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REVIEW

Role of 5-HT_{2C} receptor gene variants in antipsychotic-induced weight gain

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Tessa JM Wallace
Clement C Zai
Eva J Brandl
Daniel J Müller

Neurogenetics Section, Center for Addiction and Mental Health, Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Abstract: Antipsychotic-induced weight gain is a serious side effect of antipsychotic medication that can lead to increased morbidity, mortality, and non-compliance in patients. Numerous single nucleotide polymorphisms have been studied for association with antipsychotic-induced weight gain in an attempt to find genetic predictors of this side effect. An ability to predict this side effect could lead to personalized treatment plans for predisposed individuals, which could significantly decrease the prevalence and severity of weight gain. Variations in the serotonin receptor 2c gene (*HTR2C*) have emerged as promising candidates for prediction of antipsychotic-induced weight gain. Specifically, the well-studied −759C/T promoter polymorphism has been associated with weight gain in diverse populations, although some studies have reported no association. This discrepancy is likely due to heterogeneity in study design with respect to ethnicity, treatment duration, and other variables. Notably, the association between *HTR2C* and antipsychotic-induced weight gain appears strongest in short-term studies on patients with limited or no previous antipsychotic treatment. Other, less extensively studied promoter polymorphisms (−697C/G, −997G/A, and −1165A/G) have also emerged as potential predictors of antipsychotic-induced weight gain. Conversely, the well-studied intronic polymorphism Cys23Ser does not appear to be associated. With further research on both *HTR2C* and other genetic and environmental predictors of antipsychotic-induced weight gain, a predictive test could one day be created to screen patients and provide preventative or alternative treatment for those who are predisposed to this serious side effect.

Keywords: *HTR2C*, pharmacogenomics, promoter polymorphism

Introduction

Antipsychotics treat a variety of psychotic disorders and represent the primary treatment for schizophrenia. Among the classes of antipsychotics, most newer (atypical) antipsychotics produce fewer extrapyramidal side effects than older (typical) antipsychotics, but many are associated with weight gain that can dramatically affect patient quality of life.[1] This induced weight gain can lead to obesity, resulting in increased morbidity and mortality. Additionally, the social stigma associated with obesity further isolates patients suffering from mental illness and leads to decreased compliance with treatment.[2] The etiology of antipsychotic-induced weight gain remains largely unknown. Nonetheless, interesting findings have been obtained, for example, animal studies conducted by Kim et al,[3] implicating the histamine H_1 receptor-linked activation of hypothalamic AMP-kinase in weight gain induced by antipsychotics. Another interesting observation is that the variable propensity of patients to gain weight while on antipsychotic medication, and the concordance of atypical

Correspondence: Daniel J Müller
Pharmacogenetics Research Clinic, Neurogenetics Section, Center for Addiction and Mental Health, 250 College Street, R30, Toronto, ON, Canada M5T 1R8
Tel +1 416 535 8501 ext 6851
Fax +1 416 979 4666
Email daniel_mueller@camh.net

antipsychotic-induced weight gain in monozygotic twins and sibling pairs, suggests a strong genetic component.[4] However, the current literature suggests that antipsychotic-induced weight gain is likely to depend on a variety of both genetic and environmental factors. Thus, antipsychotic-induced weight gain is likely to represent a complex phenotype with an unknown number of implicated genes involved, each with probably small to moderate effect sizes.

The identification of genetic variants that suggest a risk for antipsychotic-induced weight gain could contribute to treatment personalization based on genetic profile. Patients found to be at high risk for antipsychotic-induced weight gain could be prescribed a medication with a lower propensity to cause weight gain or could receive preventive treatment (such as behavioral intervention or a pharmacological adjunct).[5] Identifying genetic polymorphisms associated with antipsychotic-induced weight gain could shed light on the proteins involved and allow the mechanism of antipsychotic-induced weight gain to be elucidated, potentially leading to the development of novel drug treatments. In an attempt to find such genetic predictors, many polymorphisms in biological systems associated with drug metabolism, weight regulation, and antipsychotic action have been studied for association with antipsychotic-induced weight gain over the past 15 years. In these studies, variations in the serotonin (5-HT) receptor 2c gene (*HTR2C*), located at Xq24, have thus far emerged as promising genetic findings with respect to antipsychotic-induced weight gain and with replications in independent samples. In this review, the authors will summarize those studies published until Fall 2010 and discuss limitations as well as future perspectives.

