Association of glucocorticoid and type 1 corticotropin-releasing hormone receptors gene variants and risk for depression during pregnancy and post-partum

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ABSTRACT

Women with postnatal depression (PND) appear to have abnormal hypothalamic pituitary adrenal (HPA) axis responses to stress, which might involve a genetic variability component. We investigated association of genetic variants in the glucocorticoid receptor (GR, NR3C1) and corticotropin releasing hormone receptor 1 (CRHR1) genes with increased risk for PND. Two hundred pregnant women were recruited prospectively and PND risk was assessed by the Edinburgh Postnatal Depression Scale (EPDS) during pregnancy and again 2–8 weeks post-natally (CW-GAPND study). The BclI and rs242939 single nucleotide polymorphisms (SNPs) of the GR and the haplotype-tagged rs1876828, rs242939 and rs242941 SNPs of the CRHR1 associated with genetic risk to depressive disorders were genotyped. A cut-off score of 10 was used to detect increased risk of PND. Association analysis was carried out in 140 patients that completed the study protocol. The BclI and rs242939 SNPs were over-represented in women with postnatal EPDS score ≥10 with significant allele association (p = 0.011 and <0.001, respectively) and risk ratios of 2.9 (95% CI: 1.2–6.9) for BclI, 4.9 (2–12) for rs242939 and 5.48 (2.13–14.10) for both. The rs242939 SNP was also associated with increased EPDS values during pregnancy. Moreover, the G-G-T haplotype of the CRHR1 was significantly over-represented in patients with high EPDS scores, with risk ratio of 3.22 (95% CI: 1.91–5.42). This is the first evidence that specific SNPs of genes involved in ‘stress’ responses might contribute in the genetics of high-risk for depression during pregnancy and postpartum.

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1. Introduction

In Western countries postnatal depression (PND) affects approximately 1 in 7 women, whereas in non-Western populations prevalence ranges between 5 and 60% (O’Hara and Swain, 1996; Cooper et al., 1999; Klainin and Arthur, 2009). If left untreated, PND has profound consequences on the quality of family life, social functioning as well as in the long-term emotional and cognitive development of the baby (Grace et al., 2003; Payne, 2007). Most importantly, severe forms of PND, such as puerperal psychosis, which affects 0.1–0.2% of new mothers, are linked to suicide and infanticide (Spinelli, 2009).

Despite detailed prevalence statistics, high probabilities of re-experience with future pregnancies, and well documented consequences of the disorder, PND remains difficult to identify. Routine assessment for either prenatal depression or PND is not universal. Screening guidelines for PND assessment across healthcare institutions are inconsistent. As a result fewer than half of PND cases are detected by primary healthcare professionals in routine clinical practice (Hearn et al., 1998) and in the UK screening policies rely on opportunistic case finding. The Edinburgh Postnatal Depression Scale (EPDS) which detects high levels of PND symptoms, is a widely used screening tool, however, it cannot be used for prospective identification of women at risk and is not considered to be cost-effective (Paulden et al., 2009). Clearly, PND management and outcomes would benefit substantially from early identification of women at risk and clinically effective treatments available. There is also inconclusive data about the long-term outcome of PND patients; most cases last around 3 months and resolve spontaneously without...
treatment. However, several studies demonstrated the presence of depression, with over 50% lasting over 6 months and some still being present up to 24 months postpartum (Goodman, 2004).

