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REVIEW ARTICLE

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Association of the *HTR2C* gene and antipsychotic induced weight gain: a meta-analysis

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Abstract

The 5-HT_{2C} receptor has been hypothesized to represent an important modulator in feeding behaviour. Evidence was based on the observation that knock-out mice for the 5-HT_{2C} receptor gene (*HTR2C*) develop obesity and that many atypical antipsychotics with potent 5-HT_{2C} antagonism may induce weight gain in susceptible individuals. Pharmacogenetic studies focusing mainly on the –759C/T promoter polymorphism (rs3813929) of the X-linked *HTR2C* gene revealed controversial results. We investigated the association of the *HTR2C* gene and weight gain using meta-analytical techniques, combining all published data while restricting our analysis to studies investigating the 759C/T. We also investigated whether ancestry (Caucasian vs. Asian) and clinical factors moderated any association. We found evidence for a slight association of –759C/T with weight gain and significance between studies for heterogeneity. Our meta-analysis provides support for the association of *HTR2C* in weight gain but indicates that firmly establishing the role of pharmacogenetics in clinical psychiatry requires much larger sample sizes that have been hitherto reported.

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Introduction

Schizophrenics differ in their outcome mainly because of different responses and side-effects to treatment, and clinicians do not have good instruments to choose the best antipsychotic for each individual. Weight gain is a frequently observed side-effect with many antipsychotic treatments and seems to be under-reported and under-recognized in many patients (Wetterling, 2001). Weight gain, glucose and lipid abnormalities are observed more frequently in some novel antipsychotics (Newcomer, 2005). Furthermore, obesity is a serious and increasing global health problem (Henderson, 2005; Yanovski et al., 2000). The relevance of this side-effect clearly arises from the following considerations: (1) a significant increase in weight gain may affect the compliance to pharmacotherapy and be indirectly responsible for psychosis relapses; (2) weight gain may add to schizophrenia stigma the stigma of obesity and this in turn may lead to poor adherence to the therapy; (3) weight gain may increase the risk for diabetes type II; (4) weight gain can be associated with the metabolic syndrome (Haddad, 2004). When looking for possible ethnic differences, clinical studies suggest that Afro-American patients treated with antipsychotics are at higher risk of weight gain (Blin and Micallef, 2001).

It is now well established that susceptibility to drug side-effects is influenced by genetic factors and over recent years significant progress has been made towards identification of specific alleles that confer risk (Basile et al., 2002b).

Association studies of functional candidate genes (i.e. involved in drug metabolism and drug mechanism of action) have revealed several promising candidates which might contribute to weight gain liability.

The 5-HT_{2C} receptor is a candidate molecule that could be involved both in the antipsychotic effect and weight gain liability as well as in the pathophysiology of schizophrenia and be relevant for the 'antipsychotic' mechanism of antipsychotics underlying

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the possibility that the two molecular mechanisms may overlap at least partially (Castensson et al., 2003, 2005).

HTR2C was first suggested as candidate susceptibility gene for antipsychotic-induced weight gain because pharmacological and behavioural studies show that the 5-HT_{2C} receptor is involved in the regulation of food intake in rodents (Vickers et al., 2003). There is also genetic evidence that *HTR2C* affects food appetite and body weight. Atypical antipsychotics have variable affinity for serotonergic receptors, in particular for receptors 2A/2C. The *HTR2C* gene is X-linked and its location makes haplotype analysis difficult because of genetic heterogeneity between male and female subjects. What is surprising, however, is that the correlation between the 5-HT_{2C} receptor and weight gain is anything but straightforward when the receptor profile of different new-generation antipsychotics are compared with each other. Ziprasidone, for instance, is an antagonist at the 5-HT_{2C} receptor, however, clinical evidence suggest little liability of ziprasidone for weight gain (Harvey and Bowie, 2005).

In the original association study of *HTR2C* and antipsychotic-induced weight gain, a functional SNP Ser23Cys (rs6318) was not significantly associated with weight gain (Hong et al., 2001), however, the Ser23 variant is very rare in the Asian population, thus this polymorphism can not be causative of weight gain in this ancestry.

Since the initial report only our group has investigated (Basile et al., 2001) this variant in antipsychotic-induced weight gain.

More recently, the –759C/T (SNP rs3813929) polymorphism in the HTR2C promoter was found to be associated with weight gain during initial exposure to antipsychotic medication (Reynolds et al., 2002, 2003).

Some negative results also emerged from other studies of this promoter polymorphism, however, these two studies were investigating the –759T variant in chronically treated schizophrenics switched to clozapine (Basile et al., 2002a; Tsai et al., 2002).

