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Reproductive Affective Disorders: a Review of the Genetic Evidence for Premenstrual Dysphoric Disorder and Postpartum Depression

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Abstract
Purpose of Review The purpose of this study is to review and summarize the literature exploring the genetic basis for premenstrual dysphoric disorder (PMDD) and postpartum depression (PPD).
Recent Findings There is more evidence for a genetic basis for PPD than for PMDD, but only when PPD is defined as beginning in the immediate postpartum time period.
Summary Familial, genome-wide linkage and association studies, and candidate gene studies, most in the past 10 years, have examined the genetic etiology of reproductive affective disorders, including PMDD and PPD. The most commonly studied genes include SERT, COMT, MAOA, BDNF, and ESR1 and 2. This qualitative review of the recent literature finds limited evidence so far for the genetic basis for PMDD, with both familial and candidate gene studies having negative or conflicting results. Evidence is stronger for the genetic basis for PPD, with positive associations found in family studies and in several genes associated with major depression as well as genes involved in estrogen signaling but only when PPD onset is shortly after delivery. Epigenetic biomarkers on genes responsive to estrogen have also been found to predict PPD. Our findings underscore the need for additional studies with larger samples, as well as the crucial importance of timing in the definition of PPD for genetic studies.

This article is part of the Topical Collection on *Reproductive Psychiatry and Women's Health*

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Introduction

Despite decades of work, the genetic basis for major depressive disorder (MDD) remains elusive. MDD may in fact have several or many "causes" or "broken parts" that lead to the clinical illness that we call MDD, and in fact many different clinical phenotypes are grouped together under the umbrella term MDD. This underlying biological heterogeneity, along with the fact that environmental factors likely also play a role in the development of the illness, makes it hard to identify specific genetic underpinnings of MDD [1]. One approach to sorting out the genetic basis for MDD is to identify more homogenous groups of patients with similar clinical characteristics and identify the genetic basis for their version of the illness. One such subgroup is those with "reproductive depression" or affective disorders [2]— affective episodes that are triggered in women at times of hormonal fluctuation. MDD is twice as common in women as in men during the reproductive years [3], and mild depressive symptoms are common in the general populating during periods of hormonal change (the premenstrual, postpartum, and perimenopausal periods). A minority of women experience severe affective episodes during these periods. Such reproductive affective episodes have been hypothesized to result not from differential hormone fluctuation but from an affective vulnerability to normal hormonal shifts [2]. These affective disorders can be conceptualized as a specific biological response to hormonal fluctuation in the brain that leads to a clinical presentation of affective symptoms, though the exact mechanisms are as yet unknown. Since the original proposal of the concept of "reproductive depression," a number of studies have focused on the genetic

basis of premenstrual dysphoric disorder (PMDD) and postpartum depression (PPD). This review will summarize and synthesize this literature.

Definitions

PMDD Premenstrual dysphoric disorder (PMDD) is a clearly defined disorder based on the following DSM-5 criteria: one or more of (1) marked affective lability; (2) marked irritability or anger; (3) marked depressed mood, feelings of hopelessness, or self-deprecating thoughts, and ;(4) marked anxiety, tension, and/or feeling keyed up or on edge AND one or more of (1) decreased interest in usual activities, (2) difficulty concentrating, (3) lethargy, (4) marked change in appetite or specific food cravings, (5) hypersomnia or insomnia, (6) a sense of being overwhelmed or out of control, (7) physical symptoms—breast tenderness/swelling, joint or muscle pain, bloating, or weight gain. The symptoms must occur in a majority of cycles, with remission in between, and cause clinically significant distress and/or impair functioning [4]. Many conceptualize PMDD as an affective disorder that occurs during the luteal phase and remits with onset of menses, though symptoms for some women are qualitatively different during such periods (with greater likelihood of irritability and tension). Less severe symptoms during the luteal phase are sometimes referred to as premenstrual syndrome (PMS), [5] which generally does not impair functioning. Both terms, PMDD and PMS, have been used in the literature exploring the genetic basis of this syndrome and, in addition, the literature has varied in the methods/tools used to define the condition, with the most rigorous studies using prospective daily measurements of symptoms for at least two menstrual cycles.

PPD Postpartum depression (PPD) has been defined in various ways—however, the most commonly accepted definition has been based on the DSM-IV definition: a major depressive episode (MDE) that begins within 4 weeks of delivery. The DSM-5 has expanded this definition to include MDEs that begin during pregnancy or within the first 4 weeks after delivery and renamed the condition "MDD with peripartum onset." Studies on the genetic basis of PPD have used various definitions as well as different tools, both self-rated and based on clinical interviews, to identify PPD. We will clarify the definitions used in the studies described below.