Several psychosocial risk factors for PND have been identified: the strongest predictors are past history of depression and psychological disturbance during pregnancy, as well as poor marital relationship and low social support, and stressful life events (O’Hara and Swain, 1996). A family history of depression is another risk factor for PND (Murphy-Eberenz et al., 2006), in agreement with the view that depressive illnesses are associated with high heritability, although individual episodes are frequently triggered by stressful life events. The later implicates stress-driven hormonal responses in disease pathogenesis (Spijker & van Rossum, 2009). The maternal hypothalamic-pituitary-adrenal (HPA) axis undergoes gradual changes during pregnancy because of an increasing production of placental corticotrophin-releasing hormone (CRH) (Chrousos et al., 1998). The abrupt withdrawal of placental CRH at birth results in a re-equilibration of the maternal HPA axis in the days post-delivery. Indeed, women with PND appear to have abnormal hypothalamic pituitary adrenal (HPA) axis responses to stress, possibly due to enhanced sensitivity to gonadal steroids during pregnancy (Magiakou et al., 1996; Bloch et al., 2007). It has been hypothesized that in women with symptoms of postpartum “blues” or depression, the HPA axis function fails to return to normal post-delivery and exhibits blunted adrenocorticotropic hormone (ACTH) responses to CRH challenge at 6 and 12 weeks postpartum suggesting prolonged HPA suppression (Magiakou et al., 1996; Rich-Edwards et al., 2008). Recent studies (O’Keane et al., 2011) investigating hormonal changes in the HPA axis in the days after delivery in relation to daily mood changes suggest that postpartum ‘blues’ positively correlated with ACTH; and negatively correlated with oestradiol levels during the postpartum days, and with the reduction in CRH concentrations from pregnancy. These findings support the hypothesis that the ‘reactivation’ of hypothalamic ACTH secretagogues peptides may be involved in the aetiology of the disease.

Impaired signalling of key molecules of the HPA axis such as the glucocorticoid receptor (GR) and corticotrophin releasing hormone receptor type 1 (CRH-R1) has been implicated in the pathogenesis of various depressive disorders including PND (Wisner and Stowe, 1997; Kammerer et al., 2006; Brummelte and Galea, 2010). HPA dysfunction has been identified in a wide spectrum of postpartum psychiatric disorders; for example it has been shown that increased circulating ACTH levels but not CRH or cortisol, are associated with the presence of postpartum thoughts of harming the infant (Labad et al., 2011). Measurement of maternal circulating CRH levels at mid-pregnancy has been proposed as a specific biomarker of maternal depression (Rich-Edwards et al., 2008) and this was supported by other studies suggested that the activity of the HPA axis during pregnancy is associated with maternal HPA responsiveness to stress postpartum (Meinschmidt et al., 2010). However, recent studies yielded contradictory results with positive or no association with either prenatal or postpartum depression (Yim et al., 2009; Meltzer-Brody et al., 2011).

The functional anomalies of the HPA axis in depressive disorders appear to include an inherited component due to genetic variability (Spijker & van Rossum, 2009). The genetic contribution to PND and postpartum psychosis is strongly supported by family and twin studies and genome-wide linkage analysis in conditions such as bipolar disorder and history of mood or anxiety disorder (Jones and Craddock, 2001; Forty et al., 2006; Jones et al., 2007; Kumar et al., 2007; Payne 2007; Friedman, 2009; Mahon et al., 2009). While there has been much interest in the identification of genes responsible for psychiatric illness, there remains a paucity of information relating to molecular markers and detection of PND risk.

The objective of our study was to investigate association between genetic variations (single nucleotide polymorphisms—SNPs) in the GR and CRHR1 genes, previously shown significant correlation with depression (Liu et al., 2006; Claes, 2009; Spijker & van Rossum, 2009), and increased risk for PND as determined by a raised EPDS score. To address this, a prospective cohort study was designed involving a secondary care University Hospital setting. To our knowledge, this represents the first prospective investigation of genetic variation of genes involved in HPA activity and PND risk.

2. Materials and methods

2.1. Patients-study design

For the Coventry and Warwickshire Genetic Risk for PostNatal Depression (CW-GAPND) study, 200 Caucasian women were recruited during antenatal clinic visits. The study focused on Caucasians to ensure ethnic background homogeneity of the cohort since ethnicity-related differences in PND prevalence have been reported (O’Hara and Swain, 1996; Patel et al., 2002). Symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS) questionnaire, which was completed upon the hospital visit between 20 and 28 weeks gestation (mean 25.4 ± 1.9) and again 2–8 weeks post-delivery (mean 4.6 ± 2.1). The choice of this time-period was based on previous studies suggesting that incidence of PND peaks at around 4–6 weeks (Cox et al., 1993; Evans et al., 2001; Verkerk et al., 2003). From the 200 women invited to participate, questionnaires were obtained from 140 subjects for a return rate of 70%. There was no significant difference in the socio-demographic characteristics (educational qualification, marital status, employment, support from partner, subsequent pregnancy) of responders and non-responders. Following current clinical practice, there was no follow-up of women who returned EPDS scores below the cut-off of 10.

