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# Evaluation of the 5-*HTTLPR* and 5-*HTTVNTR* Polymorphisms in the Serotonin Transporter Gene in Women with Postpartum Depression

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## ABSTRACT

**Objective:** The purpose of the present study was to evaluate the association between the 5-*HTTLPR* and 5-*HTTVNTR* polymorphisms in the serotonin transporter gene (*SLC6A4*) in Brazilian women with diagnosed postpartum depression (PPD) and the presence of depressive symptoms. **Method:** The cohort consisted of 128 white women who were characterized based on skin color and morphological characteristics. The Beck Depression Inventory was used to diagnose PPD and to score the depressive symptoms. The 5-*HTTLPR* and 5-*HTTVNTR* polymorphisms were analyzed by PCR-based methods. **Results:** No association was observed between the PPD diagnosis and either the 5-*HTTLPR* ($p = 0.48$) or the 5-*HTTVNTR* ($p = 0.77$) polymorphism. When the polymorphisms were analyzed together with haplotype data, the analyses demonstrated that women carriers of the L-12/L-12 diplotype have lower Beck Depression Inventory scores than women carrying other diplotypes ($p = 0.04$). **Discussion:** Few studies have investigated the association of *SLC6A4* polymorphisms with PPD, and the role of 5-*HTTLPR* and 5-*HTTVNTR* polymorphisms in PPD susceptibility has not been established to date. Therefore, our findings link the haplotypes of these two variants with depression symptoms, thereby contributing to our understanding of PPD susceptibility.

**Keywords:** Postpartum Depression; Serotonin Transporter; 5-*HTTLPR*; 5-*HTTVNTR*; Polymorphisms

## 1. Introduction

Postpartum depression (PPD) is mood disorder; it is similar to major depressive disorder but usually presents within the first 4 to 6 weeks after delivery [1]. A meta-analysis has estimated that PPD is prevalent worldwide and affects 10% to 15% of women [2]. In the Brazilian population, the incidence of maternal depression in the samples studied ranged from 7.2% [3] to 26.9% [4]. PPD differs from the "baby blues" because in most cases it affects the functionality of the mother and endangers the well-being of both the mother and the baby. PPD can be a devastating disease for the mother, can harm the neurocognitive and socio-emotional development of the child, and can increase the risk for mental and medical disorders in the child later in life [5]. PPD is a multifactorial disease; PPD susceptibility is related to psychological, biological (including hormonal changes and genetic vulnerability), and social factors [6]. The risk of occurrence is higher in women with a history of major depression [7], previous PPD [8], or a family history of depression [9]. Therefore, according to Forty *et al.* [9], there is a genetic component for the development of this disorder.

According to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition) [1], there is a relationship between depressive symptoms and changes in the concentration of neurotransmitters, especially serotonin (5-HT), in the brain. Decreased levels of 5-HT are among the factors contributing to the etiology of major depression [10]. The serotonin transporter (SERT) is located in the presynaptic membrane of serotonergic neurons, where it controls the intensity and duration of serotonergic signaling through the re-uptake of 5-HT in the synaptic cleft [11].

SERT is encoded by the *SLC6A4* gene located within the 17q11.1-q12 region [12] of chromosome 17. The

 

expression of this gene is influenced by its genetic variants. Two polymorphisms have been widely studied. The 5-*HTTLPR* polymorphism (resulting from an insertion/deletion) is located in the promoter region [13] and has a long allele (L: with an insertion of 44 bp) and short allele (S). The 5-*HTTVNTR* polymorphism (containing a variable number of tandem repeats) is in the second intron and has a repetition unit containing 17 bp. Three alleles of 5-*HTTVNTR* have been described and contain 9, 10, or 12 repetitions [14].

*SLC*6*A*4 has been identified as a candidate gene for mood disorders because several studies have associated *SLC*6*A*4 polymorphisms with the development of major depression [15-18] and bipolar disorder [19]. To the best of our knowledge, only two previous studies have investtigated the association between *SLC*6*A*4 polymorphisms and depression scores in postpartum women [20,21]. The results from the previous studies contradicted other studies that evaluated *SLC*6*A*4 polymorphisms for association with mood disorders in other life periods [15-23]. Our present study aimed to determine the association between the 5-*HTTLPR* and 5-*HTTVNTR* polymorphisms and both PPD diagnosis and the Beck Depressive Inventory (BDI) score (a measure of depressive symptoms) in a group of Brazilian women. These results may impact the treatment of PPD.

