Original Investigation

Influence of *CRTC1* Polymorphisms on Body Mass Index and Fat Mass in Psychiatric Patients and the General Adult Population

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IMPORTANCE There is a high prevalence of obesity in psychiatric patients, possibly leading to metabolic complications and reducing life expectancy. The CREB-regulated transcription coactivator 1 (*CRTC1*) gene is involved in energy balance and obesity in animal models, but its role in human obesity is unknown.

OBJECTIVE To determine whether polymorphisms within the *CRTC1* gene are associated with adiposity markers in psychiatric patients and the general population.

DESIGN, SETTING, AND PARTICIPANTS Retrospective and prospective data analysis and population-based samples at Lausanne and Geneva university hospitals in Switzerland and a private clinic in Lausanne, Switzerland. The effect of 3 *CRTC1* polymorphisms on body mass index (BMI) and/or fat mass was investigated in a discovery cohort of psychiatric outpatients taking weight gain–inducing psychotropic drugs (sample 1, n = 152). The *CRTC1* variant that was significantly associated with BMI and survived Bonferroni corrections for multiple comparison was then replicated in 2 independent psychiatric samples (sample 2, n = 174 and sample 3, n = 118) and 2 white population-based samples (sample 4, n = 5338 and sample 5, n = 123 865).

INTERVENTION Noninterventional studies.

MAIN OUTCOME AND MEASURE Difference in BMI and/or fat mass between *CRTC1* genotype groups.

RESULTS Among the *CRTC1* variants tested in the first psychiatric sample, only rs3746266A>G was associated with BMI ($P_{adjusted}$ = .003). In the 3 psychiatric samples, carriers of the rs3746266 G allele had a lower BMI than noncarriers (AA genotype) (sample 1, P = .001; sample 2, P = .05; and sample 3, P = .0003). In the combined analysis, excluding patients taking other weight gain–inducing drugs, G allele carriers (n = 98) had a 1.81-kg/m^2 lower BMI than noncarriers (n = 226; P < .0001). The strongest association was observed in women younger than 45 years, with a 3.87-kg/m^2 lower BMI in G allele carriers (n = 25) compared with noncarriers (n = 48; P < .0001), explaining 9% of BMI variance. In the population-based samples, the T allele of rs6510997C>T (a proxy of the rs3746266 G allele; r^2 = 0.7) was associated with lower BMI (sample 5, n = 123 865; P = .01) and fat mass (sample 4, n = 5338; P = .03). The strongest association with fat mass was observed in premenopausal women (n = 1192; P = .02).

CONCLUSIONS AND RELEVANCE These findings suggest that *CRTC1* contributes to the genetics of human obesity in psychiatric patients and the general population. Identification of high-risk subjects could contribute to a better individualization of the pharmacological treatment in psychiatry.

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A high prevalence of obesity has been described in psychiatric patients, with reported increased mortality,[1-3] due not only to the underlying illness and related comorbidities, but also to the pharmacological treatment.[4-8] Atypical antipsychotics and other drugs, such as the mood stabilizers lithium and valproate,[9-12] can induce substantial weight gain in selected patients. This is a serious adverse effect considering that obesity can lead to metabolic complications such as dyslipidemia, type 2 diabetes, and cardiovascular disease, which may ultimately reduce life expectancy by several years.[13-15]

Psychiatric, psychological, sociodemographic, and behavioral factors, as well as heritability, have been shown to influence individual susceptibility to overweight or obesity, both in the general population[16-20] and in psychiatric patients before and after treatment with potentially weight gain-inducing psychotropic drugs.[21-26] Genome-wide association studies conducted to date only explain a small fraction of body mass index (BMI) heritability[20] and more obesity susceptibility genes remain to be discovered. Whereas genome-wide association study meta-analyses have been extremely valuable, other approaches are also needed to further understand the biology of human obesity.