Recruited patients were assessed for risk factors such as family history (first degree) of depression, personal history of depression, and depressive symptomatology at recruitment using the EPDS, however, there was no stratification to high or low-risk groups in accordance with current clinical practice. According to standard clinical practice all women were assessed for presence of anaemia (by full blood count and haemoglobin measurement) and thyroid disease (by TSH measurement) and women with abnormal results were excluded from the study. Women with a history of depression before pregnancy are especially vulnerable to depressive symptoms during or after pregnancy (Rich-Edwards et al., 2006). Therefore, in order to ensure pregnancy-specific and exclude non-pregnancy related depressive illness, women with pre-existing mental illnesses or on antidepressant medications or any other medications that can influence risk of developing PND were excluded from the study. A cut-off EPDS score of 10 was used for the identification of high-risk patients for PND. This reported performance characteristics at this cut-off point is: sensitivity of 0.81 and specificity of 0.86 for detection of both major and minor depression and a sensitivity of 0.917 and specificity of 0.77 for major depression only (Hewitt et al., 2009). The study was approved by the local ethics committee and informed consent was obtained from all subjects.

Similar to previous studies (Fasching et al., 2012; Mehta et al., 2012), the CW-GAPND study protocol included antenatal use of the EPDS questionnaire to assess depressive symptoms during pregnancy between 20 and 28 weeks gestation. Several studies validated the use of EPDS as a pre-screening tool for depression during pregnancy especially in the research setting (Rubertson et al., 2011; Milgrom et al., 2008) although, it is not currently used in routine antenatal care in the UK. In this study it was used exclusively as a research instrument to screen for symptoms of PND.
at antenatal clinics and thus identify presence of pregnancy-related underlying risk.

2.2. Genomic DNA extraction

5 mL of peripheral venous blood was collected from each subject in an EDTA tube. Genomic DNA was extracted using the QIAamp DNA Mini Kit (Qiagen, UK). The quality of the DNA was determined by spectrophotometric analysis using the $A_{260}/A_{280}$ ratio. Typically values of intact, high-purity DNA were approximately 1.7–1.8. In contrast, extracted DNA with ratios below 1.6 or above 2.0 indicating possible DNA contamination were excluded.

2.3. SNP selection and genotyping

The glucocorticoid receptor SNPs genotyped were the BclI and ER22/23EK (dbSNP NCBI identifiers rs41423247 and rs6190 respectively) whereas the 3 CRHR1 SNPs were the rs1876828, rs242939 and rs242941. These were selected from previous reports that demonstrated an association with depressive disorders (Liu et al., 2006; van Rossum et al., 2006; Spijker & van Rossum, 2009). Genotyping was performed using allele-specific PCR and melting curve analysis on the LightCycler (Roche Diagnostics Ltd, Burgess Hill, UK). Primers and probes were designed and synthesised by TIB MolBiol (Berlin, Germany). The amplification mixture included 5 μL of genomic DNA as template with LightCycler FastStart DNA Master Hybridization Probes. LightCycler parameters for PCR and melting curve analysis consisted of an initial denaturation step of 95 °C for 10 min followed by an amplification stage of 40 cycles of 10 s at 95 °C, 10 s at 53 °C and 20 s at 72 °C. After amplification, the melting curve analysis was performed in one cycle of 95 °C for 20 s followed by 40 °C for 20 s and then ramping to 85 °C. A single cooling cycle of 40 °C for 30 s was then employed. A temperature transition rate of 20 °C/s was used at each step. All laboratory procedures were carried out blind to EPDS data status. At least 10% of all samples were analysed twice to confirm accuracy of allele-specific PCR results.

Following determination of each SNP genotype (wild type, heterozygous or homozygous) haplotype frequency of the hSNPs rs1876828, rs242939 and rs242941 predicted haplotypes (G-A-G, G-A-T, G-G-G, G-G-T, A-A-G, A-A-T, A-G-G, A-G-T) was determined by using the SNPStats web tool (http://bioinfo.iconcologia.net/SNPstats) (Solé et al., 2006). The software implements the expectation-maximization (EM) algorithm coded into haplo.stats package to calculate the estimated relative frequencies for each haplotype. Haplotype association analyses for SNPs were performed with unconditional logistic regression using the default setting of a log-additive model and expressed in terms of ORs and 95% CIs.

