A serotonin transporter gene polymorphism predicts peripartum depressive symptoms in an at-risk psychiatric cohort


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A B S T R A C T
Background: Peripartum major depressive disorder (MDD) is a prevalent psychiatric disorder with potential detrimental consequences for both mother and child. Despite its enormous health care relevance, data regarding genetic predictors of peripartum depression are sparse. The aim of this study was to investigate associations of the serotonin-transporter linked polymorphic region (5-HTTLPR) genotype with peripartum MDD in an at-risk population.

Methods: Two hundred and seventy four women with a prior history of MDD were genotyped for 5-HTTLPR and serially evaluated in late pregnancy (gestational weeks 31–40), early post-partum (week 1–8) and late post-partum (week 9–24) for diagnosis of a current major depressive episode (MDE) and depressive symptom severity.

Results: 5-HTTLPR S-allele carrier status predicted the occurrence of a MDE in the early post-partum period only (OR = 5.13, p = 0.017). This association persisted despite continued antidepressant treatment.

Conclusions: The 5-HTTLPR genotype may be a clinically relevant predictor of early post-partum depression in an at-risk population.

1. Introduction

Major depressive disorder (MDD) during pregnancy and the post-partum period (peripartum MDD) are common, with estimates of point prevalence ranging between 8% and 13% (CDC, 2008; Cox et al., 1993; Dietz et al., 2007; Evans et al., 2001; Gavin et al., 2005; O’Hara et al., 1991). Moreover, a burgeoning clinical and preclinical literature demonstrates an array of adverse sequelae of maternal MDD and stress during pregnancy and the post-partum period including potential life-long effects on the offspring (Brennan et al., 2008; Hammen and Brennan, 2003; Murray et al., 1996; Newport et al., 2002a,b). Some have suggested these enduring effects may be epigenetically mediated (Oberlander et al., 2008). Similar to non-puerperal MDD, psychological stress and family or personal histories of MDD increase the risk of peripartum MDD (Gotlib et al., 1991; Murphy-Eberenz et al., 2006; Paykel et al., 1980). Despite the high prevalence and negative impact on the child, the biological underpinnings of peripartum MDD are not well-defined. Alterations in stress hormones, gonadal steroids, and serotonergic activity have all been implicated in the etiology of this disorder (Bloch et al., 2000; Jolley et al., 2007; Maes et al., 2002; Newport et al., 2004; Steiner et al., 2003).

Family studies suggest a genetic contribution to the risk for peripartum MDD (Forty et al., 2006; Murphy-Eberenz et al., 2006). To date, genetic studies of peripartum MDD have emphasized polymorphisms in genes within the serotonin system, including the serotonin transporter gene (Jones et al., 2000; Sanjuan et al., 2008; Scheid et al., 2007; Sun et al., 2004). The serotonin-transporter linked polymorphic region (5-HTTLPR) is one of the best investigated polymorphisms in psychiatric genetics. Briefly,

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5-HTTLPR (Lesch et al., 1996), a repeat polymorphism in the promoter region of the serotonin transporter gene (SLC6A4) on chromosome 17, has been associated with functional differences in serotonin reuptake. Compared to the long version (16 incomplete 22 base pair repeats), the short version (14 repeats) of the 5-HTTLPR is linked to reduced serotonin transporter gene expression and serotonin uptake (Heils et al., 1996). A single nucleotide polymorphism, rs25531, within the long allele has been shown to moderate the functional impact of this genetic variant further (Hu et al., 2006).

While case-control associations of the 5-HTTLPR with MDD are largely negative (Lasky-Su et al., 2005), an increasing literature supports its interaction with adverse life events to heighten the risk for MDD. While several studies support, at least partially, the initial report of such an interaction by Caspi et al. (2003), some studies report negative results (see Uher and McGuffin (2008) for a recent review; Risch et al., 2009 for a meta-analysis). The 5-HTTLPR has also been associated with antidepressant therapeutic response (Serretti et al., 2007) but see also (Hu et al., 2007). It is thus not surprising that the 5-HTTLPR has also been chosen as a candidate polymorphism in peripartum MDD.