The role of 5-HT$_{2C}$ receptors in antipsychotic action and weight regulation

5-HT$_{2C}$ seems to be affected both in the mechanism of action of many antipsychotic drugs and in energy homeostasis. Atypical antipsychotics are mostly distinguished from typical antipsychotics by increased serotonin receptor antagonism[6] and they generally cause substantially more weight gain than typical antipsychotics.[7] Clozapine and olanzapine, which cause the most substantial weight gain, both strongly bind to 5-HT$_{2C}$.[8,9]

Agonists of 5-HT$_{2C}$ have been shown to decrease food intake[10] whereas antagonism of this receptor causes an increase in food intake.[11] Mice deficient in 5-HT$_{2C}$ develop hyperphagia leading to obesity.[12] Diets rich in fat have been associated with decreased *HTR2C* mRNA expression in rats;[13] in mice, hyperphagia has been associated with increased mRNA expression in the hypothalamus.[14] Additionally, it has been shown that 5-HT$_{2C}$ receptors might be involved in the anorexigenic effects of leptin.[15,16] Nonetheless, the agonist dexfenfluramine, which was withdrawn from the pharmaceutical market due to severe side effects, has been demonstrated not only to bind to 5-HT$_{2C}$ receptors but also to cause its anorexigenic effect in rodents by 5-HT$_{2B}$ activation.[17] In humans, the selective 5-HT$_{2C}$ agonist lorcaserin[18] caused significantly more weight loss than placebo during 1 year;[19] however, due to the fact that only 47.5% of the lorcaserin-treated patients lost 5% weight or more, one could argue that 5-HT$_{2C}$ modulation alone may not be sufficient to cause significant weight loss and that other regulatory systems may be highly involved in appetite and weight control as well.

Consequently, gene variants in *HTR2C* have been investigated relatively extensively in the past years, with 18 articles now published. One of the first *HTR2C* gene variants to be investigated was the coding Cys23Ser variant first characterized by Lappalainen et al.[20] This polymorphism has yielded mostly negative results. In contrast, the –759C/T has yielded many significant findings and some recent significant associations have also been reported for the –697C/G variant.

Accumulating evidence for antipsychotic-induced weight gain and –759C/T polymorphism

Overall, there is compelling evidence supporting the role of the –759C/T (dbSNP: rs3813929) polymorphism in antipsychotic-induced weight gain (see Table 1). To date, eight independent studies have found the variant T allele or variant genotype to have a protective effect against antipsychotic-induced weight gain.[21–28] However, seven other studies have found no significant association.[29–35] Despite the positive studies, the inconsistency of the results needs to be investigated in detail. The discrepancy is likely due to the heterogeneity of studies investigating the –759C/T polymorphism. In fact, two recent meta-analyses have found the –759C allele to be associated with risk of antipsychotic-induced weight gain but have also described significant heterogeneity among the ten studies each meta-analysis investigated.[36,37] Relevant variables such as treatment duration, ethnicity, and medication varied substantially among studies, as did measures of weight gain and control for covariates.

Table 1 Summary of genetic studies associating the single nucleotide polymorphism −759C/T with antipsychotic-induced weight gain