Obesity results from an imbalance between energy intake and energy expenditure. One component of energy balance is the control of food intake that is achieved at least in part via highly specialized neurons located in the hypothalamus and modulated by peripheral metabolic signals.[27,28] Recent research has begun to unravel some of the neuronal pathways regulating food intake, but the exact mechanisms by which peripheral signals are sensed in the hypothalamus and how these signals are then integrated and translated into a coordinated peripheral response are still unclear. We and others have recently shown that mice lacking the CREB-regulated transcription coactivator 1 (*CRTC1*) gene eat more and have less energy expenditure than wild-type mice, thus developing an obese feature, including obesity-related metabolic complications, under normal diets.[29,30] These results suggest that CRTC1 is playing a major role in the hypothalamic control of food intake. The CRTC family (also called TORCs) comprises 3 members, CRTC1, CRTC2, and CRTC3, that are expressed in different tissues.[31] CRTC1 is mainly expressed in the brain[29-33] where it may modulate leptin anorexic effect in the hypothalamus. In the cell, the inactive phosphorylated form of CRTC1 is sequestered in the cytoplasm, and its migration to the nucleus requires the concomitant activation of the phosphatase calcineurin and the inactivation of kinases of the 5′ adenosine monophosphate-activated protein kinase (AMPK) family.[34] Interestingly, antipsychotics may increase weight by selective and potent stimulation of hypothalamic AMPK,[35] which has been shown to regulate food intake and reverse the actions of the anorexigenic hormone leptin.[36] AMPK stimulation parallels the orexigenic actions of the drugs, with clozapine and olanzapine producing the most marked effects. The obese phenotype of *CRTC1*-deficient mice, the regulation of CRTC1 activity by AMPK, the hypothalamic activation of this kinase by antipsychotics, and the high prevalence of obesity in psychiatric patients prompted us to examine the role of the *CRTC1* gene in human obesity especially in the psychiatric population.

Methods

Psychiatric Samples

Written informed consent was given by all subjects or their legal representatives. The studies were approved by the ethics committee of their corresponding institutions. White subjects treated with antipsychotics and/or mood stabilizers were first recruited from outpatient psychiatric centers of Geneva University Hospital. The association of the *CRTC1* variant with BMI (calculated as weight in kilograms divided by height in meters squared) was then replicated in 2 independent samples from Lausanne University Hospital.

Samples 1 and 3

Samples 1 (n = 152) and 3 (n = 118) are 2 retrospective studies; study of sample 1 was conducted in outpatient psychiatric centers of Geneva University Hospital from 2006 to 2008, while study of sample 3 was conducted in 2 outpatient psychiatric centers of Lausanne, Switzerland (Lausanne University Hospital and a private psychiatric center), from 2010 to 2011. Treatment for more than 3 months (sample 1) and 9 months (sample 3) with clozapine, olanzapine, quetiapine, risperidone, lithium, and/or valproate (sample 1 and sample 3) and/or aripiprazole, amisulpride, and/or sertindole (sample 3) were indicated as inclusion criteria. Seventy-two percent and 52% of sample 1 and sample 3, respectively, had already received other psychotropic treatments before the current treatment. At inclusion of both samples, body weight and height were measured for all patients, while their baseline weight before the initiation of the current treatment and/or at different times during treatment was collected from the medical file or was self-reported (baseline weight was self-reported in 76% of sample 1 and 78% of sample 3). In the subset of patients for whom both data were available, self-reported weight was in agreement with weight obtained from the medical files (n = 29; r^2>0.9 for sample 1 and n = 39; r^2>0.8 for sample 3). In addition to the baseline and measured weight at inclusion, 54% and 29% of patients in sample 1 and sample 3, respectively, had at least 1 additional recorded weight from the medical files during the study duration that was also included in the statistical analysis. Finally, self-reported weights before the initiation of the first psychotropic treatment were also obtained for most of the patients (98% and 95% for sample 1 and sample 3, respectively). Both samples consisted of a single visit performed during the usual clinical psychiatric follow-up. If the patient was taking more than 1 psychotropic medication, the medication with the longest treatment duration was entered in the model and the other potential weight gain-inducing drugs of interest, including typical and atypical antipsychotics and mood stabilizers, were classified as other possible weight gain-inducing drugs, listed in eTable 1 in Supplement.

