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ORIGINAL ARTICLE

Association study of the estrogen receptor gene *ESR1* with postpartum depression—a pilot study

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Abstract Perinatal mood disorders, such as postpartum depression (PPD), are costly for society, with potentially serious consequences for mother and child. While multiple genes appear to play a role in PPD susceptibility, the contributions of specific genetic variations remain unclear. Previously implicated as a candidate gene, the estrogen receptor alpha gene (*ESR1*) is a key player in mediating hormonal differences during pregnancy and the postpartum period. This study addresses genetic factors in perinatal mood disorders, testing nine polymorphisms in *ESR1*. Two hundred fifty-seven postpartum women were screened for mood disorders, including 52 women with PPD and 32 without any symptoms of mood disorders. We detected a significant association for the upstream TA microsatellite repeat with Edinburgh Postnatal Depression Scale scores (p=0.007). The same variant was also associated with the occurrence of PPD. Separately, 11 candidate functional polymorphisms in 7 additional genes were genotyped to investigate gene–gene interaction with the *ESR1 TA* repeat, identifying a potential interaction with the serotonin transporter. Our results support a role for *ESR1* in the etiology of PPD, possibly through the modulation of serotonin signaling. Our findings for *ESR1* could have broad implications for other disorders and therapies that involve estrogens.

Keywords Postpartum depression · Edinburgh postnatal depression scale · ESR1 estrogen receptor · Genetic variation · SNP

List of abbreviations

PPD	postpartum depression
SNP	single nucleotide polymorphism
LD	linkage disequilibrium
MAF	minor allele frequency
MADRS	Montgomery–Asberg Depression Rating Scale
EPDS	Edinburgh Postnatal Depression Scale
SCID	Stuctured Clinical Interview for DSM Disorders
MINI	Mini International Neuropsychiatric Interview
MDD	Major depressive disorder
GAD	Generalized anxiety disorder

Introduction

Mood and anxiety disorders predominately affect women over men at a rate of 2 to 1, a sex difference likely determined by genomic as well as hormonal factors. Postpartum depression (PPD) affects between 10 % and 15 % of women (Steiner 1998; Steiner et al. 2003) and may constitute a major

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health-related concern for society. PPD, defined as depression within one year of delivery, is a serious, disabling disorder requiring medical attention; this condition should not be confused with "the baby blues," a much less debilitating condition that affects 50–80 % of all new mothers. Perinatal depression is associated with both physiological and behavioral adverse effects on the offspring. Children of mothers with PPD are more likely to have failure-to-thrive, behavioral problems, and suboptimal cognitive and social development, relative to children with healthy mothers (Lazinski et al. 2008). These consequences, together with high risk of non-puerperal relapse in the mother (Bell et al. 1994), indicate that PPD constitutes a serious mental health risk for women.

Multiple genes may play a role in PPD susceptibility, and the contributions of specific genetic variations to the disorder remain unclear. The role of hormones in the onset of perinatal psychiatric disorders has long been hypothesized (Nott et al. 1976; Deecher et al. 2008) because the hormonal fluctuations that accompany pregnancy and childbirth are greater than those experienced at any other time in life. Estrogens can act on multiple central nervous system pathways through a variety of mechanisms (Beyer et al. 2003), such as affecting transcription by binding to intracellular estrogen receptor encoded by *ESR1* and *ESR2* in target tissues (Stahl 2001), and also through non-classical second messenger systems (McEwen 2001; Kugaya et al. 2003; Lokuge et al. 2010, 2011a). Among several pathways, estrogens modulate serotonin transmission (Bethea et al. 2002).

PPD and major depressive disorder (MDD) share similarities, supported by genetic and family studies in both populations (Treloar et al. 1999; Murphy-Eberenz et al. 2006; Forty et al. 2006; Payne et al. 2007; Sanjuan et al. 2008; Costas et al. 2010; Figueira et al. 2010; Doornbos et al. 2009; Xie and Innis 2009; Mahon et al. 2009) with a focus on genes involved in the serotonergic pathway (Sun et al. 2004; Yu et al. 2002; Bellivier et al. 2000; Caspi et al. 2003b; Cervilla et al. 2006; Murphy et al. 2004; Mrazek et al. 2008; Anguelova et al. 2003a, b), GABA (Amin et al. 2006; Epperson et al. 2006), and other neurotransmitter systems (Zill et al. 2002; Domschke et al. 2008). Also, *ESR1* variants have been associated with MDD (Ryan et al. 2011, 2012) and anxiety (Comings et al. 1999). In a study of 1,804 postpartum women, polymorphisms in *ESR1* have been found to be associated with PPD (Costas et al. 2010), a finding that requires further testing in replication studies.