Two existing investigations have reported on the association of the 5-HTTLPR and peripartum MDD, one examining its influence on post-partum MDD (Sanjuan et al., 2008) and the other gene-environment interactions contributing to mid-pregnancy MDD (Scheid et al., 2007). Replicating previously reported gene-environment interactions in non-peripartum populations (Caspi et al., 2003; Scheid et al. (2007) reported a higher level of depressive symptoms in mid-pregnancy among women with the 5-HTTLPR short (s-) allele and a history of abuse but no main effects of the polymorphism on depressive symptoms. Sanjuan et al. (2008), investigating not the 5-HTTLPR genotype alone but a combined genotype of the 5-HTTLPR and a second tandem repeat polymorphism in intron 2 of the gene, reported that homozygosity of the long (l-) allele (present in high and medium expressing groups but not a low expressing group) was associated with greater depressive symptoms at 8 but not 32 weeks post-partum. Because post-partum depression has been associated with decreased tryptophan bioavailability (Kohl et al., 2005; Maes et al., 2002), the authors contend that this finding is congruent with the heightened sensitivity of high function serotonin transporter gene carriers to the depressiveogenic effects of tryptophan depletion (Moreno et al., 2002; Neumeister et al., 2006). It is noteworthy, however, that increased sensitivity to tryptophan depletion has also been reported for women carrying the low-expressing S-allele of this polymorphism, especially in combination with a family history of mood disorders (Neumeister et al., 2002). Because the two existing investigations of the impact of the 5-HTTLPR on the risk for peripartum MDD have focused on very different phenotypes, no independent replication of either study has yet been reported. In addition, both studies used a non-psychiatric sample.

The goal of the current study was to conduct a prospective longitudinal investigation of the association of the 5-HTTLPR on depressive symptoms in late pregnancy and the post-partum period in an at-risk cohort of women with prior histories of MDD, ascertaining whether this genetic variant might serve to identify women at highest risk for recurrent depressive illness during pregnancy or the post-partum period. We examined both the 5-HTTLPR alone and the functional classification including rs25531 (Hu et al., 2006), which has not yet been investigated in peripartum MDD. Our study thus explores mechanisms whereby the previous findings (i.e., interaction of the 5-HTTLPR with a history of abuse to predict MDD during pregnancy and a main effect of this polymorphism on post-partum MDD (Scheid et al., 2007; Sanjuan et al., 2008)), may be related to an at-risk clinical cohort. Furthermore, the current study adds a longitudinal prospective component utilizing serial data collection from late pregnancy through the post-partum period.

2. Materials and methods

2.1. Patients and psychometric assessments

Pregnant women (age ≥ 18 years) with lifetime histories of MDD, presenting to the Emory Women’s Mental Health Program (WMHP), were enrolled prior to 20 weeks gestation in a prospective observational study of the perinatal course of MDD. Women were excluded from the present study if they were actively suicidal, exhibited current psychotic symptoms, were severely anemic, had a positive urine drug screen, had an abnormal plasma TSH concentration, or were actively abusing alcohol or drugs within the past 12 months. Failure to extract high-quality DNA from blood samples was also an exclusion criterion. Written informed consent for study participation was obtained, and the Institutional Review Board of the Emory University School of Medicine approved the study.

At study entry, current and lifetime psychiatric diagnoses were assessed using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995).

At the baseline and all subsequent follow-up visits, depressive symptom severity was assessed using the 17-item Hamilton Rating Scale for Depression (HRSD17) (Hamilton, 1960), and the presence of a current MDE was determined using the SCID Mood Module. For women agreeing to participate in the genetic analyses, mood was assessed during late pregnancy (> 30 weeks gestation), early post-partum (<8 weeks), and later post-partum (9–24 weeks). Finally, all medications, maternal daily dose, and self-reported adherence were prospectively recorded at each study visit and at delivery.

2.2. DNA extraction and 5-HTTLPR genotyping

DNA was extracted from whole blood using the Qiagen M48 biorobot (Qiagen Inc.). Genotyping of the 5-HTTLPR used the following primers (forward: 5’–TGAATGAGCGACCTAAC-3’; reverse: 5’–ATACTGAGGGGGTGCG-3’). PCR was carried out in 384 well plates in a 10 μl volume with 10 ng DNA. Each PCR reaction contained 0.5 μM of each primer, 0.08 μM of dATP, dCTP and dTTP and 0.04 μM of dGTP, 0.2 μM of 7-deaza GTP (Amersham Biosciences), 5% DMSO and 1.25 units of AmpliTaq Gold (Applied Biosystems). The cycling parameters were as follows: 95 °C for 5 min, then 94 °C for 30 s, 63 °C for 30 s and 72 °C for 1 min for 1 cycle, then the annealing temperature was reduced to 62 °C for one more cycle and then to 59.5 °C for 38 cycles. 5 μl of the resulting PCR products was then digested with 5 U Mspl (New England Biolabs) in a total volume of 10 μl for 90 min at 37 °C to detect the A/G SNP rs25531 shown to influence the functional effects of the long and short alleles (Hu et al., 2006). The digested PCR products were then separated using an Applied Biosystems 3100 genetic analyzer and analyzed with Applied Biosystems Genemapper 4.0 software. Fragment lengths for the L0-allele are 291 bp, 148 for the L1, and 247 bp for the S-allele. The VL fragment is 335 bp and the XL fragment 375 bp. The L-VL or L-XL genotypes were each observed in one participant; both were excluded from the analysis.