In an independent sample, Müller et al. (2003) found association between Cys23Ser but not –759C/T and weight gain in a sample of patients treated with different antipsychotics.

Analysis of a chronic treated clozapine sample from the USA (Miller et al., 2005) as well as a study in first-episode Spanish schizophrenics (Templeman et al., 2005), confirmed the protective effect of the –759T allele against weight gain, however, the same analysis in a German sample gave negative results (Theisen et al., 2004).

Finally, in a sample of patients treated with olanzapine, a protective effect of the T allele was found, applying a more stringent cut-off for the definition of weight gain (Ellingrod et al., 2005).

The aim of the present study is to combine all published data on the association of –759T/C and weight gain using a meta-analytical approach, restricting our analysis to studies investigating the most commonly reported single marker (–759T/C), which was also that most strongly associated in the original study. We also investigated whether this association differs between individuals of differing ancestry (European vs. Asian), and depends on the time of the last observation.

Methods

Inclusion criteria

Genetic association studies of the –759C/T in unrelated schizophrenics assessed for the antipsychotic-induced weight gain, were included. Investigations reporting data of any ethnic origin were included. The principal outcome measure was the allele frequency odds ratio (OR) for the –759C/T polymorphism and subjects with significant weight gain.

Search strategy

The search was performed using the National Library of Medicine's PubMed online search engine. This database was searched up to June 2006, using the search terms 'weight gain', '5-HT2C', 'HTR2C'.

Data extraction

For each study, the following data were extracted using standard forms: author, year of publication, sample ethnicity, case and control sample size, allele frequency, mean age, sex ratio and also percentage of patients treated with clozapine. Ethnicity was coded as European, Asian and African-American.

Statistics

ORs and their standard error (S.E.) for individual studies were calculated from 2×2 tables in a case-control format. Pooled ORs were calculated using fixed-effects and random-effects approaches (DerSimonian and Laird, 1986), and the significance of the pooled ORs determined using a Z test. The assumption that the effect of allele frequency is constant across studies and between-studies variation is due to random variation was checked using a χ^2 test for heterogeneity of ORs.

Table 1. Characteristics of included sample

Study	*n*	Ancestry	Method
Reynolds et al. (2002)	123	Asian	>7% BMI (kg/m²)
Tsai et al. (2002)	80	Asian	>7% BMI (kg/m²)
Basile et al. (2002a)	73	Caucasian, African-American	>7% weight (kg)
Müller et al. (2003)	59	Caucasian, African-American, Hispanic[a]	>7% weight (kg)
Theisen et al. (2004)	97	Caucasian	>7% BMI (kg/m²)
Templeman et al. (2005)	73	Caucasian	>7% BMI (kg/m²)
Miller et al. (2005)	41	Caucasian, African-American, Hispanic	>7% BMI (kg/m²)
Ellingrod et al. (2005)	42	Caucasian	>10% weight (kg)

BMI, Body mass index.
[a] In this sample there are also four Asian Pacific and two American Indian.

In absence of significant heterogeneity, data were initially analysed within a fixed-effects framework, otherwise a random-effects framework was employed using DerSimonian and Laird methods (DerSimonian and Laird, 1986). This assumes that between-study variation is due to both random variation and an individual study effect. Random-effects models are more conservative and generate a wider confidence interval.

Meta-regression analysis was conducted to assess any moderating effects of ancestry (Asian vs. non-Asian), age, gender ratio, year of publication, % of clozapine treated.

The ORs of Reynolds et al. (2002) were compared to the pooled ORs of the remaining seven studies (sensitivity analysis) using the regression Z test as there is evidence for a greater estimate of effect size in the first published study (Trikalinos et al., 2004).

Publication bias was assessed by means of a funnel plot of individual study log OR against S.E. log OR, and formally by the method of Egger (Egger et al., 1997), which is based on a weighted linear regression of standard normal deviation of the OR (standardized effect) on the inverse of the standard error of the OR (precision). Data were analysed using the STATA version 8.0 statistical software package (StataCorp., College Station, TX, USA).

Results

A total of 10 studies published between 2002 and 2005, comprising nine independent samples, were identified by the search strategy, met the inclusion criteria and contributed to the meta-analysis. Each sample was included independently in the analysis. One study that did not utilize –759C/T was excluded. Two studies from our group were included and one study that did not report the allele frequencies was excluded. Two studies reported data on participants of Asian ancestry, three on participants of European ancestry and three of mixed European/African ancestry (Table 1). Three studies were using the cut-off of 7% body weight change, four were using the cut-off of 7% body mass index (BMI) change, one was using 10% body weight change and two used only continuous measures with no cut-off. In four studies dichotomous outcome data were inferred from percentages reported in the study tables. For the two samples from our group we applied the cut-off of 7% body weight change.

