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Brief report

"Diminished" association between the serotonin transporter linked polymorphism (*5HTTLPR*) and body mass index in a large psychiatric sample

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ABSTRACT

Background: The role of the promoter polymorphism (5HTTLPR) of the serotonin transporter gene (SLC6A4) in psychiatric illnesses has been studied extensively. Serotonergic function also regulates many central nervous system, including appetite and feeding behaviors. The 5HTTLPR short allele was found to be associated with increased body mass index and obesity risk among the general population. No data is available to support generalizability of such association among psychiatric population.
Methods: We examined the relationship between BMI and the 5HTTLPR genotype in a large sample of 1831 psychiatric patients at Mayo Clinic, Rochester, Minnesota, using a retrospective chart review.
Results: Average BMI among groups with the short/short (28.29 ± 7.27 kg/m^2), the short/long (28.07 ± 6.45 kg/m^2) and the long/long (28.15 ± 7.51 kg/m^2) genotypes of 5HTTLPR were not statistically different. This negative association persisted even with the sub-analysis of the Caucasians. However, we observed an increased rate of obesity among our psychiatric patient sample compared to the general population of Minnesota (36.6% versus 27.6%, $p=0.0001$ for males, 30.3% versus 24.4%, $p=0.0001$ for females). Also, sub-analysis showed female inpatients to have a significantly higher average BMI than outpatients (28.64 ± 8.08 kg/m^2 versus 27.13 ± 6.92 kg/m^2, $p=0.026$). This confirmed a significant association between mental health disorder and BMI.
Limitations: Retrospective study design with limited control for potential confounders.
Conclusions: In this large sample of psychiatric patients we found no significant association between 5HTTLPR genotype and BMI, which is different from the case with general population reported in the literature.

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1. Introduction

Comorbidity of a metabolic condition such as diabetes mellitus (DM) and a psychiatric condition such as depression is very common. Endocrinological mechanisms are likely involved in this process of comorbidity. One important measurement related to endocrinological conditions is body mass index (BMI), and higher BMI is associated with risk for DM. Studies have also found associations between mental disorders and higher BMI (Scott et al., 2008). Serotonergic function also regulates many central nervous system, including appetite, feeding behaviors and energy balance (Tecott, 2007).

To understand the biological mechanism of this comorbidity, investigating the genetic disposition for risk of medical and mental illness is important. The role of the promoter polymorphism (5HTTLPR) of the serotonin transporter gene (SLC6A4) has been studied in numerous psychiatric illnesses (Serretti et al., 2006), and also with several medical conditions. In particular, compared to the long allele (l) of the 5HTTLPR, the short allele (s) was found to be associated with increased BMI and obesity risk among the general population (Fuemmeler et al., 2008, Sookoian et al., 2007, 2008).

However, recently our group showed that among a psychiatric population, it is not always patients with the short allele who show heightened "reactivity", but rather those with the long/long

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(Shinozaki et al., 2012). This may indicate that the role of genetic disposition can vary largely depending on the condition of the population; i.e. general healthy population versus psychiatric patients. This suggests that, although the serotonin pathway is an important biological aspect for both depression and metabolic conditions, it is not yet well known how it affects metabolic functions of humans such as BMI.

Thus, it is important to investigate whether the association between 5HTTLPR and BMI reported among the general population can be generalized to psychiatric patients. We hypothesized that psychiatric patients with the short allele of 5HTTLPR would show higher BMI compared to those with the long/long genotype as in the case for general population. If proven not to be the case, it will suggest the importance of further investigation about the variable role of 5HTTLPR depending on the state of specific populations.

Therefore, we sought to test the relationship between BMI and 5HTTLPR in psychiatric patients at Mayo Clinic, Rochester, Minnesota, and also compared with statistics from the Centers for Disease Control and Prevention (CDC) for the general population in Minnesota. Additionally, we speculated that when stratified by psychiatric hospitalization status, those who were inpatients would have a higher average BMI than those who were outpatients at the time of genotyping. We compared a subset of subjects to test the difference between inpatients and outpatients on the measure of BMI.