For quality control, the runs included duplicated samples and positive controls established through re-sequencing.

2.3. Statistical analysis

Statistical analyses were performed using SPSS version 15.0. We used contingency tables and logistic regression to evaluate...
differences in polymorphism distribution according to diagnosis of a current MDE. Covariates included maternal age at conception, race, education, marital status, gestational age at delivery, gravidity, and parity. Each of these covariates had been associated with peripartum MDD either in previous reports or in preliminary univariate analyses using our sample. In our sample, a MDE during late pregnancy was associated with education (p < 0.1), race (p < 0.05), and gestational age at delivery (p < 0.05). An early post-partum MDE was associated with race (p < 0.05), gravidity (p < 0.05), and parity (p < 0.05). A late post-partum MDE was associated with race (p < 0.05), maternal status (p < 0.05), gravidity (p < 0.05), and paternal age (p < 0.05). Repeated measures general linear models were used to investigate genotype dependent differences in the evolution of depressive symptoms over time. Data are reported as means and standard deviations (results section and Tables) or means and standard errors (Figures). All tests were two-tailed. Alpha was set a priori to 0.05.

2.4. Power analysis

Using the software Quanto 1.1 (http://hydra.usc.edu/gxe), the power to detect a genetic relative risk of 3.0 in a sample of N = 274 with 15% affected individuals with peripartum depression and a minor allele frequency of 40.0% in a recessive genetic model was 82.6% with an alpha level of 0.05. The power to detect the genetic relative risk of 5.13 observed in the actual sample for early post-partum depression according to the SCID Mood Module was 82.6% with an alpha level of 0.05. The power to detect the genetic relative risk of 3.0 in a sample of N = 172 was 95.0% using the above parameters.

3. Results

A total of 274 women with a lifetime history of MDD were screened for inclusion. Of these women, 206 (75.2%) fulfilled inclusion criteria for the current analysis with high-quality DNA and HRSD17 during late pregnancy, while 201 also completed the SCID Mood Module at this time. Attrition following delivery yielded a total of 188 with HRSD17 and 172 with SCID Mood Module ratings during the early post-partum interval, and 183 HRSD17 and 169 SCID Mood Module ratings during the late post-partum interval. No significant differences in any of the descriptive and clinical parameters listed in Table 1 were observed between the screened sample, the included sample, and the post-attrition sample assessed during the late post-partum interval.

### Table 1
Demographic and clinical characteristics of study sample (n = 204) at study entry.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) or Pct.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.1 (4.3)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>87.8%</td>
</tr>
<tr>
<td>Asian</td>
<td>2.5%</td>
</tr>
<tr>
<td>Native American</td>
<td>2.0%</td>
</tr>
<tr>
<td>African American</td>
<td>4.4%</td>
</tr>
<tr>
<td>White Hispanic</td>
<td>3.4%</td>
</tr>
<tr>
<td>Live deliveries</td>
<td>100.0%</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks)</td>
<td>38.4 (1.30)</td>
</tr>
<tr>
<td>Gravidity</td>
<td>2.50 (1.60)</td>
</tr>
<tr>
<td>Parity</td>
<td>0.98 (0.09)</td>
</tr>
<tr>
<td>Lifetime MDD (per SCID)</td>
<td>100.0%</td>
</tr>
<tr>
<td>MDE at study entry</td>
<td>15.1%</td>
</tr>
<tr>
<td>HRSD17 at study entry (gestational week 31–40)</td>
<td>13.0 (5.4)</td>
</tr>
<tr>
<td>Treatment at study entry</td>
<td></td>
</tr>
<tr>
<td>No antidepressant</td>
<td>19.6%</td>
</tr>
<tr>
<td>Antidepressant monotherapy</td>
<td>73.0%</td>
</tr>
<tr>
<td>Antidepressant polytherapy</td>
<td>7.4%</td>
</tr>
</tbody>
</table>

