/G-rs4731426 C/G-rs2278815 A/G-rs3828942 A/G-rs17151922 G/T.

AP: Antipsychotic; min.: Minimum; OR: Odds ratio.

Table 3

Summary of longer-term (6 weeks exposure) prospective studies examining the association of leptin polymorphisms and metabolic disturbances in antipsychotic use.

Author (year)	n (% male)	Population/ diagnosis	Medications	Dose	Treatment duration	SNPs studied	Summary of results	Ref.
Templeman <i>et al.</i> (2005)	73 (75)	Spanish Caucasian, first episode psychosis	Risperidone Olanzapine Quetiapine Haloperidol Ziprasidone Amisulpride	Not available	6-week trial, then re-evaluation	<i>LEP</i> -2548G/A (rs7799039) <i>HTR2C</i> -759C/T (rs3813929)	9 months post-treatment initiation, <i>LEP</i> -2548 GG homozygotes had greater increase in BMI versus A allele carriers (5.81 ± 0.85 kg/m ² vs 3.58 ± 0.47 kg/m ² ; p = 0.033)	[100]
Zhang <i>et al.</i> (2007)	102(66)	Chinese, schizophrenia	Clozapine Other APs previously used [†]	225.4 ± 105.1 mg/day	At least 2 years on stable dose (mean 6.7 ±2.8 years)	<i>LEP</i> -2548G/A (rs7799039)	G allele carriers had a greater change in BMI than AA homozygotes (4.4 ± 3.5 kg/m ² vs 2.6 ± 3.5 kg/m ² ; p = 0.014)	[101]
Kang <i>et al.</i> (2008)	74 (68)	Korean, schizophrenia	Olanzapine	14.0 ± 5.1 mg/day	At least 3 months (453 ± 289 days)	<i>LEP</i> -2548G/A (rs7799039)	Subjects with AG genotype had more weight gain than AA genotype (8.6 ± 5.3 kg vs 4.4 ± 6.4 kg; p = 0.029) (no subjects had GG genotype)	[102]
Calarge <i>et al.</i> (2009) [‡]	74(91)	Caucasian and African-American children and adolescents (7–17 years old, ADHD (84% irritability and aggression)	Risperidone	0.03 mg/kg/day (median)	At least 6 months (median 2.6 years)	<i>LEP</i> -2548G/A (rs7799039)	A allele carriers had a higher rate of weight gain than GG after 1 year of risperidone treatment (0.56 mean z-score increase vs 0.36) and 2 years (0.78 vs 0.56) A allele also associated with higher BMI z-scores vs GG genotype after risperidone treatment	[104]
Perez-Iglesias <i>et al.</i> (2010)	205(57.5)	Caucasian (first episode, drug-naïve), schizophrenia and schizophreniform disorder	Haloperidol Olanzapine Risperidone Ziprasidone Aripiprazole Quetiapine	Not available	12 months	<i>LEP</i> -2548G/A (rs7799039) <i>LEPR</i> Q223R+ (rs1137101)	No association between either <i>LEP</i> or <i>LEPR</i> variants and change in BMI or weight gain	[103]

[†] For *LEPR* Q223R polymorphism, G allele codes for R (arginine), A allele codes for Q (glutamine).

[‡] Some patients included in this study were also taking SSRIs or 2-agonists, which can independently cause weight gain. Further analysis demonstrated that this drug did not affect the results (when controlling for use of SSRIs/ 2-agonists). Psychostimulants were also concomitantly taken, but did not appear to affect weight z-score changes over time.

ADHD: Attention deficit hyperactivity disorder; AP: Antipsychotic; SSRI: Selective serotonin-reuptake inhibitor.