## 2. Materials and Methods

### 2.1. Subjects

A cohort study consisting for pregnant women who were recruited from the Brazilian National System of Public Heath from 2006 to 2008 was utilized. All women seeking prenatal care in the public health system of Pelotas City were visited and were invited to participate in the study. All participants were all at least 18 years of age, lived in the urban area, and were capable of understanding and answering the sociodemographic questionnaire included in the study. In the study, 128 white women were included; this classification was based in skin color and morphological characteristics as described by Parra *et al.* [24]. This study was approved by the Ethics Committee of the Universidade Federal de Ciências da Saúde de Porto Alegre (n.270/07) and National Council on Ethics in Research (n.44/08). All subjects signed an informed consent form.

### 2.2. Depressive Symptoms Access

The mothers were visited at home and were interviewed; they also provided blood samples for genetic analyses within 45 to 90 days of delivery. The validated Portuguese version of the BDI [25] was employed to detect depressive symptomatology in the mother. BDI results were used for diagnosis of PPD. A cutoff score of 18 was used to differentiate between mild and moderate/severe depression.

### 2.3. DNA Analyses

The blood used for DNA extraction was collected by a trained professional in the residence of each participant. Genomic DNA was extracted from peripheral blood leukocytes by a salting-out procedure [26]. DNA fragments with the 5-*HTTVNTR* polymorphism were amplified by polymerase chain reaction (PCR) using the forward primer 5' GTCAGTATCACAGGCTGCGAG 3' and the reverse primer 5' TGTTCCTAGTCTTACGCCAGTG 3' and employing conditions that were previously described [27]. The amplification of the 5-*HTTLPR* polymorphism was performed using the forward primer 5' GCGCTCCTGCATCCCCCATTA 3' and the reverse primer 5' GGGATGCGGGGGAATACTGGT 3'; this PCR reaction produced a 297 bp (L allele) and a 253 bp (S allele) fragment [12]. The genotypes of 5-*HTTLPR* and 5-*HTTVNTR* were determined by separating the amplified products by electrophoresis on a 2.5% agarose gel containing ethidium bromide and using a 50-bp ladder to determine band sizes.

### 2.4. Statistical Analysis

Allele frequencies were estimated by gene counting. A $\chi^2$ test for goodness of fit was used to determine whether the observed allele frequencies agreed with those expected under Hardy-Weinberg equilibrium. Haplotype frequencies and linkage disequilibrium were estimated using the Multiple Locus Haplotype Analysis program version 2.0 [28,29] and Arlequin software version 3.1 [30]. A $\chi^2$ test with Yates correction was used to compare allele and genotype frequencies of the 5-*HTTLPR* and 5-*HTTVNTR* polymorphisms for individuals with a PPD diagnosis (BDI $\geq$ 18) and for individuals without a PPD diagnosis (BDI < 18). Because of the low frequency of the 9/12 genotype (5-*HTTVNTR*) in this cohort (n = 1), this woman was excluded from statistical analyses invest- tigating the association of this polymorphism with PPD diagnosis. The BDI scores were compared among carriers of different diplotypes; Mann-Whitney tests were used, and a 5% significance level was chosen. The Benjamini and Hochberg [31] false discovery rate procedure was performed to correct for multiple testing, and corrected P values were reported.

## 3. Results

The genotype frequency distributions of the 5-*HTTLPR* and 5-*HTTVNTR* polymorphisms were in agreement with Hardy-Weinberg expectations. The genotype frequencies

 

for the 5-*HTTLPR* polymorphism were 17.0% (n = 22) for S/S, 51.0% (n = 65) for L/S, and 32.0% (n = 41) for L/L. The genotype frequencies for the 5-*HTTVNTR* polymorphism were 0.70% (n = 1) for 9/12, 14.70% (n = 17) for 10/10, 44.0% (n = 51) for 10/12, and 40.60% (n = 48) for 12/12. Eleven women were not genotyped for the 5-*HTVNTR* polymorphism due to technical difficulties; therefore, the analyzed sample set included 117 individuals for this polymorphism. Linkage disequilibrium was detected between the two polymorphisms (the D' value was 0.61, p = 0.003). All four possible haplotypes were found in this cohort; the more common haplotypes were S-12 (frequency of 36.24%; n = 42), L-10 (29.71%; n = 35), L-12 (27.17%; n = 32), and S-10 (6.88%; n = 8).