3.1. Depressive symptoms, diagnostic criteria, and antidepressant treatment

Of the 206 women with DNA and HRSD17 scores, 80.6% were receiving antidepressant therapy at the late pregnancy visit, all but 15 receiving monotherapy. The most common antidepressants were sertraline (22.1%), fluoxetine (13.7%), bupropion (10.3%) and venlafaxine (9.8%). Other antidepressants included citalopram, escitalopram, paroxetine, fluvoxamine, amitriptyline, desipramine, duloxetine and nortriptyline. 83.8% of the participants were taking antidepressant medication at the early post-partum visit and 77.0% at the late post-partum visit. Among the women who were not receiving antidepressant therapy during late pregnancy, 75.8% remained off medication in the early post-partum compared to only 53.3% in the late post-partum period.

At the late pregnancy visit, the mean HRSD17 score was 13.0 ± 5.3, with 14.9% (n = 30/201) fulfilling criteria for a current MDE according to the SCID Mood Module. At the early and late post-partum visits, 13.4% (n = 23/172) and 17.8% (n = 30/169), respectively, fulfilled criteria for a current MDE. Notably, 65.2% (n = 15/23) of the early post-partum MDEs and 75.0% (n = 21/28) of the late post-partum MDEs occurred in women who were euthymic during late pregnancy. Compared to late pregnancy (using a paired t-test), the mean HRSD17 scores were lower in the early post-partum period ((t = 6.4, df = 179, p < 0.0001), with mean (SD) scores of 13.0 (5.34) in late pregnancy and 10.5 (5.78) in early post-partum) as well as the late post-partum period ((t = 3.6, df = 172, p < 0.0001) with a mean HRSD17 score of 11.3 (6.09)).

3.2. Frequency of 5-HTTLPR genotypes

Of the 206 women with high-quality DNA and HRSD17 ratings in late pregnancy, two presented with rare genotypes (L-VL (n = 1); L-XL (n = 1)) and were excluded from all further analyses. The 5-HTTLPR genotype distribution for the remaining 204 women was: (1) 18.4% SS; (2) 49.0% LS; and (3) 31.6% LL, a distribution consistent with the Hardy–Weinberg equilibrium. Of all individuals, 15.1% presented with a G allele at the rs25531 polymorphism (8.8% as LSA and 6.3% as LSG). Using the functional classification according to Hu et al. (2006), 24.3% were classified as low transporter-expressing (LS and LSG), 51.0% as medium expressing (LSA), and 22.8% as high expressing (LAA).

3.3. Association of 5-HTTLPR genotype with diagnosis of peripartum MDE

There was no significant association of the 5-HTTLPR LS genotype (additive model), presence of S-allele or functional classification
with the occurrence of a MDE in late pregnancy or the late post-partum period; however, significant differences in genotype distribution and presence of S-allele were observed in the early post-partum period (cf. Table 2 and Fig. 1). The odds ratio for an early post-partum MDE in the presence of the S-allele (S-carrier model) was 5.13 [1.16–22.7] (p = 0.017). To control for potential confounders, a logistic regression was conducted to assess the 5-HTTLPR S-allele and other predictors of a MDE during the early post-partum period. The model identified 5-HTTLPR S-allele (OR = 6.71 [1.41–31.95], p = 0.017), maternal age at conception (OR = 0.84 [0.95–0.74], p = 0.0081), and gravidity (OR = 1.60 [1.22–2.11], p = 0.00070) as significant predictors of an early post-partum MDE. The log likelihood of the main effects model was 116.14 (χ² = 22.8, df = 3, p < 0.0001). The Hosmer and Lemeshow goodness-of-fit statistic was 7.85 (df = 8, p = 0.44), indicating that the logistic model fit the data adequately.

The association between S-allele status and early post-partum MDE was remarkably stable. For example, the distribution of S-allele carriers between those with and without an early post-partum MDE was essentially the same whether the analysis considered all 172 participants with early post-partum SCID assessments (91.7% vs. 68.2%) or was limited to the participants with early post-partum SCID assessments who were euthymic during late pregnancy (92.9% vs. 69.5%). Similarly, when the analysis was limited to those receiving antidepressant therapy during the early post-partum period (n = 141), the proportion of S-allele carriers was 90.5% (n = 19/21) for those with an early post-partum MDE and 68.3% (n = 82/120) for those without an early post-partum MDE.