Sample 2

A follow-up study has been ongoing since 2007 in all psychiatric wards of Lausanne University Hospital. One hundred seventy-four patients with newly prescribed aripiprazole, amisulpride, clozapine, olanzapine, quetiapine, risperidone,

sertindole, and/or lithium or valproate were recruited. Sixty-six percent had already received other psychotropic treatments and were included in the study after having switched medication. No washout period was required. Weights and clinical variables were prospectively recorded at several points during the first 12 months according to published recommended monitoring guidelines (ie, before starting the current psychotropic drugs, then at months 1, 2, 3, 6, 9, and 12).[37,38] At the baseline and follow-up visits, the severity of disorders was rated using the Clinical Global Impression rating scale, which is a commonly used measure of psychotic symptom severity.[39] This scale measured the severity of the disorder at each visit relative to the baseline state at the introduction of the newly studied psychotropic drug, rather than the onset of the disorder. For statistical analyses, patients were dichotomized according to this scale into moderately to severely ill vs mildly ill or not ill at all. If the patient was taking more than 1 psychotropic medication, the newly introduced studied drug was considered as the main psychotropic medication, and the other potential weight gain–inducing drugs of interest, including typical and atypical antipsychotics and mood stabilizers, were classified as other possible weight gain–inducing drugs.

Population-Based Sample (Cohorte Lausannoise)

Participants in the population-based sample (Cohorte Lausannoise [CoLaus]) were recruited between June 2003 and May 2006, as previously described.[40]

Genetic Investigation of Anthropometric Traits Consortium

The Genetic Investigation of Anthropometric Traits (GIANT) consortium performed a meta-analysis of genome-wide association study data with a discovery set of 123 865 individuals of European ancestry from 46 studies for height,[41] BMI,[20] and waist to hip ratio.[42]

Genotyping and *CRTC1* Polymorphisms

To our knowledge, no functional consequences of *CRTC1* genetic polymorphisms have been reported in humans until now. Three *CRTC1* single-nucleotide polymorphisms (SNPs) were selected in the psychiatric sample based on high frequencies of the minor allele in their respective regions in white individuals: rs10402536G>A in intron 1, rs8104411C>T in the 3′ untranslated region (because the CRTC N- and C-terminal domains were reported to contain CREB binding and transactivation domains),[31] and a third coding SNP (rs3746266A>G) that leads to threonine to alanine substitution at position 328 (Thr328Ala). The rs3746266A>G SNP, which was significantly associated with BMI in psychiatric patients, was not genotyped in the population-based samples. However, among the *CRTC1* SNPs genotyped in the latter samples, the intronic SNP rs6510997C>T was found to be an adequate proxy (r^2 = 0.7; D′ = 1) of rs3746266A>G. In a second step, the psychiatric samples were genotyped for the proxy rs6510997C>T as well.

Psychiatric patients' genotyping was performed using TaqMan allelic discrimination assay (Applied Biosystems). Genotyping for the CoLaus subjects was performed using the Affymetrix GeneChip Human Mapping 500K array set and we used the Agilent SureSelect protocol for exome capture and the Illumina Genome Analyzer 2 platform for sequencing (details are available in the eMethods at http://www.chuv.ch/psychiatrie/dpc_home/dpc_infos/dpc_infos_organisation/dpc-cpn/dpc_cnp_upcc_eng.htm).