The aim of this pilot study was to conduct a targeted association analysis of PPD and nine polymorphisms in the *ESR1* gene. In the second part of our analysis, we genotyped eleven strong candidate polymorphisms in seven additional genes implicated in depression and other related mental disorders: *COMT*, *DRD2*, *HTR2A*, *MAOA*, *SLC6A3* (*DAT*), *SLC6A4* (*SERT*), and *TPH2*, to examine any impact on PDD and gene–gene interactions of these candidate genes with a variant in *ESR1*.

Methods

Subjects

A total of 257 women, including controls, were recruited at the Women's Health Concerns Clinic and on the maternity ward at St. Joseph's Healthcare, Hamilton, Ontario, Canada within the first 12 weeks postpartum. Referrals to the clinic of perinatal women with mood and/or anxiety disorders or reported stress were made by community-based health care providers. They were at least 18 years of age, had delivered a full-term healthy infant following the index pregnancy, and were able to communicate in English. Written and verbal consent was obtained from all participants.

Women were excluded if they: (a) had a current diagnosis or a history of bipolar or psychotic disorder, (b) presented with serious risk for suicide, homicide, or infanticide; (c) abused drugs and/or alcohol within the past 6 months; or (d) showed signs of a concurrent serious medical condition.

Postpartum women were interviewed at the time of enrollment using the Structured Clinical Interview for DSM Disorders (SCID; Spitzer et al. 1992) and the Mini International Neuropsychiatric Interview (MINI; Sheehan et al. 1998) to establish a psychiatric diagnosis, and the severity of depression was further assessed using the Edinburgh Postnatal Depression Scale (EPDS; Cox et al. 1987) and/ or the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg 1979). The EPDS is an effective screening tool for identifying women at risk for PPD and provides an index of depression severity (higher EPDS scores indicate greater severity). The ten-item questionnaire is most often administered during pregnancy or within 8 weeks postpartum.

Of the 257 women, 225 were diagnosed with a mood disorder. Fifty-two met criteria for "true" PPD, i.e., they had no prior history of a mood or anxiety disorder. They scored within the "severe depression" range on the MADRS (≥35) and/or on the EPDS (≥20). A further ninety-nine (99) women met the criteria for recurrent MDD and 74 women were diagnosed with postpartum adjustment disorder with mixed anxiety and depressed mood. The remaining 32 postpartum mothers did not qualify for any current and/or past psychiatric disorder and were included as controls. The ethnicity of subjects reflects the demographics in the recruitment area and is mainly Caucasian (91 %), with 2 % Asian, 2 % Hispanic, and 4 % other. Table 1 displays demographic data for the 184 subjects that were used for the association analyses.

Table 1 Selected demographics

Primary diagnosis	*n*	Average age	StDev
Controls	32	32.6	4.2
Postpartum depression	52	31.2	4.7
Major depressive disorder	52	30.5	5.4
Generalized anxiety disorder	11	29.3	4.5
Adjustment disorder	26	31.1	5.0
Others	10	31.4	7.7
Ethnicity	%		
Caucasian	93		
Asian	2		
African Canadian	1		
Hispanic	1		
Other	3		
Country of Birth	%		
Canada	80		
UK	6		
USA	3		
Europe	3		
Other			
Highest Education	%		
Grade School	8		
High School	15		
College/University	70		
Post Graduate	8		
Marital Status	%		
Married	71		
Never Married	9		
Divorced	20		
Employed Outside the Home	%		
Yes	66		
No	34		

Age and primary diagnoses of the 184 subjects used in the association study are shown. Ethnicity, country of birth, education, marriage and employment status are presented as averages from available data which is representative of the population as a whole

Sample preparation

Genomic DNA was extracted from whole blood. Cells were lysed with a sucrose Triton solution, providing a nuclear pellet for DNA purification. DNA was prepared by digestion of the pellet with SDS and proteinase K followed by NaCl "salting out" precipitation of proteins (Miller et al. 1988). The DNA in the supernatant was further purified and recovered by ethanol precipitation.

Genotyping of clinical cohort

Samples were genotyped for nine *ESR1* variants, including one microsatellite repeat polymorphism (Fig. 1 and Table 2). Polymorphisms were selected to include variants in the transcribed region of the gene, and the rest were distributed across the gene locus (Fig. 1) with a concentration in introns 4 and 5. Selection made use of haplotype information and previously published association studies (Costas et al. 2010). The three SNPs in the transcribed region (rs2077647 in exon1, rs1801132 in exon4, and rs13798577 in the 3′ UTR) were genotyped by primer extension using a SNapShot kit (Applied Biosystems, Foster City, CA). The TA repeat was amplified by PCR with fluorescently labeled primers and amplicons were analyzed with capillary electrophoresis. The remaining SNPs were genotyped by restriction length fragment polymorphism (RFLP). A 100–300-base pair region surrounding each SNP was amplified via PCR using one fluorescently labeled primer and one unlabeled primer. The resulting amplicons were digested overnight with a restriction endonuclease that selectively distinguished between the two SNP alleles. The fragments were analyzed by capillary electrophoresis (AB3730, Applied Biosystems). All ESR1 primer sequences and restriction enzymes are listed in Table 3. For the second analysis, 11 polymorphisms in 7 previously proposed candidate genes were genotyped (Table S1). *DRD2*, *MAOA*, *DAT*, *SERT*, and *TPH2* genotyping was conducted using methods described previously (Zhang et al. 2007; Pinsonneault et al. 2006, 2011; Lim et al. 2006, 2007; Smith et al. 2012). COMT rs4680 was genotyped using a TaqMan Assay (Cat #4362691, Applied Biosystems). Primers and applicable enzymes are listed in Table S2.