Heritability and Familial Aggregation

PMDD Evidence from family and twin studies dating back to 1964 [6] has suggested a genetic influence in the etiology of PMDD, though not all studies agree. Two family studies have shown that the disorder is retrospectively reported more frequently in female first-degree relatives [7, 8], though another which included both retrospective reports and prospective symptoms found no familiality [9]. Another study examined retrospective premenstrual complaints in families with either MDD or bipolar disorder and was also negative [10]. Kendler et al. [11] used conventional factor analysis and estimated a heritability of 35.1% for retrospectively reported premenstrual symptoms. They later performed a second factor analysis on a follow-up study of premenstrual complaints in the same sample and found that premenstrual complaints were modestly stable over time, with heritability estimated at 56% [12, 13]. Twin studies have generally shown a higher concordance rate in monozygotic versus dizygotic twins [13–17], though whether the genetic vulnerability is for premenstrual symptoms per se or some other heritable trait remains unclear. For example, Van den Akker et al. [13] performed a factor analysis on retrospectively reported menstrual cycle characteristics in 462 female twin pairs and concluded that premenstrual symptoms may be heritable. However, in a later study they concluded that premenstrual symptom reporting was instead associated with the personality trait of neuroticism and was not genetic in and of itself [18]. No studies that have examined the familial basis for prospectively confirmed symptoms that meet DSM-5 criteria for PMDD, perhaps because of the difficulty of obtaining prospective symptom reporting for 2–3 months in a large sample of first-degree relatives with multiple generations.

PPD Multiple studies have demonstrated that there is a genetic basis for mood episodes that begin during the postpartum time period, particularly within 4 weeks of delivery. Treloar et al. found that genetic factors explained 38% of the variance in PPD as determined by a questionnaire in a sample of 838 twin pairs [19]. Two studies have demonstrated that PPD exhibits familiality in families with MDD, with stronger correlations for depressive episodes that began in the immediate ($\leq$ 4 weeks after delivery) postpartum [20, 21]. PPD has also been demonstrated to be familial in families with bipolar disorder, again when limited to depressive episodes beginning shortly after delivery [22]. Notably, these studies used retrospective reporting and, as with the PMDD literature, the timing of the onset of symptoms may be subject to recall bias.

Genome-Wide Linkage and Association Studies

PPD In a combined linkage analysis and genome-wide association study, Mahon et al. studied a sample of women with either MDD or bipolar disorder and compared women with PPD episodes (as defined by onset within 4 weeks of delivery) to women who had a history of pregnancy but no PPD [23]. They found suggestive genome-wide linkage for PPD to regions of chromosomes 1 and 9. A follow-up single nucleotide

polymorphism (SNP) association study of the identified regions found strong association to two intergenic regions but also demonstrated modest association with HMCN1 (hemicentin 1) and METTL13 (methyltransferase like 13) on chromosome 1. These findings were not significant after correction for multiple testing. HMCN1 is highly expressed in the hippocampus, has been shown to be altered in rats by a postpartum drop in estrogen levels [24], and contains four experimentally determined estrogen binding sites [25]. METTL13 is putatively involved with methyltransferase activity, which has been shown to play a role in estrogen receptor-induced gene transcription [24].

Mehta et al. performed a genome-wide association study using peripheral blood gene expression profiles in euthymic pregnant women, comparing the expression profiles during pregnancy between women who went on to develop PPD defined as onset within the first 7 weeks postpartum and those that remained euthymic [26•]. They identified 116 transcripts that were differentially expressed between the two groups, allowing 88% accuracy in the prediction of PPD. Data mining approaches indicated an over-representation of transcripts linked to estrogen signaling, and the authors concluded that women who went on to develop PPD displayed an increased sensitivity to estrogen signaling.

Candidate Gene Studies in Both PMDD and PPD

Candidate gene studies for both PMDD and PPD have primarily focused on genes previously associated with a risk for MDD, including those coding for the serotonin transporter (SERT), catechol-O-methyl transferase (COMT), monoamine Oxidase (MAO), and brain derived neurotrophic factor (BDNF). Several studies have also focused on polymorphisms of the genes for the estrogen receptors (ESR1 and ESR2), given the hypothesized hormonal trigger for both PMDD and PPD. Candidate gene studies investigating PMDD are summarized in Table 1 and those investigating PPD are in Table 2. Below we discuss some of the more promising candidate gene studies in both disorders.