Results from the association analyses between the 5-*HTTLPR* and 5-*HTTVNTR* polymorphisms and PPD diagnosis (according to the BDI) in women are presented in **Table 1**. When the polymorphisms were analyzed alone, no association was observed between the 5-*HTTLPR* (p = 0.48) and 5-*HTTVNTR* (p = 0.77) polymorphisms and PPD diagnosis. Utilizing haplotype information for the 5-*HTTLPR* and 5-*HTTVNTR* polymorphisms demonstrated that women carriers of the L-12/L-12 diplotype have a lower BDI score (median: 0.5; inter-quartile range: 0.00 - 4.00; p = 0.04; corrected p = 0.12) than women with other diplotypes (median: 4.0; inter-quartile range: 1.00 - 10.00). These results are shown in **Figure 1**.

## 4. Discussion

The present study analyzed the PPD diagnoses of women, which were made between 45 and 90 days after delivery. No association between *SLC6A4* gene polymorphisms and PPD was found when PPD was analyzed alone. However, the results indicated that specific haplotypes of the 5-*HTTVNTR* and 5-*HTTLPR* polymorphisms were associated with depression score.

The relationship between the 5-*HTTLPR* and 5-*HTTVNTR* polymorphisms and SERT function and expression is not yet fully understood, although several previous reports have investigated the relationship. Heils *et al.* [32] performed an *in vitro* functional study and demonstrated that the promoter region initiated transcription of the 5-*HTTLPR**L allele more efficiently than it promoted transcription of the S allele. Therefore, individuals with the L/L genotype expressed more SERT than those with S/L and S/S genotypes. Other studies also found an association between the 5-*HTTLPR**S allele [16,17,33,34] and the 10 and 12 alleles of the 5-*HTTVNTR* polymorphism [19,23]; women with these alleles exhibited lower SERT transcription efficiency. Functional magnetic resonance imaging analyses have revealed that carriers of the S allele have reduced volumes of the perigenual anterior cingulate cortex and amygdala [33]. Although these studies have provided information related to the relationship between these polymorphisms and the risk of developing mental disorders, such as depression, more information is required to fully understand this functional relationship.

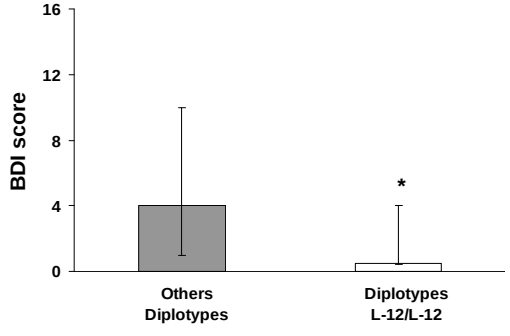


**Figure 1. Beck Depression Inventory (BDI) score according to the 5-*HTTLPR* and 5-*HTTVNTR* polymorphisms diplotypes.**

Several studies have investigated the association of the 5-*HTTLPR* polymorphism with mood disorders. According to Pascual *et al.* [23], the presence of the S allele was significantly associated with the development of a mental disorder. Caspi *et al.* [15] determined that individuals carrying the S allele had more depressive symptoms, were more frequently diagnosed with depression, and had more suicidal thoughts during stressful life events compared to individuals who were homozygous for the L allele. Xie *et al.* [6] found that individuals with one or two copies of the S allele have an increased risk of developing posttraumatic stress disorder following exposure to adverse environmental events. Moreover, Zalsman *et al.* [17] demonstrated that individuals who carry the S allele are more reactive to unfavorable environmental events often associated with major depression. Wilhelm *et al.* [16] and Taylor *et al.* [22] observed that individuals homozygous for the S allele showed greater depressive symptomatology when exposed to stress compared with those harboring the S/L or L/L genotype. Taken together, these studies indicate that the 5-*HTTLPR* genotype does not determine the development of the disorder per se. However, when exposed to stressful events, individuals with one or two copies of the S allele are more likely than L/L homozygotes to develop the disorder. Conversely, the results of Chorbov *et al.* [35] and Laucht *et al.* [36] suggest a different conclusion from the one described above. These studies found that individuals with the L/L genotype who were exposed to adverse environmental events exhibited an increased risk of depression.