When all samples ($n=8$) were included there was evidence for association of –759T and lower weight gain under a fixed model ($z=3.62$, $p=0.000$, OR 2.278, 95% CI 1.459–3.558), however, there was evidence of significant heterogeneity between the studies ($\chi^2=18.73$, d.f.$=7$, $p=0.009$). When the analysis was re-run within a random-effects framework the evidence for association had threshold significance ($z=1.91$, $p=0.056$, OR 2.292, 95% CI 0.979–5.361) (Figure 1).

The proportion of Caucasian subjects was incorporated in the meta-regression to estimate that effect of this ethnicity on the effect size of each study (Table 2), however, the regression model was not significant ($p=0.993$). The effect of Asian and African ancestry was also non-significant ($p=0.564$ and $p=0.284$ respectively). Demographic variables such age and gender did not influence the weight gain ($p=0.555$ and $p=0.689$ respectively). Percentage of first-episode patients was not a confounding factor ($p=0.393$), however, the percentage of clozapine-treated

Table 2. Predictive effect of study covariates on the study effect size

Covariates	Coeff.[a]	S.E.	*z*	*p* value	95% CI
Age	−0.291	0.493	−0.590	0.555	−1.258 to 0.676
Asian[b]	4.561	7.909	0.580	0.564	−10.941 to 20.062
AfricanAmerican[b]	−18.035	16.836	−1.070	0.284	−51.033 to 14.963
Caucasian[b]	0.073	8.408	0.010	0.993	−16.406 to 16.552
Gender[b]	−0.134	0.334	−0.400	0.689	−0.788 to 0.521
Clozapine[b]	−9.913	6.166	−1.610	0.108	−21.997 to 2.171
Year	1.364	2.582	0.530	0.597	−3.698 to 6.425
First episode[c]	6.512	7.629	0.850	0.393	−8.441 to 21.465
End-point time	−0.296	0.563	−0.530	0.599	−1.399 to 0.808
7% BMI cut-off[c]	−0.130	7.220	−0.020	0.986	−14.281 to 14.020

BMI, Body mass index.
[a] Positive coefficients indicate that the single covariate included in the meta regression model was associated with higher OR; negative coefficients indicate that the single covariate was associated with lower OR.
[b] Scored as proportion of ancestry, male or clozapine treated.
[c] Scored as 0, absent; 1, present.

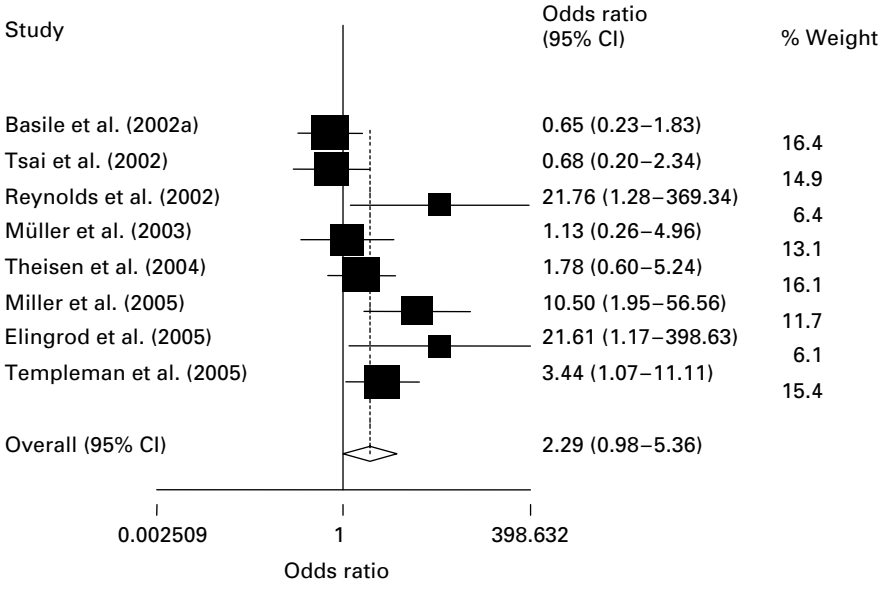

Figure 1. Forest plot of studies assessing the effect of T variant for lower weight gain: overall genotype effect for dichotomous outcomes (random-effects model). Odds ratio (OR) > 1 in favour T effect in lower weight gain; OR < 1 against T effect in lower weight gain. Meta-analysis of eight studies of allele T protection against weight gain summarized in Table 1, based on random-effects modelling of OR (size of squares reflecting approximate weighting by sample size and variance measures), with a pooled OR and its CI (diamond). Two studies did not find lower weight gain with allele T. The pooled risk ratio (vertical dotted line) is 2.29 (95% CI 2.32–3.53) which is slightly significantly ($p = 0.056$) greater than the null 1.0 (vertical line).