Statistical analysis

Genetic data were analyzed with HelixTree© (Golden Helix, Inc., Bozeman, MT) and STATA 11 (StataCorp. College Station, TX). Two outcomes, and thus two separate analyses, were conducted. The first outcome considered was EPDS score, modeled continuously with linear regression (n=156). Single variants were tested for significance based on Wald p values under three genetic models (dominant, recessive, and additive). Age was considered a confounder if the inclusion to the model changed the variant's coefficient by more

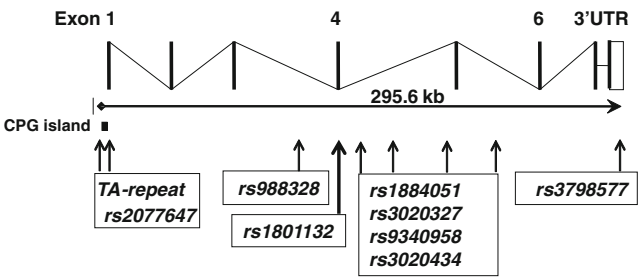


Fig. 1 Map of the coding portion of the *ESR1* gene and the approximate locations of genotyped SNPs

Table 2 ESR1 SNP information

Marker	SNP	Minor allele freq.	Genotype DD	Genotype Dd	Genotype dd	Call rate	HWE P n=257
TA repeat	*S>L*	43 %	49	119	84	98 %	0.53
rs2077647	*A>G*	43 %	49	124	82	99 %	0.87
rs988328	*A>G*	14 %	5	59	173	92 %	1.00
rs1801132	*C>G*	24 %	12	96	149	100 %	0.41
rs1884051	*A>G*	17 %	11	58	166	91 %	0.05
rs3020327	*G>A*	10 %	2	46	209	100 %	0.77
rs9340958	*C>T*	7 %	3	28	203	91 %	0.11
rs3020434	*C>T*	16 %	6	64	170	93 %	0.94
rs3798577	*T>C*	48 %	63	118	73	99 %	0.22

Genotyping information from all 257 subjects were included to determine genotype counts and allele frequencies

than 10 %. Two-variant main effect and interaction models were thoroughly investigated only for the univariate SNP with the lowest p value). The second outcome, PPD versus control (n=84), used logistic regression to model the association between PPD status in a two-variant main effect model and interaction model selecting the two variants that scored the highest in a two variant interaction model in the first outcome. HelixTree© is a commercially available genetic statistical analysis program that includes genetic association, linkage disequilibrium (LD) analysis, haplotype estimation, and regression analysis capabilities. Both Stata 11 and HelixTree© were employed for diplotype analysis and simple genetic association tests.

Results

Two hundred and fifty-seven postpartum women were genotyped for 9 polymorphisms in the estrogen receptor. SNP information including call rate, allele frequency, and Hardy–Weinberg equilibrium is listed in Table 2. We first conducted a linkage disequilibrium test and determined that the nine SNPs defined approximately six haplotype blocks, i.e., three of the SNPs were found to be in high LD with another SNP (Fig. 2). This finding enabled us to perform a correction for multiple testing for six distinct haplotype blocks. We next examined whether any of the genotyped *ESR1* SNPs were associated with EPDS scores.