SERT Gene The best studied candidate gene in both PMDD and PPD is the serotonin transporter gene (SERT). The SERT gene has two primary polymorphisms. The first is a 44-bp insertion/deletion located in the promoter region (5-HTTLPR), creating the short and long variants of the gene. The long (L) allele increases transcriptional efficacy and activity compared to the short (S) allele, and the S allele has been associated with mental health problems and depression. The 5-HTTLPR polymorphism is the most extensively studied polymorphism in both PMDD and PPD. The second polymorphism (STin2VNTR) involves a variable number of tandem repeats (VNTR) in the second intron; longer sets of repeats have been associated with mental health problems.

PMDD Melke et al. studied both polymorphisms in the SERT gene (along with another polymorphism in a noncoding region) and found no association between any SERT polymorphism and PMDD symptoms [34]. Gingnell et al. found that the 5-HTTLPR S allele was associated with neuroticism in women with PMDD; of note there was a trend toward a relationship between the S allele and risk for PMDD that was not significant [36]. Finally, neither Magnay et al. [37] nor Comasco et al. [28] found any association between the 5-HTTPLRP polymorphism and PMDD. Overall, the preponderance of the evidence does not support an association between SERT polymorphism and PMDD.

PPD In contrast, there is more evidence for a role of SERT polymorphisms in PPD, though studies have had mixed results. The 5-HTTPLRP studies demonstrate a pattern of positive studies when PPD is measured in the immediate postpartum time-period (6–8 weeks) and negative studies when PPD is measured further from delivery (S e Table 2). As noted, PPD has been shown to be familial, but only when onset of symptoms was in the first 4 weeks after delivery. The 5-HTTPLRP polymorphism may therefore play a role in the susceptibility to PPD, but only in the immediate postpartum time period. There have been far fewer studies of the STin2VNTR polymorphism in PPD, with mixed results and no clear pattern to date.

COMT Gene The catechol-O-methyltransferase (COMT) gene codes for an enzyme that breaks down catecholamine neurotransmitters including epinephrine, norepinephrine, and dopamine, and has previously been studied in depression, anxiety and stress. The Val158Met polymorphism results in a low activity enzyme in those carrying the Met allele as compared to the Val allele (reviewed in [68]). There have been conflicting results in studies of this polymorphism in MDD with positive studies with both Val/Val (high activity) and Met/Met (low activity) forms of the gene. Two studies examining the association between the COMT gene polymorphism in PMDD were negative [29, 30]. In contrast, the COMT low activity (Met/Met) polymorphism demonstrated a positive association with PPD but again only in the immediate postpartum time-period (6–8 weeks) [42, 43, 69], and not when PPD was defined at 3–6 months [42, 69].

BDNF Gene Brain derived neurotrophic factor (BDNF) has been extensively studied in depression. Lower serum levels of the protein have been found in patients with MDD, which then increase with antidepressant treatment [70, 71]. The Val66Met polymorphism alters the regulated protein secretion, and the Valine allele has been associated with psychiatric disorders.

Table 1 Gene association studies of premenstrual dysphoric disorder

References	Definition of PMDD	Sample size/country/ethnicity	Findings
Transcription Factor AP-2ß			
Damberg et al. 2005 [27]	Prospective rating for 2 cycles	176 PMDD 91 Controls Swedish sample	Negative
BDNF			
Comasco et al. 2014 [28]	Prospective rating for 2 cycles	31 PMDD 31 Controls Swedish sample	Negative Positive for impaired emotion-induced fronto-cingulate cortex activation in PMDD
COMT Val158Met polymorphism			
Huo et al. 2007 [29]	Prospective rating positive 2/3 cycles	91 PMDD 56 Controls Caucasian sample	Negative
Deveci et al. 2014 [30]	Prospective rating positive 2/3 cycles	53 PMDD 53 Controls (not followed prospectively) Turkish sample	Negative
Cannabinoid receptor			
Yildiz et al. 2015 [31]	Prospective rating positive for 2 cycles	51 PMDD 51 Controls Turkish sample	Negative
Dopamine receptor			
Yildiz et al. 2015 [31]	Prospective rating positive for 2 cycles	51 PMDD 51 Controls Turkish sample	Negative
ESR-1 (α)			
Huo et al. 2007 [29]	Prospective rating positive 2/3 cycles	91 PMDD 56 Controls Caucasian sample	Positive
Miller et al. 2010 [32]	Prospective rating positive 2/3 cycles	68 PMDD 56 Controls Ethnicity NI	Negative for PMDD Positive for personality traits associated with PMDD
ESR-2 (β)			
Takeo et al. 2005 [33]	Retrospective interview/self-report	51 postmenopausal women Japanese sample	Positive
Huo et al. 2007 [29]	Prospective rating positive 2/3 cycles	91 PMDD 56 Controls Caucasian sample	Negative
Serotonin transporter gene length polymorphism (5-HTTPLRP)			
Melke et al. 2003 [34]	Prospective rating for 2 cycles	199 PMDD 91 Controls	Negative
Praschak-Rieder et al. 2002 [35]	Prospective rating for 2 cycles	44 SAD with PMDD 43 SAD controls US and European sample	Positive for PMDD with SAD
Gingnell et al. 2010 [36]	Prospective rating for 2 cycles	27 PMDD 18 Controls Swedish sample	Negative for PMDD Positive for neuroticism in PMDD
Magnay et al. 2010 [37]	Prospective rating for 2 cycles	53 PMDD 52 Controls UK sample	Negative
Comasco et al. 2014 [28]	Prospective rating for 2 cycles	31 PMDD	Negative