Statistical Analysis

Psychiatric Sample

Univariate analyses were done using *t* tests. The association of the 3 *CRTC1* SNPs with BMI in the first sample was assessed by fitting a generalized additive mixed model (GAMM)[43,44] to allow a smooth trend for the response in time based on multiple observations for each patient (using a thin plate regression spline basis) adjusting for age, sex, smoking status, current psychotropic drug, and standardized dose. The *P* values of these 3 models were adjusted for multiple comparisons according to Bonferroni. Similar models were applied to test the association between *CRTC1* rs3746266A>G (chosen according to the analysis in sample 1) and BMI in samples 2 and 3. A random effect at the subject level was also introduced to take the dependence structure of observed data into account. The GAMMs were fitted using the mgcv package of R (settings were fixed at package defaults); to be more conservative, the uncertainty of estimated parameters was assessed by 1000 bootstraps[45] at the subject level and results were similar with those gained by 10 000 bootstraps. Whenever the *P* value for the 1000 bootstrap analysis was lower than .001 ($P < .001$), 10 000 bootstrap analysis was performed. To preserve homogeneity of the combined sample, only patients in samples 1 and 3 with less than 24 months of the current psychotropic treatment were taken into account. Because of the small number of individuals homozygous for the rs3746266 G allele (n = 6, n = 10, and n = 4 for samples 1 (n = 152), 2 (n = 174), and 3 (n = 118), respectively), the associations were analyzed using a dominant model.

The model is fitted on all observations of patients, so model coefficients provide information on both the direction and magnitude of the overall association between BMI and the genotypes for the specific period of treatment studied. The psychotropic drugs were classified according to their therapeutic class (antipsychotics vs mood stabilizers).[46]

Population-Based Studies

The associations of *CRTC1* rs6510997C>T with adiposity markers such as BMI, weight, waist circumference, and fat mass were analyzed using multiple linear regression with allele dosage (additive mode of action of the T allele) in which potential confounding factors such as age, sex, and smoking status were added as covariates in the CoLaus study, while BMI was the only marker analyzed in GIANT. We calculated the explained variance of fat mass in CoLaus by comparing R^2 from a reduced linear regression model, ie, a model including all covariates except rs6510997C>T, with R^2 from a full model including all covariates and rs6510997C>T.

All tests were 2-sided and a *P* value ≤.05 was considered statistically significant. All the analyses were performed using Stata version 11 (StataCorp) and R version 2.11.1 software.[47] Power analysis was conducted using Quanto software ver-

Table 1. Associations Between *CRTC1* rs3746266 in a Dominant Model and BMI Over Time in the 3 Separate Psychiatric Samples and the Combined Sample[a]

rs3746266A>G	Sample Size	BMI Difference Between G and AA Carriers (95% CI)	*P* Value	Explained Variance,[b] %
Sample 1	105	2.13 (0.62 to 3.49)	.001	3.5
Sample 2[c]	140	1.00 (−0.29 to 2.16)	.05	1.0
Sample 3[c]	87	3.64 (1.65 to 5.38)	.0003[d]	6.5
Combined sample[e]	324	1.81 (1.00 to 2.64)	<.0001[d]	2.6
Men	176	1.34 (0.35 to 2.40)	.007	1.7
Women	148	2.14 (0.82 to 3.46)	.001	2.8
Women ≥45 y	75	1.24 (−0.56 to 3.09)	.10	1.3
Women <45 y	73	3.87 (1.98 to 5.76)	<.0001[d]	8.7
Women <50 y	107	2.44 (0.98 to 4.02)	.0005[d]	4.1
Women <55 y	120	2.20 (0.78 to 3.69)	.002	3.3

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Results were obtained by fitting generalized additive mixed models for patients with no other weight gain–inducing drugs (other than the studied psychotropic drug), controlling for age, sex (whenever appropriate), smoking status, current psychotropic drug, and standardized doses.

[b] Explained variance by the polymorphism percentage.

[c] Two missing data.

[d] Ten thousand bootstraps were used for this analysis.

[e] To have similar treatment duration, only patients treated for up to 24 months were included.

sion 1.2.4 (2009; James Gauderman, PhD, University of Southern California, Los Angeles).

Results

eTable 2 in Supplement shows characteristics of the 444 psychiatric patients and 5338 participants of the CoLaus study. Obesity prevalence was higher in the psychiatric samples as compared with the CoLaus sample and findings derived from other general Swiss populations[40,48,49] particularly in psychiatric samples 1 and 3, which have longer treatment durations and higher median age.