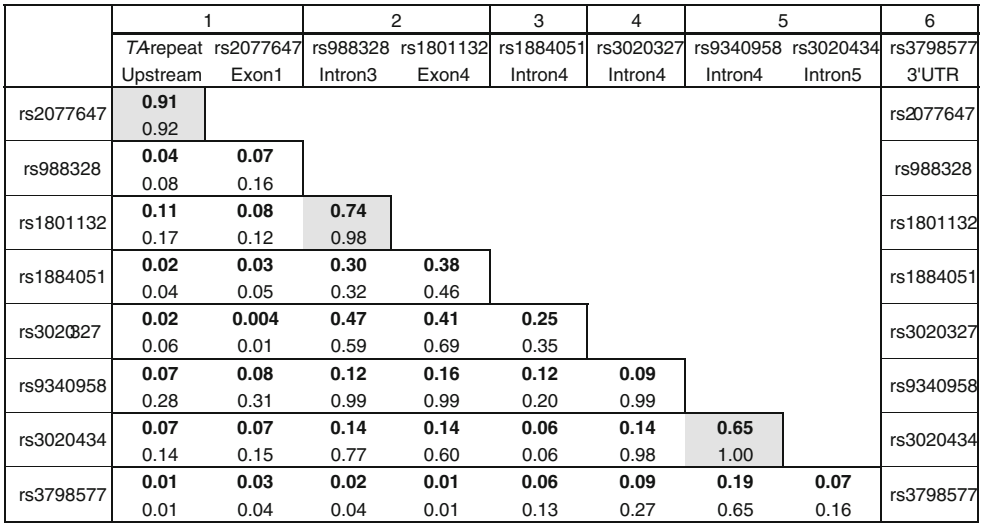
Table 3 Genotyping primers

(A) Primers and restriction enzymes that were used for RFLP analysis. The TA repeat polymorphism did not require a restriction enzyme.

Variant	Enzyme	Forward primer	Reverse primer
rs3020434	HaeIII	[6-FAM]-ATGAAGTTAGACCTTACAAAGCACATC	TCCTTGCCCCTCAGCTTG
rs1884051	BccI	[6-FAM]-GAGGAGGGAGTGGATGTTGAG	AACCATAAAAATTATTCCATCTGAGC
rs3020327	XmnI	[6-FAM]-GGCATCTGTTCAAGGACAATTTC	GAGTCGTGTATCTTTTTGTCACCTATATAG
rs988328	BsmAI	atagtcTCAGAAGAACCAGCCTATAAATAAAAACT	[6-FAM]-TTGAACTTATTTACCCAATTACCAAAG
rs9340958	Csp6I	GATGTGCAACCTTATTAGTCATTAGGAA	[6-FAM]-CACCAGCAAAACATGAAAAGC
TA repeat	N/A	[6-FAM]-GACGCATGATATACTTCACC	GCAGAATCAAATATCCAGATG

(B) Primers employed for primer extension reactions

Variant	Primer	Sequence
rs1801132	F	CAGTGCCTTGTTGGATGCTG
rs1801132	R	CCCTGTCTGCCAGGTTGGT
rs1801132	PER	GTAGGATCATACTCGGAATAGAGTAT
rs3798577	F	TGGTGTTGCATTTAGCCCTGG
rs3798577	R	AGCCACAACAATCCTGCACA
rs3798577	PEP	GGCATGGAGCTGAACAGTAC
rs2077647	F	GTTTCTGAGCCTTCTGCCCTG
rs2077647	R	TTCCCTTGGATCTGATGCAGT
rs2077647	PEF	CCTCCACACCAAAGCATC



	1		2		3	4	5		6
	TA repeat	rs2077647	rs988328	rs1801132	rs1884051	rs3020327	rs9340958	rs3020434	rs3798577
	Upstream	Exon1	Intron3	Exon4	Intron4	Intron4	Intron4	Intron5	3'UTR
rs2077647	**0.91** 0.92								rs2077647
rs988328	**0.04** 0.08	**0.07** 0.16							rs988328
rs1801132	**0.11** 0.17	**0.08** 0.12	**0.74** 0.98						rs1801132
rs1884051	**0.02** 0.04	**0.03** 0.05	**0.30** 0.32	**0.38** 0.46					rs1884051
rs3020327	**0.02** 0.06	**0.004** 0.01	**0.47** 0.59	**0.41** 0.69	**0.25** 0.35				rs3020327
rs9340958	**0.07** 0.28	**0.08** 0.31	**0.12** 0.99	**0.16** 0.99	**0.12** 0.20	**0.09** 0.99			rs9340958
rs3020434	**0.07** 0.14	**0.07** 0.15	**0.14** 0.77	**0.14** 0.60	**0.06** 0.06	**0.14** 0.98	**0.65** 1.00		rs3020434
rs3798577	**0.01** 0.01	**0.03** 0.04	**0.02** 0.04	**0.01** 0.01	**0.06** 0.13	**0.09** 0.27	**0.19** 0.65	**0.07** 0.16	rs3798577

Fig. 2 Pairwise linkage disequilibrium of 10 polymorphisms in the *ESR1* gene. Numerical values in *bold* on the *top line* of each box represent LD correlation R. The lower value, not in *bold*, represents the D prime. *Boxes shaded in gray* highlight polymorphism pairs in sufficiently high LD to be defined as a haplotype block. Haplotype blocks are numbered in the *top row*, with SNP and location in the 2nd and 3rd row, respectively

EPDS scores from the 156 women who were screened ranged from 2 to 30 and appeared normally distributed (Supplemental Fig. 1). The association *p* values from dominant recessive and additive allele tests conducted using EPDS as the phenotypic variable are shown in Table 4. Both the *ESR1 TA* repeat (L allele) and *rs2077647* (G allele) were significantly associated with EPDS score in a dominant allele test ($p=0.007$ and $p=0.03$); however, only the *TA* repeat withstood correction for multiple testing for the number of ESR1 haplotype blocks ($p=0.04$).