2.4. Sequencing

Genotype status of the SNPs was confirmed by sequencing. Sequencing samples and run on the 3130xl Genetic Analyser (Applied Biosystems, PE, USA). Data were collected and analysed using the Applied Biosystems Sequence Scanner Version 1.0 software. At least 20 random samples for each SNP were sequenced to validate allele-specific PCR results.

Fig. 1. Characteristics of EPDS scores in the cohort of the study. (a) Mean prenatal or postnatal EPDS scores, across all subjects investigated. (b) Prenatal EPDS scores of patients classified as high-risk for PND. Only 44% of these patients also exhibited increased EPDS scores prenatally. (c) Postnatal EPDS scores of subjects presented with raised EPDS scores prenatally. 52% of these patients exhibited raised postnatal EPDS scores.
2.5. Statistical data analysis

Possible correlations between the population characteristics and EPDS scores were assessed by the Spearman rank correlation test. To test whether there were differences in subject characteristics between women classified as “high PND risk” (EPDS score ≥10) and “low PND risk” (EPDS score <10), the Mann–Whitney U-tests and $\chi^2$ tests were used.

A formal sample size calculation was undertaken to power this study, as it is apparent in the significance test of the SNPs examined. For instance, a statistically significant association of raised EPDS score and G allele of the BclI SNP was identified despite the small sample size of the study. Allele (presence/absence of minor allele) and haplotype frequencies for the cohort were calculated. These matched those reported in the literature for all SNPs (van Rossum et al., 2006) and were consistent with Hardy–Weinberg equilibrium (HWE), indicating that no population selection bias occurred. For HWE assessment of each SNP, the Pearson chi-square ($\chi^2$) statistic was used. For continuous and categorical variables, respectively, Mann–Whitney U-tests and $\chi^2$ tests were used to determine the statistical significance of any difference in the distribution of SNPs examined across categories of high or low EPDS scores in the sample. In the multivariate analysis, a logistic regression analysis were performed to calculate the relative risk of EPDS score ≥10 associated with the selected genetic variants (odds ratios and 95% CI). Since we multiple adjusted for SNPs, a Bonferroni correction was employed to correct for multiple adjustment of SNPs. All analyses were carried out using STATA, version 11, software (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA).

3. Results

3.1. EPDS score characteristics of the study cohort

For the 140 patients that completed the study protocol, there was no difference in the mean EPDS score obtained either

![Fig. 2](image-url)  
**Fig. 2.** Relationship of prenatal or postnatal EPDS scores and individual SNPs. (+): Subjects positive for the minor allele; (−): Subjects negative for the minor allele. Data represent the mean ± SEM EPDS score for each SNP and analysed for statistical significance by analysis of variance.
prenatally or postnatally (4.69 SEM = 0.28; 5.19 SEM = 0.41, \( p > 0.05 \)). The majority of the recruited patients (\( n = 111, 80\% \)) had an EPDS score below 10 prenatally (Fig. 1a). Postnatal assessment revealed an EPDS score of 10 or more in thirty-four patients (24%), indicative of high-risk for postpartum depressive illness (high-risk for PND patients); 44% of these patients also exhibited increased EPDS scores prenatally (Fig. 1b). In patients with prenatal EPDS score \( \geq 10 \) (\( n = 29 \)) only 52% progressed to raised EPDS score postnatally (Fig. 1c). Similarly, investigation of relevant dichotomous variables such as smoking, medical history, educational level, employment status and housing and continuous variables such as BMI, duration of gestation failed to detect any significant difference between the two groups (EPDS \( \geq 10 \) vs <10) (Table 1). Only age during booking showed a small but statistically significant difference between groups.

