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Short Communication

# Association of a serotonin transporter gene (*SLC6A4*) 5-HTTLPR polymorphism with body mass index categories but not type 2 diabetes mellitus in Mexicans

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## Abstract

The serotonergic system has been hypothesized to contribute to the biological susceptibility to type 2 diabetes mellitus (T2DM) and body-mass index (BMI) categories. We investigate a possible association of 5-HTTLPR polymorphism (L and S alleles) in the promoter region of the serotonin transporter gene (*SLC6A4*) with the development of T2DM and/or higher BMI by analyzing a sample of 138 individuals diagnosed with T2DM and 172 unrelated controls from the Mexican general population. In the total sample genotypes were distributed according to Hardy-Weinberg equilibrium, and S allele frequency was 0.58. There was no statistical association between 5-HTTLPR polymorphism and the development of T2DM in this Mexican population sample (p = 0.12). Nevertheless, logistic regression analysis of the L allele and increased BMI disclosed an association, after adjusting for age, sex and T2DM (p = 0.02, OR 1.74, 95% CI: 1.079-2.808).

*Key words: SLC6A4* gene, 5-HTTLPR polymorphism, type 2 diabetes mellitus, body mass index.

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Over the last three decades, the rates of overweight, obesity, and type 2 diabetes mellitus (T2DM) have increased worldwide (Ogden *et al.*, 2006; Fuemmeler *et al.*, 2009;). Specifically, and with a rising prevalence of 10.6%, Mexico is among the top 10 countries with the highest number of diabetic individuals (6.1 million) (Rull *et al.*, 2005; Gonzalez-Villalpando *et al.*, 2010) where it has also been reported that the combined prevalence of overweight and obesity is 63% among Mexicans (Arroyo *et al.*, 2000; Fernald *et al.*, 2004). Obesity and T2DM frequently co-occur, indicating that these conditions share common pathological mechanisms, including complex interactions between genetic and environmental factors (Knowler *et al.*, 1993). In the search for genetic factors that confer susceptibility to obesity and T2DM, several candidate genes have been identified (Prokopenko *et al.*, 2008; Yang *et al.*, 2007). Due to their function in the brain and gastrointestinal tract, genes of the serotonergic system are included among these. Serotonin (5-hydroxytryptamine or 5-HT) is involved in the regulation of energy balance through central modulation of the activity of various downstream neuropeptide systems, as well as autonomic pathways (Iordanidou *et al.*, 2010). Some functional effects of 5-HT include mood control, urine storage, voiding, sleep regulation, body temperature, circadian functions, feeding behavior, body weight, and intestinal motility (Lesch *et al.*, 1996; Ni and Watts, 2006; Sookoian *et al.*, 2008). It is well established that 5-HT activity is regulated by the 5-HT transporter (5-HTT), whose functions include 5-HT re-uptake in

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serotonergic nerve terminals, thereby determining the magnitude and duration of postsynaptic response to 5-HT, and signaling quantity (Lesch and Mossner, 1998).

The human 5-HTT is encoded by the serotonin transporter gene (*SLC6A4*) on chromosome 17, at 17q11.2-17q12 (Lesch *et al.*, 1996). Located at 1,400 bp upstream of the transcription start site of the gene, a functional polymorphism has been described, the *SLC6A4*-linked polymorphic region or 5-HTTLPR (Collier *et al.*, 1996; Heils *et al.*, 1996). This consists of two common alleles, *i.e.*, a short (S) variant with 14 copies, and a long (L) variant with 16 copies of a 44 bp repeat element (Lesch *et al.*, 1996; Kraft *et al.*, 2005). The S allele (SS or SL genotypes) is associated with lower *SLC6A4* expression, thereby resulting in reduced 5-HT reuptake and release capability, whereas the L variant is associated with an almost threefold increase in gene transcription (Iordanidou *et al.*, 2010). Association studies of 5-HTTLPR with glucose metabolism, changes in the body-mass index (BMI) and T2DM are relatively recent. In a longitudinal study of Japanese women, analysis of the association of *SLC6A4* polymorphism with fasting blood glucose (FBG) levels indicated that the SS genotype plays a protective role, thereby improving FBG values (Yamakawa *et al.*, 2005). Meanwhile, in one of the largest cohorts studied to date, involving, 1,584 unrelated individuals, a subsample of the US National Longitudinal Study of Adolescent Health, Fuemmeler *et al.* (2008) found that SS and SL 5-HTTLPR genotypes are significantly associated with a higher BMI, for men overall, and for Hispanic men and those of European ancestry, specifically. This association was further confirmed in South American population samples of adolescents and adults of European ancestry, in which the S allele was found to be a risk factor (Sookoian *et al.*, 2007, 2008). So far, in only one study has reported the S allele as a risk factor for T2DM, in a Caucasian population from Greece, interestingly, the presence of the S allele was not found to be associated with increased BMI values (Iordanidou *et al.*, 2010).