We next conducted an analysis using a second outcome: postpartum depression case control in a partially overlapping group of 84 subjects (52 with confirmed PPD and 32 control postpartum women) using the same tests. Of the 84, 56 subjects overlapped. The other 28 subjects (17 PPD and 11 controls) did not have EPDS data and therefore had not been included in the EPDS association test. In the dominant allele test, both the *TA* repeat and *rs2077647* were significantly associated with PPD, with OR=3.05 ($p=0.02$) and 2.58 ($p=0.04$), respectively (Table 5). However, these associations did not survive correction for multiple testing.

Our next goal was to examine the effect of other candidate genes and gene-gene interactions with *ESR1*. For this purpose, we selected 11 functional polymorphisms in seven candidate genes for depression and other mental disorders. Table S1 lists the genes included in the analysis, including *ESR1*, while Table S3 contains information for each SNP genotyped. The majority of these SNPs were tested because they have previously been found to have regulatory effects (Lim et al. 2007; Zhang et al. 2007; Pinsonneault et al. 2011; Smith et al. 2012). These include catechol-O-methyl transferase (*COMT*), tryptophan hydroxylase 2 (*TPH2*), dopamine receptor D2 (*DRD2*), serotonin receptor 2A (*HTR2A*), and dopamine transporter (*SLC6A3 or DAT*). Additional variants from monoamine oxidase A (*MAOA*) and serotonin transporter (*SLC6A4 or SERT*) have been proposed to be functional (Heils et al. 1996; Pinsonneault et al. 2006; Kunnas et al. 1999).

Table 4 Genetic association summary of *ESR1* polymorphisms with EPDS score

Marker	Dominant			Additive			Recessive		
	P	Slope	Slope SE	*P*	Slope	Slope SE	*P*	Slope	Slope SE
TA repeat	0.007	2.87	1.04	0.06	1.32	0.69	0.81	0.30	1.26
rs2077647	0.03	2.31	1.05	0.08	1.25	0.71	0.57	0.73	1.29
rs988328	0.82	−0.26	1.19	0.92	−0.11	1.03	0.78	0.89	3.24
rs1801132	0.21	−1.25	1.00	0.37	−0.71	0.80	0.81	0.47	1.96
rs1884051	0.88	−0.16	1.11	0.75	0.28	0.87	0.27	2.40	2.17
rs3020327	0.46	0.88	1.18	0.31	1.11	1.08	0.17	6.15	4.43
rs9340958	0.68	0.70	1.71	0.79	0.39	1.44	0.81	−1.05	4.47
rs3020434	0.19	1.54	1.16	0.29	1.11	1.04	0.69	−1.47	3.66
rs3798577	0.50	0.78	1.15	0.55	0.42	0.69	0.75	0.37	1.13

Table 5 Genetic association of summary of ESR1 polymorphisms to postpartum depression status

Marker	Dominant allele test											
	MAF n=52	MAF n=32	Call Rate	Chi-squared *p*	Odds ratio	Confidence Interval	DD Cases	DD Controls	Dd Cases	Dd Controls	dd Cases	dd Controls
TA repeat	44 %	35 %	99 %	0.02	3.05	1.17–7.92	7	6	32	10	12	15
rs2077647	46 %	34 %	100 %	0.04	2.58	1.01–6.59	7	6	31	11	13	15
rs988328	17 %	15 %	94 %	0.91	1.06	0.39–2.86	1	0	14	9	33	21
rs1801132	27 %	27 %	100 %	0.66	0.82	0.34–1.99	4	1	19	15	28	16
rs1884051	19 %	18 %	93 %	0.89	0.93	0.34–2.53	3	1	12	8	34	19
rs3020327	15 %	6 %	100 %	0.15	2.39	0.71–8.13	2	0	11	4	38	28
rs9340958	6 %	9 %	92 %	0.82	0.86	0.22–3.34	0	1	6	3	42	24
rs3020434	12 %	12 %	95 %	0.74	1.21	0.40–3.67	0	1	12	5	38	23
rs3798577	46 %	52 %	100 %	0.84	0.91	0.35–2.34	13	11	21	11	17	10

As with the ESR1 analysis, single variant models were built using additive, dominant, and recessive genetic models. Age was examined as a possible confounding factor, but no evidence was found, and it itself is not significantly associated with EPDS scores. As we have prior knowledge guiding our targeted selection of these functional variants, we did not perform corrections for multiple testing. In addition to the *ESR1 TA* repeat, three SNPs were significant at an unadjusted level of 0.10 under at least two genetic models and level 0.05 significant under at least one genetic model (Table S4). In the additive model, the following polymorphisms were statistically significant at $p<0.05$: *COMT rs4680* $p=0.03$ and *MAOA rs1137070* $p=0.05$. In the recessive model, *COMT rs4680* was $p=0.025$ and *HTR2A rs6314* was $p=0.02$.