Duration	Medication (N)	N (f)	Ethnicity	History (in-/outpatient)	Measure	Main finding	Ref
4 mo	Clozapine	80 (28)	Han Chinese	Treatment resistant	> or <7% weight change	NS	33
6–14 wk (avg 11.2)	Clozapine (92), Olanzapine (21), Haloperidol (13), Risperidone (13)	139 (NR)	African-American and European ancestry	Chronic	> or <7% weight change	NS	29
6 wk	Olanzapine	42 (8)	European ancestry	NA (inpatient)	> or <5%, 7%, 10% weight change	T protective against 10% weight gain ($P = 0.0035$)	21
6 wk	Olanzapine	107 (54)	European ancestry (Polish origin)	Atypical naïve with 36 drug naïve (inpatient)	> or <7% and 10% BMI change	T protective against 10% BMI change ($P = 0.002$); still significant in 36 drug-naïve patients ($P = 0.05$)	22
6 mo	Clozapine	41 (15)	European ancestry (35), African-American (5), Hispanic (1)	Refractory	> or <7% BMI change	T protective ($P = 0.0026$); in European ancestry S alone ($P = 0.0052$)	25
6 and 10 wk	Chlorpromazine (49), Risperidone (46), Clozapine (8), Other (4)	123 (62)	Han Chinese	First episode (inpatients)	Change in BMI	Wild type (CC) with greater BMI increase at 6 ($P < 0.0001$) and 10 wk ($P < 0.0003$)	26
6 wk, 3, and 9 mo	Majority Olanzapine or Risperidone	75 (18)	European ancestry	First episode	Change in BMI	Variant protective at 6 wk, 3, and 9 mo ($P = 0.003$, 0.018, 0.031, respectively)	28
<42 d	Risperidone	123 (55)	Han Chinese	No atypical (inpatients)	Weight gain (kg) adjusted for baseline	Variant (C/T or T/T in women, T in men) protective ($P = 0.04$)	23
NA	Clozapine (44), Olanzapine (40), Risperidone (26), Other (26)	127 (47)	>95% European ancestry	Chronic (majority outpatients)	Obesity	NS	31
6 wk	Olanzapine (33), Clozapine (24), Risperidone (8), Combination (52)	128 (48)	Eastern European (8), Western European (110), Turkish (10)	Mixed (both)	> or <7% weight change	C associated with weight gain ($P = 0.04$)	24
>3 mo	Olanzapine	79 (26)	Korean	No clozapine or olanzapine treatment, majority chronic	> or <7% weight change	NS	32
8–24 wk	Olanzapine	164 (64)	Japanese	Most with previous treatment (inpatients)	% BMI change	NS	34
4 wk	Risperidone (53), Olanzapine (12), Amisulpride (5), Quetiapine (4), Typical (10)	84 (45)	Korean	Treatment free for 3 mo (inpatients)	> or <5% and 7% weight change	T less likely in 5% ($P = 0.03$) and 7% ($P = 0.048$)	27

(*Continued*)

Table 1 (*Continued*)

Duration	Medication	N (f)	Ethnicity	History (in-/outpatient)	Measure	Main finding	Ref
4 mo	Olanzapine (61), Risperidone (42)	108 (108)	Croatian	Majority antipsychotic naïve (outpatient)	> or <5% weight change	NS	30
NA	Oral: Olanzapine (31), Clozapine (21), Risperidone (16), Depot (27), Other (37), None (2)	134 (47)	NA	NA (outpatient)	Obesity and metabolic syndrome	NS	35

Abbreviations: avg, average; BMI, body mass index; d, day; f, female; mo, month; N, number of patients; NA, not available; NR, not reported; NS, not statistically significant; Ref, reference; wk, week.

The definition of weight gain

The definition of weight gain varies considerably across studies. Some studies used the amount of kilograms gained, change in body mass index (BMI), or percentage of baseline weight gained in a quantitative analysis, whereas other studies used qualitative analysis with cut-off values (eg, more than 5%, 7%, or 10% change in weight or BMI). This discrepancy in measures of weight gain is one of the factors limiting comparison among studies.

Ethnicity

Ethnicity can be a serious confounder in genetic studies, as the frequency of gene variants may vary across different populations. Furthermore, linkage disequilibrium patterns may vary across ethnicities. This latter factor is especially important if the true risk-conferring variant remains unknown and significant findings are reported for variants in linkage disequilibrium with those undetected or unknown true risk variants. Studies on −759C/T have investigated different ethnicities such as Europeans, African-Americans, and different Asian populations (Japanese, Chinese, and Korean) where the protective effect of the T allele has been found in Europeans, Chinese, and Korean samples.[21–28] European populations have been the most frequently studied and in five of seven studies a protective effect of the T allele has been found, suggesting a significant effect in this population.[21,22,24,25,28] One of the two negative studies used the phenotype obesity instead of percent weight gain as their outcome measure, possibly limiting the interpretation of their results.[31] In summary, the −759C/T polymorphism appears to be most consistently associated in European populations, with promising findings also in the less studied Asian populations (see Table 2). Overall, more research is needed to substantiate these results in Europeans and further test this association in other populations.