The aim of the present study was to investigate whether there was an association of the 5-HTTLPR polymorphism of the *SLC6A4* gene with T2DM or BMI (as a measure of obesity) in a Mexican population sample.

A total of 138 unrelated subjects diagnosed with T2DM (42 males and 96 females) and 172 unrelated controls (48 males and 124 females) from Mexican general population were studied. All individuals were recruited at the Hospital "Secretaria de Salud, Hospital General de Reynosa, Dr. Jose Maria Cantu Garza" Tamaulipas, Mexico. Inclusion of subjects in the diabetic group was based on medical diagnosis, according to the criteria recommended by the WHO for T2DM (Deckers *et al.*, 2006). Subjects with either diagnosis or a first-degree family history of type T2DM were excluded from the control sample. BMI was calculated as the ratio between weight and the square of the height (kg/m2). Subjects were also divided into overweight/obese (BMI > 25) and non-obese (BMI < 25) groups. The study protocol for human experimentation was previously approved by the local ethics committee (PROMEP/103.5/08/3243). Informed consent was obtained from each subject before participation in the study.

Genomic DNA was isolated from peripheral blood for genotyping, according to Gustincich *et al.* (1991). Polymerase Chain Reaction (PCR) for 5-HTTLPR polymorphism genotyping was performed as previously described Cook *et al.* (1997),with minor modifications. The forward primer used was HTTp2A, 5'-TGAATGCCAGCACCTAACCC-3', and the reverse primer HTTp2B, 5'-TTCTGGTGCCACCTAGACGC-3'. The final amplicon product consisted of 406/450-bp fragments (S and L alleles, respectively). PCR was carried out in a total volume of 25 μL containing 200 μM of each dNTP (dATP, dCTP, and dTTP), 100 μM of dGTP and 7-deaza-dGTP, 1 unit of *Taq* polymerase (High Fidelity; Invitrogen), 1.5 mM of MgSO4, 5% DMSO, and 10 mM of Tris-HCl. Amplification was carried out in a Thermal Cycler C1000 System through 40 cycles consisting of 30 s at 95 °C, 30 s at 61 °C, and 1 min at 71 °C, followed by 10 min at 72 °C. PCR products were separated by electrophoresis on a 6% polyacrylamide gel at 120 V for 3 h. Bands were visualized using a silver nitrate staining protocol. Subjects were classified into three genotypes: individuals homozygous for the short allele SS, those heterozygous for the short and long allele LS, and those homozygous for the long allele LL.

Data are shown as means and ± standard deviation (SD). Deviation from Hardy-Weinberg equilibrium was confirmed by $X^2$–test analysis of genotype distribution. The association between 5-HTTLPR and T2DM|BMI, as an obesity|overweight measure, was defined by logistic-regression analysis, assuming an additive model. Considering gender, age and T2DM as the appropriate covariates, associations were adjusted accordingly. The odds ratios (ORs) with 95% confidence intervals (CIs) are presented in the tables with respect to the risk allele. A $P$ value of 0.05 was considered significant. Statistical analysis was performed using PLINK version 1.07 (Purcell *et al.*, 2007), and SPSS version 17.0 (SPSS, Chicago, IL, USA). Quanto Software version 1.2.4 (Gauderman and Morrison, 2006) was used for calculating the power of the sample. On considering 10.6% diabetes prevalence among Mexican individuals (Rull *et al.*, 2005), a frequency of 42% for the analyzed polymorphism and an additive genetic model, allowed to estimate that the sample size of the present study had an 80% power at an alpha of 0.05 to detect an effect size of 1.6.