Two-variant main effect and interaction models were thoroughly investigated only for the univariate SNP with the lowest p value (the *ESR1 TA* repeat). For the gene–gene interaction models, both the *ESR1 TA* repeat and the 2nd SNP were considered in the additive genetic mode. Each of the 11 SNPs was considered for the interaction with *ESR1 TA* repeat. Table 6 shows the list of interaction *p* values (Wald *p* value) in ascending order. Three interaction models were significant at the 0.05 level and are highlighted with a box. These include interaction with one SNP in the dopamine transporter *DAT*, and two genes that are involved in serotonergic signaling: *SLC6A4* (*SERT*) and the *serotonin receptor 2A* (*HTR2A*). The *ESR1 TA* repeat interacted most significantly with *SERTLPR*. Since these data were unadjusted for multiple comparisons, only the most significant model was further examined.

In the best scoring interaction model, the interaction *p* value was 0.007 for *ESR1 TA* repeat–*SERTLPR* (Table 7). The model *p* value was 0.013, with R-squared 7 %, which increased from 2.4 % when only *ESR1* was included in the model. The risk alleles in this interaction appear to be between the S allele of the *SERTLPR* and the *L* allele of the *ESR1-TA* repeat. Interpretations of the model are depicted in the 3×3 table (Table 8), which includes means and standard deviations of EPDS and subject counts stratified by genotype. For clarity, *SERTLPR* genotypes are indicated with an underscore. The Total row shows that, ignoring the *ESR1 TA* repeat, the mean EPDS is 14.9, 15.0, and 14.9, respectively, for each *SERTLPR* genotype ("LL," "LS," and "SS"), reinforcing the fact that *SERTLPR* is not associated with EPDS by itself. However, among the *ESR1 TA* repeat "LL" subjects (those homozygous for the minor L allele), the trend increases with *SERTLPR* genotype, from "LL" to "SS" (11.8, 16.3, 19.0), and for *ESR1 TA* repeat "SS" subjects, the trend decreases from "LL" to "SS" (15.0, 12.1, 11.8). The subjects with the highest EPDS occur with *SERT* "SS" and *ESR1 TA* repeat "LL" (value of 19.0—though only 4 subjects had this genotype combination).

Table 6 EPDS interaction models testing the *ESR1* TA repeat with the 11 remaining SNPs employing an "additive X additive" model

2nd SNP	Interaction W *p* value
SERTLPR	0.007
HTR2A rs6314	0.01
SLC6A3 rs27072	0.01
MAOA rs1137070	0.10
SLC6A3 rs6347	0.17
MAOA pVNTR	0.21
TPH2 rs7305115	0.28
HTR2A rs6311	0.48
SLC6A3 In8VNTR	0.52
DRD2 rs2283265	0.58
COMT rs4680	0.99

The Wald *p* value of the interaction coefficient is listed in the final column

Table 7 *ESR1 TA* repeat and *SERTLPR* interaction with EPDS score

Predictor	Coef.	Std. Err.	*t*	*p* value	95 % CI
ESR1 TA repeat	−0.92	1.07	−0.86	0.39	(−3.04, 1.19)
SERTLPR	−2.02	1.06	−1.91	0.06	(−4.12, 0.07)
Interaction	2.69	0.99	2.72	0.007	(0.73, 4.65)
intercept	15.52	1.19	13.08	0	(13.18, 17.87)

Linear regression with EPDS score as outcome. The first two coefficients listed are the main effects of *ESR1 TA* repeat and *SERTLPR*, respectively, and the third coefficient is the interaction

Because the *ESR1 TA* repeat interaction with the *SERTLPR* was significant for EPDS score, we also examined the same interaction in the occurrence of postpartum depression: PPD versus control (n=84). These two variants were chosen as they scored the highest in a two variant interaction model in the first outcome. We employed three methods to examine a gene interaction (Tables 9, 10, and 11). The first method used logistic regression to model the association between PPD status and the *ESR1 TA* repeat and the *SERTLPR* in a two-variant main effect model and interaction model. While there was no statistical interaction between these two variants using the dominant genetic models (to account for the smaller sample size and fewer minor alleles), the main effects model indicates a relationship. In the main effects model, the OR for *ESR1 TA* repeat L allele increased from 3.8 to 4.3 (p=0.007) when adjusted for *SERTLPR* genotype (Table 9). In a second method, after dividing the cohort into cases and controls, all of the subjects that had at least one copy of the minor allele for both the *TA* repeat (L) and the *LPR* (S) were summed. These numbers were inserted into a two by two contingency table. The remaining subjects, those lacking at least one minor allele in both variants, in each case/control category were summed for the other half of the table (Table 10). Genotypes for both variants were available for 47 PPD subjects and 28 controls. For the other nine subjects, complete genotype data were not available. We found that the combination of the minor alleles in *SERTLPR* (*S* allele) and *ESR1 TA* repeat (*L* allele) was significantly elevated in PPD cases, 27 out of 47 compared to 5 out of 28 controls (Fisher's p=0.0008). The third method was a logistic regression of specific allele combination frequencies of case subjects compared to controls (Table 11). The *L*,*S* diplotype representing the *ESR1 TA L* allele and the *SERTLPR S* allele, differed significantly (p=0.002) between the cases (21 %) and controls (6 %).