3.2. Association between SNP and EPDS scores

Data were also analysed for potential association between individual SNPs genotyped and EPDS scores. Results showed that the presence of the minor allele of the polymorphisms Bcll, ER22/23EK (R23K) and CRHR1(1) (rs1876828), had no effect on the mean prenatal (or postnatal) EPDS score of all subjects included in the study (Fig. 2a,b). However, a significant association was found between the CRHR1(2) (rs242939) SNP and EPDS score; pregnant women with the G allele exhibited an increased mean EPDS score compared to the A allele, either prenatally (9.29 vs 5.69, \( p < 0.0001 \)) or postnatally (9.03 vs 5.40, \( p < 0.0001 \)) (Fig. 2b) suggesting that the association is not specific for postpartum-onset depression. Interestingly, a weak but statistically significant association (\( p = 0.03 \)) was identified between the T allele of the CRHR1(3) (rs242941) SNP and the postnatal EPDS score only (Fig. 2b), suggesting a positive effect of this SNP on EPDS score only during the postnatal period.

We next focused on the potential association between single SNP and increased EPDS score (high-risk PND patients). We observed significant allele association with the Bcll and CRHR1(2) SNPs (\( p = 0.011 \) and 0.003, respectively), which were overrepresented in high-risk PND patients. No association was found between PND risk and the allele frequencies of the ER22/23EK, CRHR1(1) and CRHR1(3) SNPs (Table 1). Women with the Bcll (C/G) and CRHR1(2) (A/G) minor alleles exhibited significantly increased likelihood of EPDS score \( \geq 10 \) (OR: 2.9, 95% CI 1.2 to 6.9 and 4.9, 2 to 12, respectively) (Fig. 3). Furthermore, the risk ratio for high EPDS score increased when both the Bcll and CRHR1(2) were present with simultaneous presence of Bcll and CRHR1(2) was increased to 5.48 (2.13–14.10) suggesting independent contribution of the two SNPs. The risk of high EPDS score remained statistically significant and was not altered when either of Bcll or CRHR1(2) were present along with ER22/23EK, CRHR1(1) and CRHR1(3) SNPs suggesting absence of any synergistic or antagonistic interactions.

3.3. Association of haplotype-tag SNPs and EPDS score

Moreover, since the CRHR1 SNPs (rs1876828, rs242939 and rs242941) are haplotype-tag SNPs (htSNPs) we investigated the association of the various haplotypes for the SNPs rs1876828, rs242939 and rs242941 with high EPDS score. Estimation of haplotype distribution showed that only the G-A-G, G-A-T, A-A-G and G-G-T haplotypes were present in >10% of the cohort (49, 29, 21 and 11% respectively) (Fig. 4a). The common (major allele) haplotype G-A-G showed a population frequency of 0.4 (0.43 for the low-risk and 0.29 for the high-risk) and the variant (minor allele) haplotype C-G-T had a population frequency of 0.11 (0.066 for the low-risk and 0.21 for the high-risk). Using the chi-square test, a global test of haplotype distribution of these four haplotypes showed a significant difference between patients with high and low EPDS scores (\( \chi^2 = 29.091, \text{d.f.} = 3, p < 0.0001 \)). Compared to non-G-A-G and non-G-G-T groups respectively, patients with the G-A-G haplotype had significantly lower and with the G-G-T haplotype increased likelihood of EPDS \( \geq 10 \) (\( p = 0.01 \) and \( p < 0.0001 \), respectively) with odds ratio (OR) & 95% CI of 0.72 (0.53–0.97) and 3.22 (1.91–5.42) respectively (Fig. 4b). Almost 50% (48.6%) of the G-G-T haplotypes were found in subjects with EPDS \( \geq 10 \) (high-risk PND group), whereas only 18% of the G-A-G haplotype were in the high-risk group (Fig. 4c).

4. Discussion

The CW-GAPND study protocol was designed to test at the clinical setting the potential use of SNPs in prospectively identifying women with high (\( \geq 10 \)) EPDS score and thus increased risk for PND. We focused on GR and CRHR1 gene SNPs that might impact on responses to psychobiological stressors during pregnancy or the postpartum period. A positive association with high EPDS score was identified for the Bcll but not the ER22/23EK polymorphism. Moreover, investigation of the haplotype tagged SNPs rs1876828, rs242939 and rs242941 of the CRHR1 gene, suggested that patients carrying the minor allele of the rs242939 SNP present with significantly higher EPDS either pre- or postnatally. Most importantly, the haplotype G-G-T and independently the (G) minor allele of the rs242939 showed a strong association with EPDS
score $\geq 10$ and high-risk for PND, whereas the G-A-G haplotype appeared to exert a protective effect on EPDS score.