Antipsychotic prescribed

Most studies investigating the role of −759C/T in antipsychotic-induced weight gain have studied patients treated with olanzapine and clozapine, These two atypical antipsychotic medications are frequently studied due to their high propensity to induce weight gain.[1] Interestingly, all three studies investigating patients treated primarily with medications other than clozapine and olanzapine have also found a significant association between −759C/T and antipsychotic-induced weight gain.[23,26,27] These results suggest the T allele has a protective effect against the more moderate weight gain caused by risperidone and chlorpromazine, as well as

Table 2 Breakdown of studies investigating –759C/T based on characteristics of the patient population

Variable	Category	Statistically significant	Not statistically significant
Treatment duration	<2 mo	[21] [22] [23] [24] [26] [27] [28]	[29]
	≥2 mo	[25] [28]	[30] [32] [33] [34]
Medication	Majority high risk[a]	[21] [22] [24] [25] [28]	[29] [30] [31] [32] [33] [34] [35]
	Majority not high risk	[23] [26] [27]	NA
Ethnicity	Chinese	[23] [26]	[33]
	Korean	[27]	[32]
	Japanese	NA	[34]
	European ancestry	[21] [22] [24] [25] [28]	[30] [31]
	African ancestry mixed with European ancestry	NA	[29]
Treatment history	Atypical naïve, antipsychotic naïve, or first episode	[22] [23] [26] [28]	[30]
	Chronic/ treatment resistant	[25]	[29] [31] [33]
Environmental factors	Inpatients	[21] [22] [23] [26] [27]	[34]
	Outpatients	NA	[30] [31] [35]

Note: [a]Clozapine or olanzapine.
Abbreviations: mo, month; NA, not applicable.

against the substantial weight gain seen in clozapine- and olanzapine-treated patients (see Table 2).

Treatment duration

The most prominent difference between studies reporting a significant protective effect of the T allele and studies reporting no significant association is the duration of observed treatment-induced weight changes (see Table 2). The majority of studies investigating patients with short-term treatment (1–2 months) found that –759C/T was associated with antipsychotic-induced weight gain[21–24,26–28] while only one study with a shorter treatment duration found no significant association between –759C/T and antipsychotic-induced weight gain.[29] Conversely, of the five studies investigating patients treated for at least 2 months, only two found a significant association between *HTR2C* and antipsychotic-induced weight gain.[25,28] However, Templeman et al[28] found a protective effect of the –759T allele also at 6 weeks, as well as after 3 and 9 months; nonetheless, this study included first-episode patients where the association with the 5-HT_{2C} gene may be more pronounced as well. The study by Miller et al[25] reported a significant effect after 6 months only when using a 7% cut-off threshold and in a multiple linear regression, whereas change in kilograms and change in BMI only revealed non-significant trends.

Taken together, these results suggest that –759C/T polymorphism may exert its effect mostly on antipsychotic-induced weight gain in the short term. This may at least partially explain some of the inconsistent findings across studies.

Previous treatment

The potential confounding effects of prior antipsychotic treatment are not well characterized and are often not well controlled for; in fact, it has been suggested that the most substantial weight gain occurs in antipsychotic-naïve patients.[38] Therefore, differences in previous treatment among patient populations may partially account for the discrepancy of results among studies. Four studies in first-episode, antipsychotic-naïve, or atypical antipsychotic-naïve patients found a significant positive association between the –759C allele and antipsychotic-induced weight gain,[22,23,26,28] and only one study in mainly first-episode patients did not find such an association.[30] Of four studies done in chronic or treatment-resistant patients with a long history of previous antipsychotic treatment, only one found –759T to have a protective effect against weight gain.[25] These findings are consistent with treatment duration data showing that the –759C/T polymorphism may account for more of the variation in weight gain at the onset of antipsychotic treatment (see Table 2).