CRTC1 Polymorphisms and Psychiatric Samples

For the psychiatric sample 1, the influence of 3 polymorphisms within the *CRTC1* gene on BMI was investigated by fitting a GAMM separately for each polymorphism: rs10402536G>A (β = 0.025; $P_{adjusted}$ = .872), rs8104411C>T (β = 0.133; $P_{adjusted}$ = .814), and rs3746266A>G (β = −2.125; $P_{adjusted}$ = .003). The *CRTC1* polymorphism rs3746266A>G was associated with BMI and this polymorphism was used for replication in psychiatric samples 2 and 3. eTable 3 in Supplement shows genotype frequencies in the individual psychiatric samples and the combined sample.

To eliminate any possible cause of weight gain induced by other concomitant psychotropic and nonpsychotropic medications, we first analyzed patients taking only the main psychotropic drugs with no other weight gain–inducing drugs listed in eTable 1 in Supplement. A total of 336 psychiatric patients were thus investigated. The median BMI at the beginning of the current psychotropic treatment was significantly lower for carriers of the rs3746266 G allele as compared with those with AA genotypes in samples 1 (*P* = .03) and 3 (*P* = .003), but not in sample 2 (*P* = .51), as well as in the combined sample (*P* = .0009) (eTable 4 in Supplement). The same associations were observed with the current BMI at the end of the study follow-up period (eTable 4 in Supplement). eFigure 1 in Supplement shows the BMI at different periods for carriers of the *CRTC1* rs3746266A>G genotype in the psychiatric samples. However, no significant association was observed between *CRTC1* rs3746266A>G genotype and BMI before the initiation of the first psychotropic treatment in samples 1 (n = 83; *P* = .43) and 3 (n = 83; *P* = .53) and by combining them (n = 166; *P* = .46) (eTable 4 in Supplement).

The GAMM analyses showed a significant association between *CRTC1* rs3746266A>G and BMI, with G carriers having a 2.13-kg/m^2 lower BMI than those with the AA genotype in sample 1 (*P* = .001; n = 105) (**Table 1**). Similar significant results were found in sample 3 (*P* = .0003; n = 87) and in the combined sample (*P* < .0001; n = 324) and were borderline for sample 2 (*P* = .05; n = 140), with carriers of the G allele having a 3.64-, 1.81-, and 1.00-kg/m^2 lower BMI as compared with carriers of the AA genotype, respectively (Table 1). Interestingly, after adjustment for the severity of the psychiatric disorder in sample 2 (the severity rating was only available in this sample), we observed an even stronger association between BMI and *CRTC1* rs3746266A>G, with G allele carriers having a 1.5-kg/m^2 lower BMI than carriers of the AA genotype (*P* = .02; 95% CI, 0.12-2.87).

A stratified sex analysis in the combined psychiatric sample (n = 176 and n = 148 for men and women, respectively) showed a significant association of *CRTC1* rs3746266A>G in both sexes with, however, the association being stronger in women (Table 1). Because of the difference in fat distribution and cardiovascular risk factors in women with age, additional analyses showed the strongest protective effect of the G allele in women younger than 45 years, with a BMI decrease of 3.87 kg/m^2 for the G allele carriers (n = 25) compared with carriers with AA genotypes (n = 48; *P* < .0001), while no significant association was found in women older than 45 years (n = 75; *P* = .10). Similar significant results were obtained when using a threshold of 50 and 55 years (Table 1).

The influence of the other weight gain–inducing drugs along with the main psychotropic drugs was also analyzed in the whole sample (n = 444) and BMI remained significantly associated with the *CRTC1* rs3746266A>G genotype in the GAMM model (eTable 5 in Supplement).

eTable 6 in Supplement shows the association of the calculated percentage of fat mass with the rs3746266A>G genotype in the combined psychiatric sample, with the strongest effect observed in women younger than 45 years. Thus, in these women, the polymorphism explains 9% and 10% of the variance in BMI and calculated percentage of fat mass, respectively (Table 1 and eTable 6 in Supplement).