Specific to PPD, our results showed no association between the 5-*HTTLPR* genotype alone and PPD in white women (**Table 1**). This conclusion agreed with

 

**Table 1. 5-*HTTLPR* and 5-*HTTVNTR* genotype frequencies in women with diagnosed postpartum depression according to the Beck Depression Inventory (BDI) classification. The number of women (n) is given between parentheses.**

| 5-*HTTLPR* | | | | |
|---|---|---|---|---|
| Genotypes | S/S | L/S | L/L | p |
| NON-PPD | 16.90% (19) | 50.40% (57) | 32.70% (37) | 0.48 |
| PPD | 13.30% (2) | 66.70% (10) | 20.00% (3) | |
| 5-*HTTVNTR* | | | | |
| Genotypes | 10/10 | 10/12 | 12/12 | p |
| NON-PPD | 15.10% (16) | 41.50% (44) | 43.40% (46) | 0.77 |
| PPD | 9.00% (1) | 45.50% (5) | 45.50% (5) | |

several studies that found no significant relationship between the 5-*HTTLPR* polymorphism and the development of mood disorders, such as major depression [37], depression and attempted suicide [38], depression and stressful life events [39], and bipolar disorders [40]. In a meta-analysis, Risch *et al.* [18] observed no association between the 5-*HTTLPR* genotype, either alone or in conjunction with stressful events, and risk for depression in either gender.

Our results showed no an association between the 5-*HTTVNTR* polymorphisms and PPD in white women. Additionally, Alaerts *et al.* [40] did not find an association between the 5-*HTTVNTR* polymorphisms and bipolar disorder, and Assal *et al.* [41] found no relationship between the 5-*HTTVNTR* polymorphisms and agitation/aggression, depression, or anxiety. However, in a previous study, the increased frequency of the 5-*HTTVNTR**12 allele was observed in subjects with bipolar disorder but not in subjects diagnosed with major depression [19]. Kumar *et al.* [42] observed an association between the 5-*HTTVNTR**10 allele and puerperal psychosis.

To the best of our knowledge, only two previous studies have investigated the relationship between serotonin-related polymorphisms and PPD. Sanjuan *et al.* [20] reported that at 8 weeks postpartum, high expression of specific SERT genotypes (L/L of 5-*HTTLPR* and 12/12 of 5-*HTTVNTR* polymorphisms) was associated with an increase in the Edinburgh Postnatal Depression Scale (EPDS) score. Doornbos *et al.* [21] indicated that female 5-*HTTLPR**L carriers trended toward increased depresssion scores at 6 weeks postpartum. In our study, no significant associations between the *SLC6A4* gene polymorphism and PPD diagnosis were detected when the analyses were performed separately for each polymerphism (**Table 1**). When the two genetic variants were analyzed together with their haplotypes, women carrying the L-12/L-12 diplotype exhibited a lower BDI score compared to women carrying other diplotypes (**Figure 1**). This conclusion is different than that reported by Sanjuan *et al.* [20]. However, these two studies are not entirely comparable because different scales were used for PPD diagnosis, and the postpartum period for each study was different. Additionally, our findings are partially corroborated by several studies that found an association between the presence of the 5-*HTTLPR**S [6,15-17,22] and 5-*HTTVNTR**10 alleles [42] with mood disorders; in our study, the L-12/L-12 diplotype was associated with a lower BDI score, indicating that this diplotype could partially protect an individual from developing PPD.

Our findings are important because few studies have investigated the association of specific haplotypes of the 5-*HTTLPR* and 5-*HTTVNTR* polymorphisms with PPD. In summary, we present evidence that postpartum women carrying the L-12/L-12 diplotype exhibit fewer depression symptoms than those carrying other diplotypes. Moreover, this result implicates genetic variations in the SERT gene as playing a role in the etiology of PPD. An inherent limitation to our study is the small sample size, which may not have enough power to detect an association of polymorphisms with small effects on depressive symptoms. The sample size is small because women in the postpartum period are not easily enrolled in research studies, due to the intensive time requirement of caring for their children. However, the present analyses may be considered as an exploratory study for understanding PPD susceptibility in a specific life period; the postpartum period is influenced most notably by hormones of the hypothalamus-pituitary-gonad axis.

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