There are limited studies investigating the genetic impact on risk for PND across all pregnant women. Genetic polymorphisms of the serotonergic transmission and monoamine-related genes have been previously associated with the development of postnatal depression (Doornbos et al., 2009; Costas et al., 2010; Fasching et al., 2012; Mehta et al., 2012). Thus, the focus on molecules regulating stress responses and prospective cohort design of the study are the two main strengths. The prospective recruitment of pregnant women who were not clinically depressed and longitudinal assessment for PND risk in the early postpartum period, preserved the temporality of the observed associations, and also minimise the potential confounding effects of unmeasured factors (such as residual confounding), and also establish specificity of SNPs with PND. We acknowledge that the cohort size of the study does not provide adequate power for all SNPs associations and this is a weakness of the study; hence further work using a larger cohort would be necessary. The CW-GAPND study was based on a convenience sample of a fixed number of participants, and there was no attempt for formal assessment of the power calculation based on the expected effect size of the primary outcome of interest. The power of the study for the three associations with these patient numbers was calculated at 44%, 86% and 21% for the BclI, rs242939 and rs242941 polymorphisms respectively. A minimum of 80% is considered as an adequate study power and this was achieved for one SNP only. To achieve this power for all SNPs a cohort of minimum 594 patients would be required, although other factors that influence association studies such as differences in allele frequencies, age and ethnicity should also be taken into account. Use of a larger cohort will be able to determine the potential impact of other important parameters such as of allele dosage effect (i.e. homozygous vs heterozygous). Another potential issue of the study is the identification strategy used for determining PND risk, and the lack of an instrument capable of providing definite diagnosis. The EPDS questionnaire is an established tool, most frequently used in clinical practice, and the chosen cut-off score of $\geq 10$ is widely used and offers reasonable performance characteristics with both sensitivity and specificity above 80% for detection of both major and minor depression (Cox et al., 1993; Schaper et al., 1994; Hewitt et al., 2009). However, different cut-off points could lead to variations in measures of accuracy of the test (i.e. sensitivity and specificity) and thus difficulties may arise in results interpretation and impact assessment. This might explain the higher prevalence of high-PND risk of 24% observed in the cohort population, which may also reflect the higher rate of adverse socio-economic factors in our population including poor social support, teenage pregnancies, immigrant population and unemployment. Certainly, further refinement would be required by investigating performance of the SNP association analysis with different EPDS scores or different identification strategies.

We focused our approach on genetic variants of the HPA axis previously associated with depression. The HPA axis serves as a key interface between environmental stressors and the development of depression and functional differences due to genetic variation may alter individual responses to stressful events and may regulate vulnerability to stress-related psychiatric disorders. The presence of depressive symptoms during pregnancy appears to be associated with altered regulation of GR sensitivity (Katz et al., 2012). GR sensitivity appears diminished with progression of pregnancy and increasing maternal depressive symptoms; peripheral expression of GR co-chaperone genes may serve as a biomarker for risk of