Nongenetic factors were also found to be associated with BMI in the GAMM model. Indeed, age (0.09-kg/m^2 increase in BMI per year of age; $P < .0001$) and the type of psychotropic medication (1.41-kg/m^2 higher BMI in patients receiving antipsychotics compared with mood stabilizers; $P = .003$) were associated with BMI in the combined psychiatric sample. These 2 factors were consistently associated with BMI in each of the psychiatric samples and in analyses stratified by sex. A positive association of BMI with the severity of the disorder was observed for sample 2 as well, in which moderately to severely ill patients had a 0.50-kg/m^2 lower BMI than less severely ill patients ($P = .02$), which could be explained by lower food intake in the severely ill patients during the follow-up visits. Interestingly, by adding physical activity to the GAMM model, nearly a 2-kg/m^2 lower BMI was noticed for patients doing more than 60 minutes of physical activity per day compared with lower levels of physical activities. These results were consistent in the separate and combined psychiatric samples (data not shown).

Data regarding appetite and physical activity were available at different points in the prospective study (sample 2) and at the inclusion time for samples 1 and 3. No significant association was found between these 2 variables and *CRTC1* rs3746266A>G. More details are presented in the eMethods.

CRTC1 Polymorphisms in the General Adult Population

The rs6510997C>T SNP was used as a proxy of rs3746266A>G in the general adult population. By analyzing the rs6510997C>T SNP in the psychiatric samples, we found the same association with BMI as for rs3746266A>G, confirming that the former SNP can be used as a proxy of the latter (eTable 7 in Supplement). We also looked up the rs6510997C>T variant in the GIANT consortium (n = 123 807 individuals)[20] and found a strong direction-consistent association with BMI. Each copy of the T allele decreased BMI by 0.02 SD unit ($P = .01$).

Table 2 shows the adjusted fat mass values by *CRTC1* rs6510997C>T in the CoLaus study. The values decreased from 21.84 kg (SE, 0.11) to 21.48 kg (SE, 0.16) to 21.21 kg (SE, 0.47) in carriers of the CC, CT, and TT genotypes (n = 5338; $P = .03$), respectively. After stratification by sex, no significant association of this SNP with fat mass was observed in women (n = 2808; $P = .07$) or men (n = 2530; $P = .23$). However, rs6510997C>T was associated with fat mass in premenopausal women (n = 1192; $P = .02$) but not postmenopausal women (n = 1616; $P = .66$). Interestingly, the association of rs6510997C>T with fat mass was stronger in premenopausal women taking oral contraception (n = 224; $P = .02$), in whom it explained 1.34% of fat mass variance, and was not significant in premenopausal women who did not take oral contraceptives, despite a larger sample size (n = 968; $P = .12$). We observed no clear effect of postmenopausal hormonal therapy on the reported associations.

There was no significant association of rs6510997C>T with BMI ($P = .68$), weight ($P = .76$), or waist circumference ($P = .60$) in the overall CoLaus sample, neither in men ($P > .50$) nor women ($P > .50$).

Using exome-sequencing data available for a subset (n = 413) of the CoLaus individuals (eMethods), we identified 8 rare, possibly damaging missense variants in the *CRTC1* gene, according to predictions by PolyPhen.[50] Only 1 individual was homozygous for the minor allele at position 18 853 754 (National Center for Biotechnology Information build 37), and his sex- and age-corrected BMI was 38.0. Thus, rare BMI-increasing *CRTC1* variants with large effect may exist.

Discussion

Our results suggest a role for the *CRTC1* gene in the regulation of human body weight and fat mass, which is consistent with data from animal models.[29,30] The *CRTC1* nonsynonymous polymorphism rs3746266A>G was associated with BMI in 3 independent psychiatric samples in which lower BMI values were measured in carriers of the G allele compared with noncarriers. The sex-stratified analysis in the combined sample showed a protective effect for the G allele both in men and women. However, the strongest and most clinically relevant association was observed in women younger than 45 years, for whom carriers of the G allele had a 3.87-kg/m^2 lower BMI than noncarriers. Additionally, we calculated the percentage of fat mass using a formula based not only on BMI, but also on age and sex, 2 factors that have profound impact on fat mass. The calculated fat mass was found to be significantly associated with *CRTC1* rs3746266A>G in the psychiatric samples, with direction-consistent results. Furthermore, the protective effect of the T allele of rs6510997C>T (a proxy of rs3746266A>G) against fat accumulation was also observed in a large population-based sample (CoLaus). The effect size of this association is clinically relevant and in a consistent direction with the one observed in the psychiatric cohorts. This effect was essentially seen in premenopausal women and, more specifically, in women taking contraceptive pills. Finally, these results were confirmed in 123 807 individuals from the GIANT consortium, with the T allele being associated with lower BMI.