Because the association with an early post-partum MDE appeared to be driven by S-allele carrier status (i.e., an S-allele-dominant model), all subsequent analyses were based on an S-allele-dominant genetic model. This model is consistent with the reported dominance of the S allele with regard to lower serotonin transporter expression and activity (Heils et al., 1996).

3.4. Association of S-allele carrier status with severity of peripartum depressive symptoms

A repeated measures ANOVA of all patients found no significant main effect of carrier status nor time × status effect for change of HRSD17 score from late pregnancy to early post-partum. However, when the analysis was restricted to those who were euthymic during late pregnancy and continuing antidepressant therapy into early post-partum (N = 119), significant main effects of time (F₁,₁₁₇ = 16.33, p < 0.0001) and S-allele carrier status (F₁,₁₁₇ = 8.28, p = 0.005) but no significant interaction were observed (cf. Fig. 2). In an exploratory analysis, another repeated measures ANOVA of change in HRSD₁₇ score from late pregnancy to early post-partum was performed to assess the effect of the S allele in women who were depressed during late pregnancy controlling for antidepressant treatment status. This analysis demonstrated a trend for an interaction between time (late pregnancy vs. early post-partum

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Table 2

<table>
<thead>
<tr>
<th>Assessment window</th>
<th>SCID criteria (%)</th>
<th>5-HTTLPR genotype</th>
<th>5-HTTLPR S-allele</th>
<th>5-HTTLPR functional classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SS</td>
<td>SL</td>
<td>LL</td>
</tr>
<tr>
<td>Late pregnancy (31 weeks to delivery)</td>
<td>No MDE</td>
<td>20.71</td>
<td>49.70</td>
<td>29.59</td>
</tr>
<tr>
<td></td>
<td>MDE</td>
<td>10.00</td>
<td>50.00</td>
<td>40.00</td>
</tr>
<tr>
<td>Early post-partum (1–8 weeks)</td>
<td>No MDE</td>
<td>21.43</td>
<td>46.75</td>
<td>31.82</td>
</tr>
<tr>
<td></td>
<td>MDE</td>
<td>20.83</td>
<td>70.83</td>
<td>8.33</td>
</tr>
<tr>
<td>Late post-partum (9–24 weeks)</td>
<td>No MDE</td>
<td>21.53</td>
<td>46.33</td>
<td>31.94</td>
</tr>
<tr>
<td></td>
<td>MDE</td>
<td>9.38</td>
<td>59.38</td>
<td>31.25</td>
</tr>
</tbody>
</table>

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Fig. 1. Distribution of 5-HTTLPR S-allele carriers (SS + SL vs. LL) between patients with and without current MDE in late pregnancy, early and late post-partum. p = 0.017 (Fishers’ Exact test) for early post-partum and p > 0.05 for the two other time points.
and 5-HTTLPR S allele ($F_{21,1} = 3.37, p = 0.081$) but no main genotype effect (cf. Fig. 2).

3.5. Association of S-allele carrier status with estimated gestational age at delivery

We observed no genotype effect on estimated gestational age at delivery in the sample as a whole, as well as the subsamples on and off antidepressant medication and with or without current MDE in late pregnancy.

4. Discussion

The current study provides further evidence for the influence of the 5-HTTLPR genotype on early post-partum depression. In our at-risk sample, S-allele carrier status was a strong predictor (OR = 5.13) for developing a MDE in the early post-partum period, within 8 weeks of delivery. This association persisted for new onset episodes (i.e., those euthymic in late pregnancy but depressed in early post-partum) in women who were receiving antidepressant therapy throughout the entire observation period. Overall, the 5-HTTLPR genotype might therefore be a clinically relevant predictor of post-partum depression in an at-risk psychiatric population, with S-allele carrier status predicting a substantial risk of early post-partum depression in women with prior histories of MDD, despite continued antidepressant medication.

Furthermore, our study, utilizing an at-risk psychiatric sample, supports several of the previously reported findings on the 5-HTTLPR in peripartum depression in non-psychiatric community samples (Scheid et al., 2007; Sanjuan et al., 2008). Similar to Sanjuan et al. (2008), we observed significantly lower HRSD depressive symptom scores in the post-partum period as compared to mid to late pregnancy. Surprisingly, however, MDE rates as determined by the SCID Mood Module were highest in the late post-partum. We suspect that these conflicting findings may be a consequence of an inflationary effect of late pregnancy physical symptoms on HRSD scores, producing higher pregnancy euthymic scores than post-partum euthymic scores.

Like Scheid et al. (2007), we report no main effect of the 5-HTTLPR on depressive symptoms in the late pregnancy period in the sample overall.