patients showed a tendency towards lower OR ($z = -1.61$, $p = 0.108$). Study design variables such as end-point time and cut-off criteria appeared not to influence the outcome ($p = 0.599$ and $p = 0.986$ respectively). The year of publication was also analysed as a covariate and did not have any significant effect on the obtained OR ($p = 0.597$).

When the first published sample (Reynolds et al., 2002) was removed from the analysis there was still evidence for the association of T allele and lower

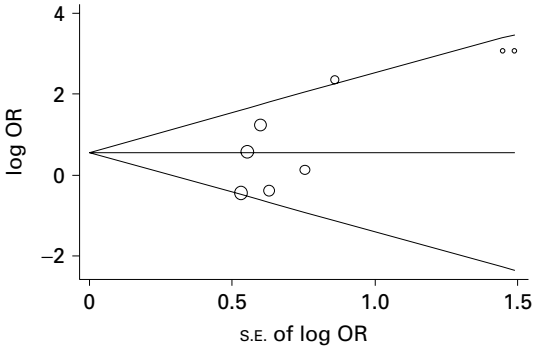

Figure 2. Begg's funnel plot of publication bias with pseudo 95% confidence limits. Size graph of studies by weight.

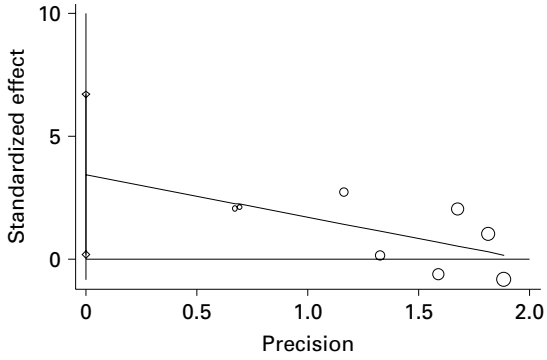

Figure 3. Egger's publication bias plot. The slope of the regression line indicates a presence of bias with small samples with low precision having a large standardized effect and large samples with high precision having small standardized effect.

weight gain ($z=2.68$, $p=0.007$, OR 1.881, 95% CI 1.184–2.988) with significant between-study heterogeneity ($\chi^2=14.83$, 6 d.f., $p=0.022$). However, when the remaining studies were re-run under a random-effects model there was no longer evidence for association ($z=1.57$, $p=0.116$, OR 1.920, 95% CI 0.851–4.332). The difference in OR of the first published study and the pooled ORs of the remaining samples was significant for both fixed-effects models ($z=3.11$, $p=0.002$) and random-effects models ($z=2.30$, $p=0.021$).

A Begg's funnel plot with 95% confidence limits is presented in Figure 2. This illustrates a certain asymmetry with predominance of small and positive studies over small and negative studies. Egger's test also indicated evidence of publication bias (intercept=3.449, $t=2.60$, $p=0.041$, 95% CI 0.197–6.700), as the 95% CI of the regression line of standardized effect on the precision of the OR did not encompass the origin (Figure 3).

Discussion

Since the –759T variant was first tested as susceptibility gene for weight gain in 2002, several studies have investigated the association between this gene and weight gain. A recent review article of *HTR2C* and pharmacogenetics concluded that this gene is strongly implicated in antipsychotic-induced weight gain (Reynolds et al., 2005), however, our meta-analysis of 588 subjects reporting data on –759T supports the existence of an association between this individual marker and the side-effect only under a fixed model.

Weight gain is probably the most actual side-effect in antipsychotic treatment due to the wide use of new antipsychotics, on the other hand the pharmacogenetics of antipsychotics has focused more on side-effects like tardive dyskinesia (Lerer et al., 2005), therefore we were able to find only a few studies exploring weight gain.