2. Participants and methods

2.1. Participants

All of the investigations performed in this study were approved by the Mayo Foundation Institutional Review Board. A retrospective electronic medical record review identified 1831 psychiatric patients at Mayo Clinic ages 18–90 (average age 44.8 ± 14.9) who received psychiatric care at Mayo Clinic between 2006 and 2011 and whose medical records contained 5HTTLPR genotype. As the primary reason for genotype testing in the psychiatric population is to serve medication selection for patients who have difficulty tolerating or responding to antidepressant medications, the majority of patients have a diagnosis of a depressive disorder.

2.2. Data acquisition

The query tool "Data Discovery and Query Builder (DDQB)" was used to identify and collect the clinical data (Alsara et al., 2011). Genotyping was performed as a part of clinical laboratory testing during psychiatric inpatient care or an outpatient visit. Height and weight were recorded in the electronic medical record, and the BMI was calculated from those values, using the following formula: BMI=Weight (kg)/Height^2 (m^2). In order to capture the potential association between BMI and psychiatric condition, BMI values closest to the time of genotype testing and psychiatric evaluation were used. The average interval between genotyping and BMI measurement was 51.1 days. In the inpatient setting, BMI was recorded at time of admission.

2.3. Data analysis

Associations between the 5HTTLPR genotype and BMI were analyzed by ANOVA. Fisher's exact test was used to compare subgroups (obese, overweight, and normal/less than normal) in psychiatric patients' BMI data against the CDC data for the 2010 general Minnesota population. Lastly, the BMI values between inpatients and outpatients from our psychiatric patients were compared by *t*-test.

3. Results

Among 1831 subjects (mean age 44.8 ± 14.9 years), 1195 were female (65.3%). Of the 1784 subjects with known ethnicity information on record, 1624 were Caucasian (91.0%). Among 933 with known status of treatment setting, 716 (76.7%) were inpatients. The distribution of 5HTTLPR genotypes for the 1831 psychiatric patients was as follows: 317 patients were s/s homozygotes (17.3%), 907 patients were s/l heterozygotes (49.5%), and 607 patients were l/l homozygotes (33.2%). Hardy-Weinberg equilibrium was computed as $X^2=0.48$, and was not significant. The genotype distributions did not differ as a function of age, gender, ethnicity, inpatient versus outpatient status, or obese versus non-obese patients.

There was no significant effect of the 5HTTLPR genotype on BMI. Average BMI among patients with the s/s genotype (28.29 ± 7.27 kg/m^2), the s/l genotype (28.07 ± 6.45 kg/m^2) and the l/l genotype (28.15 ± 7.51 kg/m^2) were not statistically different [F(5.8,48.5)=0.12, $p=0.89$]. To avoid potential ethnic stratification, 1624 Caucasian subgroup was analyzed separately, and there was no statistical difference [F(30.6,48.5)=0.63, $p=0.53$]. (Table 1).

In comparison with the 2010 CDC data for the general population of Minnesota, the rate of obesity in the study population is significantly higher in both male (36.6% versus 27.6%, $p=0.0001$) and female (30.3% versus 24.4%, $p=0.0001$) psychiatric patients. However, among females, the percentage of those in the overweight group is significantly lower in our psychiatric patients than the general population (female 25.0% versus 31.6%, $p=0.0018$), although no such difference was observed among males (Table 2).

(http://apps.nccd.cdc.gov/BRFSS/sex.asp?cat=OB&yr=2010&qkey=4409&state=MN)

To explore whether treatment status was associated with average BMI differences, we identified 933 patients with known current treatment status (inpatients versus outpatients). When stratifying the psychiatric patients into these groups, it was noted that female inpatients ($N=495$) had a significantly higher average BMI than outpatients ($N=150$) (28.64 ± 8.08 kg/m^2 versus 27.13 ± 6.92 kg/m^2, two-tailed $t(283.07)=2.24$, $p=0.026$). However, no such difference was found in male patients.

Table 1
5HTTLPR genotype and BMI among 1831 total and 1624 Caucasian patients.

5HTTLPR	Total group		Caucasian only	
	N (%)	BMI (kg/m^2)	N (%)	BMI (kg/m^2)
s/s	317 (17.3)	28.29 ± 7.27	269 (16.6)	28.56 ± 7.37
s/l	907 (49.5)	28.07 ± 6.45	813 (50.1)	28.01 ± 6.41
l/l	607 (33.2)	28.15 ± 7.51	542 (33.4)	28.16 ± 7.54
ANOVA	[F(5.8,48.5)=0.12, $p=0.89$]		[F(30.6,48.5)=0.63, $p=0.53$]	