Discussion

In a pilot genetic association analysis of PPD and polymorphisms in ESR1, two variants in the *ESR1* gene, the *TA* repeat and *rs2077647* were significantly associated with

Table 8 Means and standard deviations of EPDS scores with subject counts, arranged by genotype

	Mean	*SERTLPR*			
	SD Frequency	L L	L S	S S	Total
ESR1 TA repeat	L L	11.8	16.3	19.0	15.2
		6.8	5.9	4.2	6.4
		10	17	4	31
	S L	16.0	16.2	16.6	16.2
		6.4	5.4	4.9	5.6
		24	35	11	70
	S S	15.0	12.1	11.8	13.1
		6.4	6.5	7.1	6.6
		18	23	11	52
	Total	14.9	15.0	14.9	14.9
		6.5	6.1	6.35	6.3
		52	75	26	153

ESR1 TA repeat genotypes are arranged by row, while the *SERTLPR* genotypes (underscored) are arranged by column

Table 9 One of the three methods examining the interaction of the *ESR1 TA* repeat and the *SERTLPR* in postpartum depression: Main effect model for *ESR1 TA* repeat and *SERTLPR*: dominant genetic models were used due to low sample size and low allele frequencies

Logistic regression				*N*=75
				LR chi2(2)=11.24
Log likelihood=−43.94				Prob>chi2=0.004
Predictor	Odds ratio	Std. Err.	*p* value	95 % CI
ESR1 TA repeat	4.32	2.33	0.007	(1.50, 12.43)
SERTLPR	3.02	1.65	0.043	(1.04, 8.81)

Adjusting for the *SERTLPR*, the *TA* repeat OR increases from 3.78 to 4.32. Adjusting for *ESR1 TA* repeat, the OR for *SERTLPR* increases from 2.53 to 3.02 and now has level 0.05 significance. Comparisons made on the same 75 subjects

EPDS scores in 156 postpartum women. Additionally, these same *ESR1* variants were associated with the occurrence of PPD, in a group of subjects and controls having only partial overlap with the EPDS results. In both cases the minor alleles were associated with poorer outcomes.

Limitations to our study include most notably small sample size which leads to low power. Another issue, inherent to examination of epistatic interactions, is multiple testing which was not corrected for in our interaction analyses. Instead we sought to minimize spurious results by limiting our investigation to known and proposed functional polymorphisms for the interaction study. Consequently, and as this is a pilot study, our findings must be viewed with caution. Nevertheless, in a broader context, our results further support a role for *ESR1* in the etiology of PPD, corroborating similar findings by others (Costas et al. 2010). In a prospective association study of 44 genes in Spanish women with PPD, four SNPs in the fourth and fifth introns of *ESR1* scored significantly (p=0.007 and 0.0008, respectively; Costas et al. 2010). Although the two studies revealed different variants and different regions of the gene (LD between the regions is low: R=0.07, D′=0.28), they contribute to a growing body of evidence that *ESR1* is involved in PPD.

The *ESR1* dinucleotide *TA* repeat has been linked to bone density (Sano et al. 1995), harm avoidance (Gade-Andavolu et al. 2009) and mRNA expression (Kunnas et al. 1999). The *ESR1 TA* repeat is in linkage disequilibrium with rs2077647, a synonymous SNP in exon 1. The *TA* repeat and *rs2077647* have been linked to arterial stiffness (Peter et al. 2009), and *rs2077647* is part of a haplotype associated with child onset mood disorders (Mill et al. 2008). *rs2077647* has also been associated with malignancies (Anghel et al. 2010).