We found no association of rs6510997C>T with BMI in the CoLaus population-based sample. Body mass index may less accurately capture adiposity than estimated fat mass using bioimpedance.[51,52] In CoLaus, fat mass enabled capture of 3 times more subjects with high cardiovascular risk than BMI.[52] The CoLaus sample is better powered to detect an association of the rs6510997C>T SNP with fat mass (62% power for a variant explaining 0.06% of fat mass variance) than with BMI (11% and 18% power for a variant explaining 0.01% and 0.02% of BMI variance, respectively), whereas a 20-fold larger population-

Table 2. Association of rs6510997C>T With Body Fat Mass in the CoLaus General Adult Sample Study[a]

Sample	Fat Mass, kg, Adjusted Mean (SE)	Sample Size	*P* Value for Linear Trend	Explained Variance,[b] %
CoLaus				
CC	21.84 (0.11)	3395		
CT	21.48 (0.16)	1744		
TT	21.21 (0.47)	199	.03	0.06
Men only				
CC	19.92 (0.14)	1614		
CT	19.81 (0.19)	814		
TT	19.08 (0.55)	102	.23	0.03
Women only				
CC	23.57 (0.17)	1781		
CT	22.99 (0.24)	930		
TT	23.08 (0.75)	97	.07	0.08
Women, premenopausal				
CC	20.83 (0.26)	767		
CT	20.00 (0.36)	389		
TT	18.90 (1.18)	36	.02	0.33
Women, postmenopausal				
CC	25.57 (0.24)	1014		
CT	25.21 (0.32)	541		
TT	25.98 (0.96)	61	.66	0.01
Women, premenopausal, no contraceptive pill				
CC	20.73 (0.29)	626		
CT	20.09 (0.41)	314		
TT	19.29 (1.37)	28	.12	0.18
Women, premenopausal, with contraceptive pill				
CC	21.29 (0.55)	141		
CT	19.50 (0.75)	75		
TT	17.87 (2.30)	8	.02	1.34
No drug				
CC	19.38 (0.16)	1357		
CT	19.08 (0.22)	710		
TT	19.00 (0.63)	88	.26	0.05
Any drug				
CC	23.51 (0.15)	2038		
CT	23.07 (0.22)	1034		
TT	22.75 (0.66)	111	.06	0.07
Drugs possibly increasing weight[c]				
CC	23.87 (0.28)	630		
CT	23.13 (0.38)	348		
TT	22.29 (1.15)	38	.06	0.24
Other drugs				
CC	23.32 (0.18)	1408		
CT	23.09 (0.26)	686		
TT	23.16 (0.80)	73	.52	0.01

[a] Data are fat mass (in kilograms) adjusted for age, sex (whenever appropriate), height, lean mass, and smoking.

[b] Explained variance by the polymorphism percentage.

[c] Drugs are listed in eTable 1 in Supplement.

based sample used in the GIANT consortium has enough power to observe an association with BMI (94% and >99% power for a variant explaining 0.01% and 0.02% of BMI variance, respectively). Taken together, these observations suggest that psychiatric illness and/or potentially weight gain-inducing psychotropic drugs might play a role in genetically mediated energy homeostasis and that the association of CRTC1 variants with BMI in the general population is much weaker.