Gender distribution among the 310 participants was 71% females and 29% males. According to the WHO criteria for diagnosis, 138 individuals had T2DM (44.5%), whereas 172 were non-diabetic (55.5%). The distribution of BMI, according to WHO classification and differences

between subgroups, are shown in Table 1. Genotype distribution of the *SLC6A4* gene among the analyzed groups is shown in Table 2. 5-HTLPR polymorphism was found to be in Hardy-Weinberg equilibrium in the total sample (p = 0.24). Although logistic regression analysis indicated no statistically significant association of the 5-HTTLPR polymorphism with T2DM (p = 0.17), BMI was shown to be a discrete predictor of T2DM in the Mexican population (Table 3). This same association was found when BMI was analyzed as a continuous variable under the linear regression model (p = 0.03, 1.874 [0.1336-3.615]). The L allele was associated with overweight/obesity BMI values by logistic regression analysis (p = 0.02; 1.74 [1.079-2.808]) (Table 4), independent of age, gender or T2DM.

The high prevalence and increasing number of Mexicans suffering from obesity and T2DM represent a huge burden on healthcare (Mier *et al.*, 2008; Gonzalez-Villalpando *et al.*, 2010), whence the prime importance of identifying risk factors for susceptibility to these conditions. The Mexican population we investigated showed a statistical difference in age distribution between the diabetic and non-diabetic groups, as expected, since T2DM is a chronic condition increasing in prevalence, as the population ages. As previously shown (Iordanidou *et al.*, 2010), our analysis confirmed BMI as a discrete predictor of T2DM. Although described in Caucasians (Iordanidou *et al.*, 2010), in the present Mexican population sample, no association between 5-HTTLPR polymorphism of the *SLC6A4* gene and T2DM was detected. Nonetheless, frequency of the previ-

**Table 3** - Logistic regression analysis of the association between T2DM and the L allele of the *SLC6A4* 5-HTTLPR polymorphism.

| Covariates | OR | 95% CI | p |
|---|---|---|---|
| L allele | 0.7375 | (0.5022-1.083) | 0.12 |
| Age | 1.062 | (1.041-1.084) | < 0.001* |
| Gender | 0.8936 | (0.5094-1.568) | 0.69 |
| BMI(kg/m$^2$) | 1.048 | (1.008-1.09) | 0.01* |

Model Adjusted by Age, Sex and BMI.
* = Statistically significant.

**Table 4** - Logistic regression analysis of the association between overweight and the L allele of the *SLC6A4* 5-HTTLPR polymorphism.

| Covariates | OR | 95% CI | p |
|---|---|---|---|
| L allele | 1.74 | (1.079-2.808) | 0.02* |
| Age | 1.012 | (0.9924-1.032) | 0.23 |
| Gender | 1.292 | (0.6948-2.404) | 0.41 |
| T2DM | 2.415 | (1.284-4.543) | 0.006* |

Model Adjusted by Age, Sex and T2DM.
* = Statistically significant.

**Table 1** - Characteristics of the analyzed groups.

| Phenotypes | Non-diabetic group n = 172 | Diabetic group n = 138 | p | BMI < 25 n = 69 | BMI > 25n = 217 | p* |
|---|---|---|---|---|---|---|
| Age (Years) | 45 ± 16.5 | 54 ± 10.8 | < 0.001* | 46 ± 17.36 | 50.40 ± 13.55 | 0.05 |
| Gender (M/F) | 48 (28%)/124 (72%) | 42 (30%)/96 (70%) | | 21 (30%)/48 (70%) | 60 (27%)/157 (73%) | |
| Presence of T2DM | | | | 31% | 52% | |
| BMI > 25 | 69% | 84% | | | | |
| Body weight (kg) | 70.06 ± 16.40 | 74.87 ± 16.13 | 0.003* | 56.74 ± 8.25 | 77.89 ± 14.33 | < 0.001* |
| BMI (kg/m$^2$) | 26.92 ± 10.2 | 28.6 ± 6.8 | 0.06 | 22.63 ± 1.7 | 31.12 ± 4.6 | < 0.001* |

Values are mean ± SD.
* = Statistically significant.