When addressing possible gene–gene interactions, we detected interactions between several genes including those encoding serotonergic signaling proteins (SERT and HTR2A). Studied in more detail, a significant interaction was observed between the S allele of the *SERTLPR* and the *L* allele of the *ESR1 TA* repeat with Edinburgh depression score (EPDS) in 154 subjects. We also detected the same interaction using a second outcome: PPD status in an overlapping cohort that included subjects without EPDS information. The S allele of the *SERTLPR* and the L allele of the *ESR1 TA* repeat conferred risk in PPD cases (p=0.002). The *SERTLPR* itself was not significantly associated with PPD alone in either outcome, suggesting epistatic interactions. However, the judgment on the biological significance of the *SERTLPR* is still uncertain, given the mixed results of previous association studies (Caspi et al. 2003b;

Table 10 One of the three methods in examining the interaction of the *ESR1 TA* repeat and the *SERTLPR* in postpartum depression: Fisher's exact test of a 2×2 contingency table of PPD subjects and controls indicating the number of subjects possessing at least one copy of both the *SERTLPR* S allele and *TA* repeat L allele

	Subjects with both minor alleles	Others	Total	Fisher's exact *p*
PPD	27	20	47	p=0.0008
Control	5	23	28	
Total	32	43	75	

The Fisher's exact p value is 0.0008. Only samples with genotypes in both variants were included in the analysis

Table 11 One of the three methods in examining the interaction of the *ESR1 TA* repeat and the *SERTLPR* in postpartum depression: Logistic regression analysis of the *ESR1 TA* repeat/*SERTLPR* interaction as a diplotype

	Cases n=47	Controls n=28	Univariate *p*
L,L	25 %	26 %	0.88
L,S	21 %	6 %	0.002
S,L	31 %	42 %	0.14
S,S	23 %	26 %	nd
Sample:	75	Selected Markers:	
chisq:	9.90	*ESR1 TA repeat*	
p value:	0.02	*SERTLPR*	

ESR1 TA repeat is listed first followed by *SERTLPR*, which is underscored. nd indicates that the p value was not calculated, but it was not significant

Lim et al. 2006). Taken together, the results of the different interaction models in our study suggest a role for *ESR1* in serotonergic signaling. The *SERTLPR* S allele has been associated with lower *SERT* gene expression, resulting in decreased serotonin reuptake (Heils et al. 1996), but a molecular genetics analysis of the *SERTLPR* alleles has failed to reveal any detectable difference (Lim et al. 2006). The S allele has been correlated with depression and/ or anxiety (Lesch et al. 1996; Caspi et al. 2003b), MDD during pregnancy (Scheid et al. 2007), and with PPD (Binder et al. 2010; Mehta et al. 2012). An additional study found a link between the *SERTLPR* and PPD, but the association was with the L allele (Sanjuan et al. 2008). *SERT* has also been associated with stress in depression (Caspi et al. 2003a) and anxiety (Lesch et al. 1996). While there is ample evidence for an effect of the *SERTLPR* on clinical phenotypes, the results in the current study still require caution in assigning causative relationships.

We also detected an interaction between *ESR1* and two SNPs in the *dopamine transporter* (*SLC6A3*) although the interaction was not further investigated since it was not as strong as that with the *SERTLPR*. Recent reports have described a connection between dopamine signaling and depression (Chaudhury et al. 2013; Tye et al. 2013).

The idea that estrogen signaling may modify activity in serotonergic pathways has been proposed before (Lokuge et al. 2011b; Michopoulos et al. 2011). There have been numerous studies in animal models (McQueen et al. 1997; Pecins-Thompson et al. 1998; McQueen et al. 1999). In a study of ovariectomized rhesus macaques, chronic administration of estrogen led to reduced SLC6A4 mRNA expression (Pecins-Thompson et al. 1998), while a study in rats showed that estrogen leads to an increase in *SLC6A4* expression (McQueen et al. 1997, 1999). Mood disorders have been reported to be alleviated by estrogen administration (Fink et al. 1998; Halbreich et al. 1995; Ahokas et al. 2000). Ahokas et al. (2000) showed that treatment of refractory PPD with estradiol produced an improvement in depressive symptoms that coincided with the rise in serum estradiol, and this occurred in women who had previously received and failed to respond to treatment with antidepressants or psychotherapy.

Estrogen has long been suspected to play a role in the onset of PPD. Increased incidence of depression has been linked to a fall in plasma estradiol concentrations. During pregnancy, significant increases in plasma estrogens occur with the placenta becoming the primary source of estrogens by week 9 of gestation. On the other hand, women experience approximately a tenfold drop in circulating levels of estradiol postpartum with the removal of the placenta at delivery (Albrecht and Pepe 1990). Women with a personal history of PPD are sensitive to changes in estradiol and progesterone levels when given exogenous hormones, whereas control subjects with no such psychiatric history are not (Bloch et al. 2000). This suggests that some women are more sensitive to the hormonal changes that accompany the perinatal period.

The results of our pilot study support a role for *ESR1* in the etiology of PPD. One mechanism may be through the modulation of serotonin signaling. Our findings for the estrogen receptor *ESR1* have broad implications for other disorders and therapies that involve estrogens (e.g., the management of menopause-associated mood disorders), especially those where sex-differences are clearly pronounced (e.g., psychiatric disorders, cardiovascular diseases, and cancers).

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