Environmental and lifestyle factors

Many other factors have the potential to affect weight regulation in patients taking antipsychotic medication. Due to logistic limitations, no studies specifically measured relevant variables such as metabolic rate, caloric intake, and exercise level of patients. Instead, studies focusing on hospital inpatients, who often have balanced diets and relatively similar activity levels, can be used to remove some of the variation due to diet and exercise. Noncompliance may also be a less significant issue in inpatients. Six studies have been conducted in inpatients with relatively similar exercise options receiving nutritionally balanced hospital meals. Five of these studies found a significant association with antipsychotic-induced weight gain[21–23,26,27] and one found no association.[34]

These results suggest that –759C/T is a stronger predictor of weight gain in patients who are less affected by heterogeneous variables such as unbalanced meals and varied exercise levels (see Table 2).

Summary for –697C/G

Two studies have investigated –697C/G (rs518147) for association with antipsychotic-induced weight gain. One study of 107 European atypical-naïve patients treated with olanzapine found the C allele to be protective against a 10% increase in BMI ($P < 0.001$), an effect that was still significant in the subgroup of 36 antipsychotic-naïve patients ($P = 0.008$). A high linkage disequilibrium (LD) was also found with –759C/T.[22] Mulder et al[31] also investigated this polymorphism for association with obesity in European antipsychotic-treated patients but they found no association with this polymorphism. Due to the initial positive result the –697C/G remains a promising candidate for further study (see Table 3).

Summary for Cys23Ser

Ten studies have investigated the role of Cys23Ser (rs6318, 68G/C) (see Table 4). Of these studies, only one found an association with antipsychotic-induced weight gain.[34] Therefore, although it is able to be assumed that factors such as lack of power to detect association findings for Cys23Ser contribute to those mainly negative findings, published studies today indicate no major impact on antipsychotic-induced weight gain of that polymorphism.

Additional polymorphisms studied

Five other polymorphisms in the *HTR2C* gene have been investigated for association with antipsychotic-induced weight gain (see Table 5). Mulder et al[31] investigated three novel polymorphisms for association with obesity in a sample of 127 primarily European atypical antipsychotic-treated patients. This study found the C allele of rs1414334 to be associated with obesity likely related to antipsychotic treatment, but found no association with –997G/A (rs3813928) or the *HTR2C*:c.1-142948(GT)n 13 repeat. Notably, –997G/A and –759C/T were found to be in complete LD, as were the repeat polymorphism c.1-142948(GT)n and –697C/G. Another study also investigated –997G/A along with –1165A/G (rs498207) for association with body weight gain in a sample of 128 European patients treated mainly with clozapine and olanzapine. This study found a marginal association among the –1165A allele ($P = 0.049$) and the –997G allele and weight gain ($P = 0.038$); it also described a high LD between the *HTR2C* polymorphisms investigated.[24] A repeat polymorphism [(GT)12–18/(CT) 4–5] was found to be in weak LD with Cys23Ser and –759C/T was not associated with weight gain in 139 African-American patients.[29] Both –997G/A and –1165A/G are promoter polymorphisms, suggesting a further role of *HTR2C* promoter variation in antipsychotic-induced weight gain.

Summary of haplotype studies

Haplotype analysis has been conducted in four studies (see Table 6). De Luca et al[29] investigated haplotypes of –759C/T, Cys23Ser, and a [(GT)12–18/(CT) 4–5] repeat polymorphism, and found the C-Ser-long haplotype to be associated with increased weight ($P = 0.042$). However, these results should be taken with caution due to the small number of patients (n = 13) with this haplotype. Gunes et al[39] investigated a haplotype of –759C/T, –697C/G, and Cys23Ser and found that patients with the C-C-Ser haplotype had a higher BMI ($P = 0.029$). They also found obese patients were more likely to have the C-G-Cys haplotype ($P = 0.015$). Opgen-Rhein et al[24] found the A-G-C haplotype of –1165A/G, –997G/A, and –759C/T to be over-represented in patients gaining more than 7% of their body weight after 6 weeks of treatment ($P = 0.0049$). Additionally, Godlewska et al[22] found haplotypes of –759C/T and –697C/G to be