Table 1 (continued)

References	Definition of PMDD	Sample size/country/ethnicity	Findings
		31 Controls Swedish sample	
Serotonin transporter VNTR polymorphism			
Melke et al. 2002 [34]	Prospective rating for 2 cycles	199 PMDD 91 Controls	Negative
Serotonin 1A receptor C(−1019) G polymorphism			
Dhingra et al. 2007 [38]	Prospective rating for 2 cycles	53 PMDD 51 Controls White European sample	Positive
Yen et al. 2014 [39]	Prospective rating positive for 2/3 cycles	59 PMDD 74 Controls Taiwanese sample	Negative Positive for poor working memory in luteal phase in PMDD

BDNF brain derived neurotrophic factor gene, *COMT* catechol-O-methyl transferase gene, *ESR* estrogen receptor gene, *NI* not indicated, *SAD* seasonal affective disorder, *VNTR* variable number of tandom repeats

Mice homozygous for the BDNF polymorphism exhibit increased anxiety-like behavior that fluctuated over the estrous cycle [72], making BDNF a candidate gene for PMDD and possibly PPD. However, results to date are disappointing. The one completed study in PMDD was negative though the Met allele was associated with impaired emotion-induced fronto-cingulate cortex activation in women with PMDD [28]. Two studies have been done in women with PPD: one was negative at 8 weeks postpartum [40] and the second was positive at 6 weeks postpartum, but only in women with a psychiatric history [41]. The association was negative for PPD measured at 24 weeks, underscoring the importance of timing in gene association studies in PPD.

ESR Genes Reproductive depressions are thought to be abnormal responses to normal changes in gonadal hormone levels. Previous work has demonstrated that exposure to and withdrawal from normal levels of gonadal steroids results in depressive symptomatology in women previously diagnosed with either PMDD or PPD [73, 74]. One possible mechanism for this phenomenon is polymorphic variation in genes encoding gonadal steroid receptors, leading to variability in response to gonadal steroids. The ESR genes have therefore been studied in both PMDD and PPD. There are two subtypes of estrogen receptors: α (ESR1) and β (ESR2). ESR1 and ESR2 have comparable affinities for estradiol but differ in tissue distribution and other ligand affinities [75].

PMDD There have been four studies with PMDD and ESR genes, two for each subtype, with conflicting results for each. Huo and colleagues [29] found that four different single nucleotide polymorphisms (SNPs) in intron 4 of ESR1 were more likely to occur in subjects with PMDD versus healthy controls. They also studied ESR2 and did not find an association. The same group published a second study that did not find an association between PMDD and ESR1 but did find an association between certain psychological traits in the women with PMDD and SNPs in ESR1 [32]. Finally, Takeo and colleagues studied 51 postmenopausal women and found an association between the short-short (ss) genotype of the ESR2 and a history of PMS [33]. However, this was based on a retrospective diagnosis determined by research assistants using DSM-IV research criteria, rather than clinician-based diagnosis or use of validated scales. It remains unclear if polymorphisms of the ESR genes underlie the pathogenesis of PMDD.

PPD Only ESR1 has been studied in PPD. Costas et al. [50] examined 44 candidate genes for association with PPD in a large sample ($N = 1804$) of Spanish women. Each woman was interviewed at 2–3 days, 8 weeks, and 32 weeks postpartum. The participants initially completed an EPDS, and those who scored ≥ 9 were then interviewed with the Diagnostic Interview for Genetics Studies (DIGS), which uses DSM-IV criteria for an MDE. Ultimately, 162 women were classified as meeting criteria for PPD within 32 weeks of delivery. In a case-control association study, four out of seven SNPs with a P value less than 0.01 were from the ESR1 gene. However, no SNP remained significant after correction for multiple tests. A second study [51] enrolled 257 women within 12 weeks of delivery and assessed mood at the time of enrollment with either an EPDS or a Montgomery Asberg Depression Rating Scale (MADRS), as well as a structured clinical interview (using either the Structured Clinical Interview for DSM-IV (SCID) or the Mini International Neuropsychiatric Interview (MINI)). EPDS scores were