Fig. 4. Relationship between specific CRHR1 haplotype and risk for PND. (a) Distribution of different CRHR1 haplotypes among the CW-GAPND cohort. Rare haplotypes with frequency <1% are excluded. (b) Forrest plot of risk ratios for increased risk for PND associated with presence of different CRHR1 haplotypes. (c) Distribution of different CRHR1 haplotype among groups classified as high or low risk for development of PND based on an EPDS score $\geq 10$. 
developing depressive symptoms during pregnancy. The GR gene SNPs investigated such as the Bcll and ER22/23EK are linked with clinical phenotypes, possibly due to altered function of GR and therefore may increase the risk of depressive disorders by altering cortisol responses to psychosocial stress (Spijker & van Rossum, 2009). In particular the ER22/23EK SNP has been reported to relate to decreased cortisol suppression to dexamethasone (van Rossum and Lamberts, 2004), whereas the Bcll polymorphism seems to be associated with attenuated cortisol responses. Interestingly, our study identified a significant association with high PND risk of only the G minor allele of the Bcll SNP, found despite no effect on the prenatal or postnatal EPDS score, a finding that is consistent with results from non-pregnant depressed population (van Rossum et al., 2006). Similar findings have also reported in a group of pre-menopausal women and suggested that homozygous carriers of both Bcll and ER22/23EK SNPs have increased risk of developing a major depressive episode (van Rossum and Lamberts, 2004; Krishnamurthy et al., 2008). The lack of association between the ER22/23EK SNP and high EPDS score in our study suggests that patients at risk for PND might represent a subgroup with distinct gene–environment interactions and unique genetic characteristics that exhibit increased vulnerability to pregnancy-associated triggers. The high-risk PND group of the CW-GAPND cohort also exhibited a strong association with rs424393, a CRHR1 SNP previously been associated with major depression in a group of Han Chinese patients (Liu et al., 2006). In fact this SNP was associated with raised EPDS values both before and after delivery and were thus not specific for postpartum-onset depression. It is increasingly recognised that multiple genetic variations with discrete functional effects in a number of genes regulating the HPA axis may alter susceptibility to stress-related psychiatric disorders and a system genetics approach is required to fully elucidate the impact of gene × environment interactions. There is already evidence for the association of genetic variants in genes intricately tied to the CRH system with depression and anxiety, such as the GR gene or the serotonin transporter (Ressler et al., 2010). In agreement with this, we noted a combined effect of the simultaneous presence of the Bcll and rs424393 SNPs that appeared to further increase the odds of raised EPDS score and high PND risk, raising the possibility of gene × gene interactions between CRHR1 and GR loci.

The CW-GAPND study provides the first preliminary evidence of genetic association between gene variants of the ‘stress’ endocrine axis and risk for depression during pregnancy and post-partum. It also offers additional benefits in understanding the biological basis of disease. Polymorphisms of genes regulating stress responses appear to be promising targets for further investigations. Certainly, a larger prospective study of a replication sample that will include a larger prospective study of a replication sample that will include a larger prospective study of a replication sample that will include a larger prospective study of a replication sample. In particular the ER22/23EK SNP has been reported to relate to decreased cortisol suppression to dexamethasone (van Rossum and Lamberts, 2004), whereas the Bcll polymorphism seems to be associated with attenuated cortisol responses. Interestingly, our study identified a significant association with high PND risk of only the G minor allele of the Bcll SNP, found despite no effect on the prenatal or postnatal EPDS score, a finding that is consistent with results from non-pregnant depressed population (van Rossum et al., 2006). Similar findings have also reported in a group of pre-menopausal women and suggested that homozygous carriers of both Bcll and ER22/23EK SNPs have increased risk of developing a major depressive episode (van Rossum and Lamberts, 2004; Krishnamurthy et al., 2008). The lack of association between the ER22/23EK SNP and high EPDS score in our study suggests that patients at risk for PND might represent a subgroup with distinct gene–environment interactions and unique genetic characteristics that exhibit increased vulnerability to pregnancy-associated triggers. The high-risk PND group of the CW-GAPND cohort also exhibited a strong association with rs424393, a CRHR1 SNP previously been associated with major depression in a group of Han Chinese patients (Liu et al., 2006). In fact this SNP was associated with raised EPDS values both before and after delivery and were thus not specific for postpartum-onset depression. It is increasingly recognised that multiple genetic variations with discrete functional effects in a number of genes regulating the HPA axis may alter susceptibility to stress-related psychiatric disorders and a system genetics approach is required to fully elucidate the impact of gene × environment interactions. There is already evidence for the association of genetic variants in genes intricately tied to the CRH system with depression and anxiety, such as the GR gene or the serotonin transporter (Ressler et al., 2010). In agreement with this, we noted a combined effect of the simultaneous presence of the Bcll and rs424393 SNPs that appeared to further increase the odds of raised EPDS score and high PND risk, raising the possibility of gene × gene interactions between CRHR1 and GR loci.

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Contributions

N.E contributed to the design of study, recruitment of patients and collection of clinical details, data analysis and manuscript preparation; LD contributed to the molecular methods development, performed the experiments and data analysis and managed the literature searches; D.N contributed to the recruitment of patients, collection of clinical details and data analysis; K.N-B undertook data statistical analysis and manuscript preparation; S.C.S contributed to the design of study, data analysis and manuscript preparation; D.K.G. contributed to the design of the study, guided data interpretation and manuscript writing. All authors have approved the submitted version.

Author disclosure

The authors have no conflict of interest to disclose. 

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