Our meta-analysis also observed significant heterogeneity between studies and there are many variables that could account for the observed between-study heterogeneity in the meta-analysis of –759T. The fact that the meta-regression including the ratio of different ancestries is not significant suggests that population stratification is not the explanation for this heterogeneity. In terms of clinical confounders, we found that the protective effect of the T allele might be less relevant when the weight gain is induced by clozapine suggesting that the molecular mechanism of weight gain with this antipsychotic could be different from other compounds. Clozapine is an antipsychotic with high weight gain, and the patients included in this meta-analysis are mainly clozapine-treated patients. Clozapine also has a unique pharmacodynamic profile with strong D_4 blocking (Ashby and Wang, 1996). We therefore speculate about the possible interaction between *HTR2C* and *DRD4* genes in conferring susceptibility to weight gain, in fact genetic variation in *DRD4* can be implicated in the reward associated with food intake (Levitan et al., 2004).

Regarding the differences in drug treatment we have indicated only the antipsychotic used for the treatment, and schizophrenics are usually treated with more than one psychotropic, however, it is very difficult to extract this kind of information about other drugs in the treatment that could have an effect on 5-HT_{2C}. Therefore, future studies should take in account the comprehensive medication history

of the patients assessed for weight gain. Egger's test was statistically significant, and it should be noted that it is a relatively conservative test, suggesting that publication bias is truly present. Various types of publication bias may arise during publication of the primary studies (Naylor, 1997), in fact when we compared the effect size of the original study with that of the remaining studies we found a significant difference. There was also evidence of significant publication bias with a relative excess of positive studies and a paucity of small negative studies. Taken together these findings are indeed the most likely explanation of the observed heterogeneity between studies.

Meta-analysis techniques require the combination of comparable data, which was only possible for the eight studies included, however, due to the use of disparate definitions of significant weight gain across studies the heterogeneity was high in this meta-analysis even though study design factors were not significant in our meta-regression.

The meta-analytical technique we employed to re-analyse outcome data systematically excluded studies without data suitable for re-analysis. The fact that some studies did not include any measure of deviation (i.e. S.E.M. or S.D.) forced us to analyse weight gain as a binary variable with a different cut-off, increasing the heterogeneity and losing part of the information; however, we gave priority to the sample size rather than the homogeneity because the major weakness of weight gain studies is their very limited power. Furthermore, since weight gain is measured as a continuous trait in nature, in future studies the actual variance in samples should always be provided to allow testing of the heterogeneity of variances in order to fully take into account the trait variation within single studies.

It should be noted that, although a robust variable, weight gain requires follow-up and a time of observation that makes it difficult to register changes in large samples, in fact one of the most important differences of the studies included in the calculation was the time of the last observation carried out. These difficulties are the reason why the studies available have a small sample size and are underpowered to uncover the genetic effect on this phenotype. This meta-analysis has tried to override this limitation by pooling eight different samples and achieving a sample size in excess of 500 subjects.

The previous reviews of the pharmacogenetics of weight gain (Basile et al., 2001; Collier, 2003; Correll and Malhotra, 2004; Müller et al., 2004; Wilffert et al., 2005) showed how heterogeneous is the selection of functional candidate genes in this field, however, the –759T/C seems to be the major focus of many pharmacogenetic investigations allowing us to apply the meta-analytical technique. Although there are also other psychodrugs like agomelatine that have a strong *HTR2C* blocking effect with no weight gain, *HTR2C* blocking is a necessary pharmacological property to induce weight gain, although not enough to cause on its own this side-effect. This evidence should encourage gene–gene interaction aimed at detecting different receptor genes that can be in epistasis with *HTR2C*. In fact, a major limitation of *HTR2C* association studies of weight gain is that there are no studies that have considered this receptor in interaction with other genes, therefore the epistasis between *HTR2C* and other genes cannot be ruled out.

HTR2C remains one of the most interesting candidate genes in weight gain despite the fact that under a random-effects model this meta-analysis lost significance, and it should be borne in mind that *HTR2C* spanned more than 300 kb with a diverse range of transcripts in the brain and periphery and that any variants might conceivably influence the susceptibility to weight gain.

This meta-analysis argues in favour of the possibility that –759T is associated with lower weight-gain risk during antipsychotic treatment, however the effect size of this combined sample is still small compared to the investigations of other psychiatric phenotypes, therefore we cannot advise that the 5-HT_{2C} receptor should be avoided as a target in future drug discovery research, until further studies exclude or confirm the effect of this gene on antipsychotic-induced weight gain.

Furthermore, future studies should report possibly both BMI and weight change as outcome measures to overcome certain limitations of the literature and we strongly suggest that continuous data (mean $\pm$ S.D.) should be reported for both genotype groups (C or T) and that the binary outcome (i.e. weight gain vs. non-weight gain) should be analysed adopting the 7% BMI change as the standard cut-off to facilitate the meta-analysis.

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Statement of Interest

None.

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