Table 2 Gene association studies of postpartum depression

References	Definition of PPD	Sample size/country/ethnicity	Findings
BDNF			
Figueira et al. 2010 [40]	EPDS ≥ 12 at 8 weeks	227/Brazil/NI	Negative 8 weeks
Comasco et al. 2011 [41]	EPDS ≥ 12 at 6 weeks and 6 months	275/Sweden/NI	Positive in women with a psychiatric history at 6 weeks Negative 6 months
COMT Val158Met polymorphism			
Doornbos et al. 2009 [42]	EPDS at 6 weeks and 3 months	89/Netherlands/Caucasian	Positive 6 weeks Negative 3 months
Comasco et al. 2011 [41]	EPDS ≥ 12 at 6 weeks and 6 months	275/Sweden/NI	Positive 6 weeks Negative 6 months
Alvim-Soares et al. 2013 [43]	EPDS ≥ 13 at 8 weeks	116/Brazil/ Caucasian	Positive 8 weeks
Corticotrophin releasing hormone receptor 1			
Engineer et al. 2013 [44]	EPDS ≥ 10 at 2–8 weeks	140/UK/Caucasian	Positive 2–8 weeks
Schneider et al. 2014 [45]	EPDS at 6–9 months	361/Germany/Caucasian	Negative 6–9 months
Stergiakouli et al. 2014 [46]	EPDS at 8 weeks	8340/UK/NI	Negative 8 weeks
Tan et al. 2015 [47]	Clinical interview, time-period NI	696/Singapore/Chinese	Negative, time-period NI
CYP2D6			
Josefsson et al. 2004 [48]	EPDS ≥ 10 at 6–8 weeks and 6 months	145/Sweden/NI	Negative 6–8 weeks Negative 6 months
Dopamine receptor type 4			
Ivorra et al. 2010 [49]	EPDS at 8 weeks	317/Spain/NI	Negative 8 weeks
ESR-1(α)			
Costas et al. 2010 [50]	EPDS/DIGS at < 1, 8 weeks and 8 months	1804/Spain/NI 162 women met DSM-IV criteria for a MDE in the first 32 weeks	Positive (but not statistically significant) within 8 months
Pinsonneault et al. 2013 [51]	EPDS and/or MADRS, within 3 months	156/Canada/primarily Caucasian	Positive, within 3 months
Fatty acid desaturase gene polymorphisms			
Xie and Innis 2009 [52]	EPDS ≥ 10 at 8 weeks and 6 months	69/Canadian/Caucasian	Negative 8 weeks Positive 6 months
FKBP5			
Schneider et al. 2014 [45]	EPDS at 6–9 months	361/Germany/Caucasian	Negative 6–9 months
Glucocorticoid receptor			
Engineer et al. 2013 [44]	EPDS ≥ 10 at 2–8 weeks	140/UK/Caucasian	Positive 2–8 weeks
Schneider et al. 2014 [45]	EPDS at 24–36 weeks	361/Germany/Caucasian	Negative 6–9 months
Stergiakouli et al. 2014 [46]	EPDS at 8 weeks	8340/UK/NI	Negative 8 weeks
Tan et al. 2015 [47]	Clinical interview, time-period NI	696/Singapore/Chinese	Negative, time-period NI
Hemicentin-1 (HMNC1)			
Alvim-Soares et al. 2014 [53•]	MINI interview at 8 weeks	110/Brazil/European	Positive 8 weeks
Hydroxysteroid (11-beta) dehydrogenase 1			
Iliadis et al. 2017 [54]	EPDS at 8 weeks	769/Sweden	Positive 8 weeks Neuroticism played intermediary role
MAOA			
Doornbos et al. 2009 [42]	EPDS at 6 weeks and 3 months	89/Netherlands/Caucasian	Positive 6 weeks Negative 3 months
Ivorra et al. 2010 [49]	EPDS at 8 weeks	317/Spain/NI	Negative 8 weeks
Comasco et al. 2011 [41]	EPDS ≥ 12 at 6 weeks and 6 months	275/Sweden/NI	Positive 6 weeks Negative 6 months
Methylenetetra-hydrofolate reductase receptor 1 (MTHFR)			
Lewis et al. 2012 [55]	EPDS at 8–32 weeks and at 8–84 weeks	6809/UK/Caucasian	Negative 8–32 weeks Positive 8–84 weeks
Oxytocin receptor			
Jonas et al. 2013 [56]	CESD ≥ 27 at 6 months	432/Canadian/Caucasian	Negative 6 months
Mileva-Seitz et al. 2013 [57]	CESD at 6 months	187/Canadian/Caucasian	Positive 6 months
Bell et al. 2015 [58]	EPDS ≥ 12 at 8 weeks	545/UK/Caucasian	Positive 8 weeks (in mothers not depressed in pregnancy)
Serotonin transporter gene length polymorphism			