**Table 2** - Genotype and allele frequencies of the *SLC6A4* 5-HTTLPR polymorphism in the analyzed groups.

| 5-HTTLPR polymorphism | Phenotypes | | | | | |
|---|---|---|---|---|---|---|
| | Non-Diabetic Group | Diabetic Group | Total | BMI < 25 | BMI > 25 | Total |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Genotypes | | | | | | |
| LL | 33 (20) | 16 (12) | 49 (16) | 7 (11) | 37 (18) | 44 (16) |
| LS | 88 (51) | 74 (53) | 162 (52) | 35 (50) | 118 (54) | 153 (53) |
| SS | 51 (29) | 48 (35) | 99 (32) | 27 (39) | 62 (28) | 89 (31) |
| Alleles | | | | | | |
| L | 154 (45) | 106 (39) | 260 (42) | 49 (36) | 192 (45) | 241 (42) |
| S | 190 (55) | 170 (61) | 360 (58) | 89 (64) | 242 (55) | 331 (58) |

ously reported T2DM risk allele S was higher. Increased frequencies of the S allele have already been reported in Native American, Japanese, Chinese and Korean populations the highest frequencies, even reaching 80% (Goldman *et al.*, 2010). On analyzing BMI values, with adjustment of age, gender and T2DM as covariates, the role of T2DM as a predictor of obesity was clearly shown (Table 4). While Yamakawa *et al.* (2005) reported that the S allele was protective, as regards FBS levels, our results showed a direct association of the L allele with increased BMI, independent of age, gender or T2DM. These results differ from those reported by Sookoian *et al.* (2007, 2008), showing the S allele to be a risk factor for higher BMI among adolescent and adult men from Argentina, as is also shown by Fuemmeler *et al.* (2008) in Caucasian and Hispanic adolescents from the U.S.A. Nonetheless, all these studies are in agreement by pointing out that *SLC6A4* polymorphism is associated with BMI, and ethnicity may be a contributing factor towards the differences between our study and previous reports. From a functional perspective and through *in vitro* studies, it is assumed that the L allele is associated with relatively increased *SLC6A4* transcription, thereby resulting in increased transporter levels and more rapid 5-HT uptake (Lesch *et al.*, 1996; Greenberg *et al.*, 1999), whence the inference that there may be a reduction in extracellular serotonin among LL homozygous carriers (Glenn, 2011). In contrast to the L allele, it has been shown that the S allele is associated with lower transcriptional activity and reduced 5-HT reuptake efficiency (Heils *et al.*, 1996). Hence, it can be tentatively argued that patients with SS or SL genotypes have greater availability of 5-HT at their central serotonergic synapses, thereby intensifying satiety and reducing food intake, and so inducing lower BMI and decreased fat mass (Monteleone *et al.*, 2006). Interestingly, in animal models and humans, an increase in 5-HT levels leads to eating less, whereas a decrease in 5-HT activity precipitates compulsive or binge eating (Blundell, 1986).

Due to the relatively small number of subjects in this study, Type II error, through the lack of observed association between the analyzed polymorphism and T2DM, cannot be ruled out. Further analysis with a larger sample is warranted. Another limitation in this preliminary study was the paucity of additional phenotypes investigated, such as insulin and lipid levels, and other relevant clinical measurements. Since the Mexican population resulted from an admixture of Native Americans and Europeans (Spanish) with a smaller contribution from African groups, the probability of population stratification cannot be ruled out. Nevertheless, the information reported in this preliminary investigation is relevant, because of the high impact of obesity as a health problem in Mexico. In addition, the allele frequencies of *SLC6A4* polymorphism determined in this population sample constitute a useful reference for genetic studies.

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