Table 3 Summary of genetic studies associating the single nucleotide polymorphism –697C/G with antipsychotic-induced weight gain

Duration	Medication	N (f)	Ethnicity	History (in-/outpatient)	Measure	Main finding	Ref
NA	Clozapine (44), Olanzapine (40), Risperidone (26), Other (26)	127 (47)	>95% European ancestry	Chronic (majority outpatients)	Obesity	NS	31
6 wk	Olanzapine	107 (54)	European ancestry	Atypical naïve with 36 drug naïve, not treatment resistant (inpatient)	> or <7% and 10% BMI change	C protective against 10% BMI change ($P < 0.001$); still significant in 36 drug-naïve patients ($P = 0.008$).	22

Abbreviations: BMI, body mass index; f, female; NA, not available; NS, not statistically significant; Ref, reference; wk, week.

Table 4 Summary of genetic studies associating the single nucleotide polymorphism Cys23Ser with antipsychotic-induced weight gain

Duration	Medication	N (f)	Ethnicity	History (in-/outpatient)	Measure	Main finding	Ref
6–14 wk (avg 11.2)	Clozapine (92), Olanzapine (21), Haloperidol (13), Risperidone (13)	139 (NR)	African-American and European ancestry	Chronic	> or <7% weight change	NS	29
69.8 (±40) wk	Clozapine	152 (76)	German descent	All with previous treatment, majority treatment resistant	% change in weight	NS	49
<42 d	Risperidone	123 (55)	Han Chinese	No atypical (inpatients)	Weight gain (kg) adjusted for baseline	Minor allele not observed	23
6 wk	Clozapine (24), Olanzapine (33), Risperidone (8), Combination (52)	128 (48)	Eastern European (8), Western European (110), Turkish (10)	Mixed (both)	> or <7% weight change	NS	24
4 wk	Olanzapine (35), Risperidone (32), Amisulpride (22), Quetiapine (16), Clozapine (16), Ziprasidone (9), Other typical (50)	102 (56)	European ancestry	48% with previous treatment (inpatients)	Change in BMI	NS	50
8–24 wk	Olanzapine	164 (64)	Japanese	NA (inpatients)	% BMI change	Ser23 a risk factor in stepwise linear regression, but not associated with change in BMI	34
4 mo	Clozapine	93 (33)	Chinese	Treatment refractory	Weight change	NS	51
6 wk	Clozapine	80 (28)	European ancestry (58), African-American (22)	NA	Weight change	NS	52

Abbreviations: avg, average; BMI, body mass index; d, day; f, female; mo, month; NA, not available; NR, not reported; NS, not statistically significant; Ref, reference; wk, week.

associated with weight gain ($P = 0.001$). However, due to the different polymorphism combinations analyzed in each study, comparison is limited. Nonetheless, significant results further suggest that the *HTR2C* gene variants are associated with antipsychotic-induced weight gain and implicate a need for further studies including *HTR2C* haplotypes.

Functional studies

Some of the study results presented thus far bear the limitation that the functional relevance (eg, altered gene expression, altered protein conformation, altered mRNA stability, and so forth) of the polymorphisms remains unknown to date. Studies that investigated polymorphisms with known functional relevance should therefore be given more attention. To date, five studies have investigated the functional effects of *HTR2C* promoter variants. In two neuroblastoma cell lines, Hill and Reynolds[40] investigated haplotypes containing –997G/A, –759C/T, and –697C/G polymorphisms as well as the GT dinucleotide repeat polymorphism at –1028 varying from 11 to 21 repeats in length. They found –697C or –759T allele containing haplotypes decreased promoter activity. No effect was observed for the other two polymorphisms. Conversely, haplotypes containing either the –997A/–759T or –697C polymorphisms have been associated with increased activity.[41] Additionally, Buckland et al[42] associated the –759T and –997G alleles with increased transcriptional activity in vitro. McCarthy et al[43] found no significant difference between the major haplotype and haployptes containing –759T and –697C in humans, but they did find that haplotypes containing –759C and –697C showed a 21% decrease in activity in vitro. Two studies have also found the length of the GT repeat to have no effect on transcription rate.[42,44]