On the other hand, our genetic associations in the post-partum period are not consistent with Sanjuan et al. (2008). While we also found a significant association of 5-HTTLPR genotype with early but not late post-partum depression, the direction of our association was opposite. In our sample, low-expression S-allele carriers rather than high expression genotypes had the highest incidence of MDE and severity of depressive symptoms. This might indicate that our findings in a demographically homogeneous psychiatric sample cannot be extrapolated to women in community settings who have no prior histories of MDD. In fact, the contrasting results might lead to speculation that the change in post-partum depressive symptom severity observed in a community sample has a distinct etiopathogenesis from peripartum recurrence in women with prior histories of MDD. Sanjuan et al. (2008) contend that their data indicate that high function serotonin transporter allele carriers are at heightened risk for post-partum depression because they are more likely to deplete tryptophan stores. In contrast, the current data, in agreement with the majority but not all previously reported pharmacogenetic and gene × environment associations (Caspi et al., 2003; Serretti et al., 2007), suggest that the low function S-allele is the risk allele.

Contrary to the community setting, the majority of women in this study were receiving continued antidepressant therapy, so that the heightened risk for post-partum MDD in S-allele carriers in our sample may be a product of the reported potential for this group to escape from previously efficacious pharmacological treatment (Serretti et al., 2007). However, the time-point specific effects of this genetic association would suggest that non-response to antidepressant treatment cannot be the only explanatory factor but that specific interactions with the biological and/or environmental changes and the 5-HTTLPR in this patients group in early post-partum are likely.

The current study results suggest that the predictive value of the 5-HTTLPR for post-partum depression depends on the timing of the symptom onset. The 5-HTTLPR was a significant predictor of a depressive episode in the early post-partum period, but not in late pregnancy or the later post-partum period. This might be related to the unique set of stressors associated with caring for a newborn, including sleep restriction, which may specifically interact with 5-HTTLPR genotype to predict depressive symptoms. In addition, early post-partum depression (onset before post-partum weeks 6–8) has been identified to be associated with higher familiarity and thus possibly genetic load than post-partum depression with later onset (before 6 months post-partum) (Forty et al., 2006). This could indicate that the biological underpinnings of early vs. later post-partum depression are different and could explain why the observed genetic association was only seen using the early definition of post-partum onset.

A clear limitation of this study is sample size, and unless replicated in larger independent studies, our findings may be a product of random error. This weakness is partially counterbalanced by the prospective longitudinal nature of the data collection as well as the homogenous sample characteristics. Due to the prospective design, we were able to control for late pregnancy MDD in our analyses of the risk for post-partum MDD. As demonstrated in the results section, over 35% of women fulfilling criteria for a post-partum MDE had fulfilled the same criteria in late pregnancy. An exploratory analysis of women with MDE in late pregnancy suggests that the genotype effects on depressive symptoms might be different in this group (see Fig. 2). Separate analyses of post-partum onset depression as compared to depression that is continuous from pregnancy into the post-partum period thus seem warranted.

The current study is the first to report on associations of the 5-HTTLPR genotype in a psychiatric sample followed through the post-partum period. If replicated, these data suggest that 5-HTTLPR...
polymorphisms have distinct effects on the risk for post-partum MDD in patient vs. general population groups.

Our data may bear significant clinical import. In our homogeneous high risk sample, over 13% of women experienced a MDE during the first 8 weeks post-partum, despite continued antidepressant treatment. In this group, S-allele carriers represent over 90% of the cases. If this finding is replicated, more aggressive treatment planning and monitoring could be indicated for at-risk women carrying the 5-HTTLPR S-allele.

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Author contributions

Elisabeth B. Binder has supervised and analyzed all genotyping, performed all statistical analyses and contributed to study design and drafting of the manuscript. D. Jeffrey Newport has supervised patient recruitment, contributed to the design of the study, prepared the clinical dataset and contributed to drafting of the manuscript. Elizabeth B. Zach has contributed to the patient recruitment and characterization and clinical data entry. Alicia K. Smith has contributed to the quality control of DNA collection and preparation as well as critical revision of the manuscript. Todd C. Deaveau has performed all genotyping. Lori L. Altshuler and Lee S. Cohen have critically revised the manuscript. Zachary N. Stowe is the primary investigator of the clinical study and has supervised patient recruitment, contributed to the design of the study and drafting of the manuscript. Joseph F. Cubells has supervised the genetic analyses, contributed to study design and critically revised the manuscript.

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