Table 2 (continued)

References	Definition of PPD	Sample size/country/ethnicity	Findings
(5-HTTPLRP)			
Sanjuan et al. 2008 [59]	EPDS/DIGS at < 1, 8 weeks and 8 months	1804/Spain/Caucasian	Negative < 1 week Positive 8 weeks Negative 8 months
Doornbos et al. 2009 [42]	EPDS at 6 weeks and 3 months	89/Netherlands/Caucasian	Positive 6 weeks Negative 3 months
Binder et al. 2010 [60]	SCID and HRSD at < 8 weeks, 9–24 weeks	206/EUA/NI	Positive < 8 weeks Negative 9–24 weeks
Ivorra et al. 2010 [49]	EPDS at 8 weeks	317/Spain/NI	Negative 8 weeks
Comasco et al. 2011 [41]	EPDS ≥ 12 at 6 weeks and 6 months	275/Sweden/NI	Positive in women with a psychiatric history at 6 weeks Negative 6 months
Mitchell et al. 2011 [61]	WHO composite international diagnostic interview based on DSM-IV criteria	1206/US/NI	Negative at 1 year
Gelabert et al. 2012 [62]	SCID and EPDS ≥ 10 at 1–24 weeks	187/Canadian/Caucasian	Positive (S) 1–24 weeks
Mehta et al. 2012 [26•]	EPDS at < 1 week and 6–8 months	419/German/Caucasian	Negative < 1 week Negative 6–8 months
Khabour et al. 2013 [63]	EPDS ≥ 13 at 4–6 weeks	370/Jordan/NI	Negative 4–6 weeks
Pinheiro et al. 2013 [64]	MINI plus EPDS ≥ 13 at 6–13 weeks	207/Brazil/NI	Positive 6–13 weeks
Zhang et al. 2014 [65]	Clinical interview and multiple measures including EPDS ≥ 13 in the year postpartum	412/China/Han Chinese	Positive within the year postpartum
Zhang et al. 2015 [66]	Cases had been admitted with a diagnosis of PPD with onset between 6 weeks and 6 months postpartum	260/China/Han Chinese	Positive within 6 months postpartum
Serotonin transporter VNTR polymorphism			
Sanjuan et al. 2008 [59]	EPDS/DIGS at < 1, 8 and 8 months	1804/Spain/Caucasian	Negative < 1 week Positive 8 weeks Negative 8 months
Ivorra et al. 2010 [49]	EPDS at 8 weeks	317/Spain/NI	Negative 8 weeks
Mitchell et al. 2011 [61]	WHO composite international diagnostic interview	1206/US/NI	Negative at 1 year
Gelabert et al. 2012 [62]	SCID and EPDS ≥ 10 at 1–24 weeks	187/Canada/Caucasian	Positive 1–24 weeks
Tryptophan hydroxylase 1 and 2			
Fasching et al. 2012 [67]	EPDS at < 1 week and 6–8 months	361/Germany/Caucasian	Negative < 1 week Positive 6–8 months
Khabour et al. 2013 [63]	EPDS ≥ 13 at 4–6 weeks	370/Jordan/NI	Negative 4–6 weeks

BDNF brain derived neurotrophic factor. *CESD* Center for Epidemiological Studies Depression Scale, *COMT* catechol-O-methyl transferase gene, *CYP2D6* cytochrome P450 2D6 gene, *DIGS* diagnostic interview for genetic studies, *EPDS* Edinburgh Postpartum Depression Scale, *ESR* estrogen receptor gene, *FKBP5* FK506 binding protein 5 gene, *HRSD* Hamilton Rating Scale for Depression, *MAOA* monoamine oxidase A gene, *MADRS* Montgomery Asberg Depression Rating Scale, *MINI* Mini international neuropsychiatric interview, *NI* not indicated, *SCID* structured clinical interview for DSM-IV, *VNTR* variable number of tandom repeats, *WHO* World Health Organization

available from 156 women and were significantly associated with two ESR1 gene polymorphisms, the TA repeat (L allele) ($p = 0.007$) and rs2077647 (G allele) ($p = 0.03$). Only the TA repeat association remained positive after correction for multiple testing ($p = 0.04$). The same variants were also associated with the clinical diagnosis of PPD, defined as meeting DSM-IV criteria for an MDE within 12 weeks postpartum in women with no previous history of a mood disorder, but this association did not remain significant after correction for multiple tests. These results point to a possible association between ESR1 and PPD and need to be replicated in larger samples.