It has been hypothesized that an increased *HTR2C* transcription, leading to a more active 5-HT_{2C} system, might be protective against antipsychotic-induced weight gain, since subjects may be less sensitive to the metabolic changes caused by the medication.[45] Conversely, Hill and Reynolds[40]

Table 5 Summary of genetic studies associating other single nucleotide polymorphisms (SNPs) with antipsychotic-induced weight gain

SNP	Duration	Medication	N (f)	Ethnicity	History (in-/outpatient)	Measure	Main finding	Ref
–997G/A	NA	Clozapine (44), Olanzapine (40), Risperidone (26), Other (26)	127 (47)	>95% European ancestry	Chronic (majority outpatients)	Obesity	NS	31
–997G/A	6 wk	Olanzapine (33), Clozapine (24), Risperidone (8), Amisulpride (2), Quetiapine (2), Combination (52)	128 (48)	Eastern European (8), Western European (110), Turkish (10)	Mixed (both)	> or <than 7% weight change	Associated with weight gain in haploview ($P = 0.038$)	24
rs1414334	NA	Clozapine (44), Olanzapine (40), Risperidone (26), Other (26)	127 (47)	>95% European ancestry	Chronic (majority outpatients)	Obesity	C associated OR 2.8; 95% CI: 1.03–7.62	31
–1165 A/G	6 wk	Olanzapine (33), Clozapine (24), Risperidone (8), Amisulpride (2), Quetiapine (2), Combination (52)	128 (48)	Eastern European (8), Western European (110), Turkish (10)	Mixed (both)	> or <7% weight change	A/AA associated with weight gain ($P = 0.052$) in haploview ($P = 0.0049$)	24
[(GT)12–18/(CT) 4–5] repeat	6–14 wk (avg 11.2)	Clozapine (92), Olanzapine (21), Other (26)	139	African-American	Chronic	> or <7% weight change	NS	29
c.1-142948$(GT)_n$ (13 or 16 repeat)	NA	Clozapine (44), Olanzapine (40), Risperidone (26), Other (26)	127 (47)	>95% European ancestry	Chronic (majority outpatients)	Obesity	NS	31

Abbreviations: avg, average; CI, confidence interval; f, female; NA, not available; NS, not statistically significant; OR, odds ratio; Ref, reference; wk, week.

Table 6 Summary of genetic studies associating haplotypes with antipsychotic-induced weight gain

SNPs	Duration	Medication	N (f)	Ethnicity	History (in-/outpatient)	Measure	Main finding	Ref
–759C/T, Cys23Ser repeat	6–14 wk (avg 11.2)	Clozapine (92), Olanzapine (21), Other (26)	139 (NR)	African-American and European ancestry	Chronic	% weight change	Long-C-Ser (n = 13) increased weight ($P = 0.042$)	29
Cys23Ser, –759C/T, –697C/G	>6 mo	Olanzapine (28), Clozapine (18)	46 (20)	European ancestry	Majority with previous atypical treatment (outpatient)	BMI	Higher BMI in C-C-Ser ($P = 0.029$); C-G-Cys over-represented in obese patients ($P = 0.015$)	39
–1165 A/G, –997G/A, –759C/T	6 wk	Clozapine (24), Olanzapine (33), Risperidone (8), Amisulpride (2), Quetiapine (2), Combination (52)	128 (48)	Eastern European (8), Western European (110), Turkish (10)	Mixed (both)	> or <7% weight change	A-G-C over-represented in cases ($P = 0.0049$)	24
–759C/T, –697C/G	6 wk	Olanzapine	107 (54)	European ancestry	Atypical naïve with 36 drug naïve, not treatment resistant (inpatient)	> or <7% and 10% BMI change	Haplotypes associated with >10% change in BMI ($P = 0.001$)	22

Abbreviations: avg, average; BMI, body mass index; f, female; mo, month; NR, not reported; Ref, reference; SNP, single nucleotide polymorphism; wk, week.

suggest that the decrease in transcription they found with the −759T and −697C alleles could instead protect against antipsychotic-induced weight gain.