The stronger association found in women compared with men could be caused by a differential role of the leptin-mediating satiety pathway in the enhancement of CRTC1 activity. Women have much higher leptin levels than men,[53] and

female sex was found to predict stronger weight gain during antipsychotic treatment.[54] Interestingly, studies examining the influence of polymorphisms in the leptin or leptin receptor genes on weight increases induced by antipsychotics also showed sex-specific differences.[55,56] CRTC1 transgenic animal models did not show sex differences in body weight or obesity.[29,30] However, mice used in these studies were knockout for *CRTC1*, while the present polymorphism is associated with decreased BMI and/or fat mass, suggesting a possible gain of function that could interact with leptin and show differences between males and females. The difference found between women in the 2 age groups, with the protective effect of the minor allele (rs3746266 G or rs6510997 T) being attenuated with age, suggests a complex mechanism with potential interactions with gonadal sex hormones. Interestingly, although the sample size was small, women taking oral contraceptives appear to be more protected against fat accumulation when carrying the minor allele of rs6510997C>T than the other premenopausal women. Thus, estrogen levels appear to modulate the effect of the *CRTC1* polymorphism on fat accumulation. A hypothetical mechanism of the effect of CRTC1 and its interaction with sex hormones is presented in eFigure 2 in Supplement. A recent meta-analysis of genome-wide association studies reported an association of an intronic SNP of *CRTC1* (rs10423674A>C) with the age of menarche,[57] supporting a potential interaction between sex hormones and CRTC1.

Because most of the patients had a long history of psychiatric illness, they were not drug naive, having previously received and experienced weight gain due to multiple treatments before the current one, a high prevalence of overweight and obesity was visible at the initiation of the current treatment. Thus, BMI at the beginning of the current treatment was already different between *CRTC1* genotypes, with the G carriers showing lower BMI. However, no significant influence of *CRTC1* genotypes was observed on BMI before the initiation of the first psychotropic treatment in samples 1 and 3. This suggests that weight gain induced by the psychotropic treatment contributes at least partially to the strong influence of *CRTC1* genotypes on BMI in psychiatric patients. Interestingly, a recent study showed an influence of a *CRTC3* polymorphism on BMI only in a population with a high prevalence of obesity. CRTC3 is mainly expressed in adipose tissue and has been shown to be involved in energy balance in mice.[58] Higher energy expenditure and less adipose tissue mass were observed in *CRTC3*-knockout mice compared with their littermates, leading to lower weight gain under a hypercaloric diet. The *CRTC3* rs8033595 polymorphism was associated with several anthropometric indices in 2 Mexican American populations (n = 779 and n = 987), with a high prevalence of obesity, but this finding could not be replicated in populations with other ethnicities with lower prevalence of obesity.[58]

Several limitations of this study need to be acknowledged. Most patients were not drug naive and had already developed weight gain due to previous treatments. It was therefore not possible to determine with certainty whether the strong association of *CRTC1* genotypes with BMI and fat mass in psychiatric populations was due to the psychiatric illness and/or to the pharmacological treatment. Extensive hormonal measurements were not available for our samples, so the role of sex hormones on the association of *CRTC1* variants with adiposity could not be explored. Baseline self-reported weights before the current treatment were only available in a subset of the patients. It was only considered when measured weight was not available, though in the patients for whom both data were available, a strong correlation was found between self-declarations and the medical files. Weights before the first psychotropic treatment were only self-reported. In addition, the potential influence of other environmental and social factors on weight could not be accounted for because of the naturalistic design of the psychiatric studies. However, the fact that the results were replicated in 2 independent psychiatric samples and in 2 large population-based samples strengthens the validity of our data. This study included white people and results cannot be generalized to other ethnic groups. Finally, these results do not allow the determination of whether the rs3746266A>G genetic polymorphism, although leading to an amino acid change, is the causative variant or merely a proxy of 1 or more yet unidentified variants. Further studies are needed to elucidate the biochemical mechanisms underlying the observed associations.

To our knowledge, this is the first study showing an association of *CRTC1* polymorphisms with BMI and fat mass in humans. Our results suggest that *CRTC1* plays an important role in the high prevalence of overweight and obesity observed in psychiatric patients. Besides, *CRTC1* could play a role in the genetics of obesity in the general population, thereby increasing our understanding of the multiple mechanisms influencing obesity. Finally, the strong associations of *CRTC1* variants with adiposity in women younger than 45 years support further research on the interrelationship between adiposity and the reproductive function.

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