Other Candidate Genes A number of other negative or unreplicated candidate gene studies have been conducted in PMDD, PPD or both. See Tables 1 and 2 for a full listing of candidate gene studies on PMDD and PPD to date.

Candidate Gene Studies in PPD Alone

Three other candidate genes that have been studied in PPD but not PMDD deserve mention.

OXTR Gene Oxytocin plays a key role in regulating emotion, social interaction, and stress reactivity and is also central to normal birth, lactation, and mother–infant attachment [76, 77]. In addition, reductions in oxytocin measured in plasma have been associated with PPD [78, 79]. Two studies

examined SNP variations in the Oxytocin Receptor (OXTR) gene and their association with the development of PPD at 24 weeks postpartum and had opposite findings [56, 57]. Interestingly, a more recent study examined variation in the OXTR gene but measured PPD at 8 weeks postpartum and found a positive association [58]. These findings need to be replicated, and the timing of onset of symptoms should be taken into account.

HMNC1 Gene As noted above, Mahon et al. [23] demonstrated a modest association between PPD in women with mood disorders and the Hemicentin 1 gene (HMNC1) in a genome-wide linkage and association study. Following up on this finding, Alvim-Soares et al. [53•] genotyped 110 Brazilian women of European descent who completed both an EPDS and a MINI interview at 8 weeks postpartum. They found that heterozygosity at the HMNC1 polymorphism was associated with depressive symptoms. Given that this gene was originally identified by a genome-wide linkage and association study, the confirmation of an association between HMCN1 and PPD is an important finding and needs to be replicated, preferably in larger samples.

MAOA Gene The monoamine oxidase A (MAOA) gene codes for an enzyme that breaks down amine neurotransmitters including serotonin, dopamine, and norepinephrine. MAOA levels have been shown to be elevated in patients with MDD [80] and a high activity polymorphism of the MAOA gene has been studied in MDD (reviewed in [81]) and other psychiatric disorders. There is a functional polymorphism consisting of an untranslated VNTR in the promoter region that is associated with higher activity of the enzyme and, in turn, vulnerability to MDD [81]. There have been three studies of the MAOA gene polymorphism in PPD. Two were positive at 6 weeks postpartum but negative at 3 and 6 months postpartum [42, 69], and a third was negative at 8 weeks postpartum [49]. These results underscore the importance of timing for the definition of PPD.

Epigenetic Studies

Kaminsky and colleagues have published a series of studies identifying two epigenetic biomarkers of PPD. In the first publication [82•], genetic loci that were responsive to high dose estrogen in the mouse hippocampus were identified, and these loci were cross-referenced to DNA methylation differences in samples of blood from pregnant women with mood disorders who were followed prospectively through pregnancy and after delivery. The initial sample included pregnant women who were clinically well during pregnancy and either did or did not develop PPD. Two loci were identified at the HP1BP3 and TTC9B genes which, based on methylation differences, were able to correctly identify whether a woman did or did not develop PPD with an 87% accuracy. In a replication analysis, these biomarkers also functioned to segregate PPD status in women who developed depression during pregnancy and continued to be depressed in the postpartum time-period with 88% accuracy. These results were replicated in an independent sample of 51 pregnant women with pre-existing mood disorders, as well as in a sample of 240 pregnant women without a previous psychiatric diagnosis, with an accuracy of at least 80% [83•]. The exact functions of TTC9B and HP1BP3 are currently unknown, but bioinformatics analysis suggests that both may be involved in mediating synaptic plasticity, and both have ties to estrogen signaling [82•]. TTC9B has been shown to be responsive to gonadal hormones [84], and HP1BP3 associates with ESR2 in cell culture [85]. Interestingly, HP1BP3 knockout mice exhibit impaired maternal care, leading to a dramatic reduction in pup survival [86]. Identification of biomarkers capable of predicting PPD is an important step forward in screening and prevention. Further work on the functions of these two genes and their role in PPD may ultimately help elucidate the biological underpinnings of PPD.