In 1995 Lappalainen et al[20] identified and tested the *HTR2C* Cys23Ser variant and found no significant difference in response to serotonin in *Xenopus* oocytes expressing the 23Ser allele. Fentress et al[46] also concluded that this variant had no functional effect in vitro and concluded that association findings might be caused rather by LD with another, functional relevant single nucleotide polymorphism. Conversely, Okada et al[47] observed an altered baseline activity and receptor response in vitro caused by the 23Ser variant and concluded that the polymorphism might be highly relevant for regulation of human behavior and antipsychotic-induced weight gain. In summary, it remains unclear whether the Cys23Ser variant alters the functionality of the *HTR2C* gene. Other factors such as post-transcriptional editing and splicing of *HTR2C* mRNA will also needed to be analyzed.[48] Further functional studies are required to determine potential effects of *HTR2C* variants.

Conclusions

Polymorphisms in *HTR2C* have emerged as likely contributors to antipsychotic-induced weight gain. In particular, the −759C allele has shown a positive association with antipsychotic-induced weight gain in several independent studies. The inclusion of diverse populations with varied ethnicity, prescribed medication, and previous antipsychotic exposure may explain some of the inconsistencies.[37] Notably, this association appears primarily important in the early course of weight gain and in patients with limited prior exposure to antipsychotic medication.

In addition, the promoter polymorphisms −697C/G, −997G/A, and −1165 A/G have also emerged as potential predictors of antipsychotic-induced weight gain, both in early association studies and in functional studies of promoter haplotypes. However, the relatively well-studied exonic Cys23Ser polymorphism does not appear to be associated with weight gain.

Taken together, studies in *HTR2C* polymorphisms suggest a significant association of *HTR2C* promoter polymorphisms with antipsychotic-induced weight gain. However, given the findings in the meta-analyses and the notion that antipsychotic-induced weight gain is supposedly a complex phenotype, the effect sizes of the *HTR2C* polymorphisms are rather small and on its own, *HTR2C* is unlikely to be used for predictive testing in the clinic.

Future perspectives

Personalized medicine is increasingly becoming a promising tool for the treatment of a wide range of diseases. The ability to predict treatment response using genetic and clinical variables will allow for individualization of treatment where outcome (response) can be maximized for each patient and harmful side effects can be avoided.

Antipsychotic-induced weight gain remains a concerning side effect of most atypical antipsychotic treatments due to the secondary health issues and the decreased patient compliance it causes. Currently, few reliable clinical and demographic risk factors have been established for antipsychotic-induced weight gain, but genetic studies are beginning to converge on specific genetic polymorphisms that are associated with this side effect. Polymorphisms in *HTR2C*, most notably the −759C/T polymorphism, have emerged as likely contributors to antipsychotic-induced weight gain. Promising early findings regarding the −697C/G polymorphism have also been reported. Although the −759C/T polymorphism will likely contribute to the creation of a clinical algorithm to guide antipsychotic treatment, it is unlikely that this individual polymorphism will explain enough of the variation to predict side effect profile on its own. Therefore, further research is needed to examine novel markers in the 326kb spanning *HTR2C* gene. Among others, a promising strategy will be to perform next-generation sequencing in order to assess the entire variability of this gene. Such a strategy is likely to unravel yet more variants that, although rare, may have large effect sizes. In addition, epigenetic analyses addressing DNA methylation and histone acetylation are warranted along with micro-RNA analyses and RNA editing, in order to incorporate DNA sequence-independent mechanisms impacting on the expression of the 5-HT_{2C} gene.

Further, studies investigating antipsychotic-induced weight gain should ideally be conducted using prospective designs, assessing weight as a quantitative measure (eg, changes in kilograms) corrected for initial body weight and in initial (or early) phases of antipsychotic exposure.

With this research, an algorithm incorporating multiple polymorphisms and clinical variables could in the future obtain the predictive power to determine individual patients at risk for antipsychotic-induced weight gain and allow for medication selection to avoid this devastating side effect.

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Disclosure

The authors report no conflicts of interest in this work.

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