Conclusions

Both PMDD and PPD have evidence for a genetic basis based on family and heritability studies, though the evidence for PMDD is mixed and it remains unclear if the heritability of PMDD is related to a trait linked to the syndrome, such as a personality trait, or to the syndrome itself. A number of candidate gene association studies have been completed for each condition without a clear identification of genetic etiology for either, though findings are generally stronger in PPD, with positive findings for genes previously associated with MDD as well as those responsible for estrogen signaling. Still, much work remains to be done.

Although both PMDD and PPD are both reproductive depressions and occur in the setting of hormone withdrawal, evidence to date indicates that the genetic etiology is likely to be different for each condition. This makes sense as, by definition, PMDD is time-limited and resolves over the course of a week or two, while PPD meets length of time criteria for an MDE and does not necessarily resolve with the return of normal hormone levels. It is thus unsurprising that there is stronger evidence for the involvement of genes that have been associated with the etiology of MDD for PPD including the SERT, COMT, and MAOA genes.

One issue that may be at play in the PMDD literature is the difficulty of finding cases, which in turn limits sample sizes. PMDD is estimated to occur in 3–5% of women (as opposed to the 15–20% who suffer from PPD). Potential cases and controls are generally required to meet PMDD criteria for 2

out of 3 prospectively rated menstrual cycles. This requirement limits sample sizes due to the work involved and to the elimination of women who may have substantial symptomatology but do not strictly meet the criteria. It is also difficult to conduct linkage and familiality studies in PMDD except on the basis of self-report (which is notoriously unreliable for PMDD) due to the necessity of obtaining multi-generational data. Finally, several association studies for specific genes were negative for association with PMDD but had positive findings for other clinical features associated with PMDD, such as personality traits. These results suggest that some genetic polymorphisms may influence some of the characteristics associated with PMDD but not the risk for PMDD itself.

In the PPD literature, many of the studies used EPDS scores (rather than clinician diagnosis) as a proxy for PPD. This approach increases sample sizes and ease of data collection, but does mean the results are applicable to depressive symptoms rather than to strict clinical criteria for a PPD. Another observation is that the timing of PPD definition is very important. There is more evidence for a genetic basis for PPD when it is defined as an episode with onset shortly after delivery. Family studies indicated a genetic basis for PPD, but only when onset was within 4 weeks after delivery. Several genes demonstrated positive associations with PPD, but only when onset was within weeks (rather than months) of delivery. Thus, depression that begins months after delivery may have a different biological basis from depression that begins shortly after delivery.

Several lines of evidence point to a role for estrogen signaling for both PMDD and PPD. Currently, the data appear to be mixed for involvement of polymorphisms of ESR1 and ESR2 in PMDD, with one positive study and one negative study for each type of ESR. Further investigation is warranted. Although there are only two studies of ESR1 in PPD, both were positive (though one did not remain significant when corrected for multiple tests). In addition, there are several other lines of evidence pointing to a significant role for estrogen in PPD. These include the over-representation of transcripts linked to estrogen signaling in a genome-wide association study using peripheral blood gene expression profiles [26•], the fact that two genes identified by a genome-wide linkage and association study are modified by estrogen [23] and the fact that epigenetic biomarker studies that accurately predicted PPD identified genes in the hippocampus that were responsive to high dose estrogen [82•, 83•].

Two other genes deserve discussion. HMCN1 was initially identified by the only genome-wide linkage and follow-up association study done to date for PPD [23]. Although its role in PPD is not obvious, a candidate gene association study confirmed the gene's association with PPD [53•]. These findings should be replicated in a larger sample, and the gene should be further investigated for its possible role in PPD. A more obvious gene candidate is OXTR, which has had three association studies in PPD- with mixed results. Future work with this gene should examine time points closer to the time of delivery to determine if timing of onset of PPD influences results.

Clearly there is more work to do on the genetic basis of PMDD and PPD. Overall there is mixed evidence for a genetic vulnerability to PMDD, though larger studies need to be completed. Based on the current literature, the genetic basis for PPD appears to be a mixture of genes that predispose to MDD and those involved in estrogen signaling. Future studies should concentrate on replication of these findings in well-characterized samples, with attention paid to the timing of onset of symptoms. Elucidation of the genetic basis for PPD has the potential to shed light on the biological mechanisms underlying not only PPD but MDD as well.

Compliance with Ethical Standards

Conflict of Interest Katherine McEvoy, Lauren M. Osborne, and Julie Nanavati each declare no potential conflicts of interest.

Jennifer L. Payne holds a patent for the epigenetic biomarkers of postpartum depression. Dr. Payne reports a grant from SAGE Therapeutics and personal fees from Astra Zeneca, Eli Lilly, Johnson & Johnson, and Abbott Pharmaceuticals; and reports serving on the Relapse Adjudication Committee for Janssen Research & Development, LLC.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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